Neuroscience and Biobehavioral Reviews 66 (2016) 92–103

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Cortical and subcortical gray matter shrinkage in alcohol-use disorders: a voxel-based meta-analysis

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ARTICLE INFO

Article history:
Received 22 October 2015
Received in revised form 17 February 2016
Accepted 24 March 2016
Available online 21 April 2016

Keywords:
Meta-analysis
Alcohol-use disorder (AUD)
Gray matter volume
Voxel-based morphometry (VBM)

ABSTRACT

Although gray matter (GM) damages caused by long term and excessive alcohol consumption have long been reported, the structural neuroimaging findings on alcohol-use disorders (AUD) are inconsistent. The aim of this study was to conduct a meta-analysis, using a novel voxel-based meta-analytic method effect-size signed differential mapping (ES-SDM), to characterize GM changes in AUD patients. Twelve studies including 433 AUD patients and 498 healthy controls (HCs) were retrieved. The AUD group demonstrated significant GM reductions in the corticostriatal-limbic circuits, including bilateral insula, superior temporal gyrus, striatum, dorsal lateral prefrontal cortex (DLPFC), precentral gyrus, anterior cingulate cortex (ACC), left thalamus and right hippocampus compared to HCs. GM reduction in the right striatum is significantly negatively related to duration of alcohol dependence, while GM shrinkage of the left superior, middle frontal gyrus, and left thalamus is related to lifetime alcohol consumption. The findings demonstrate that the GM abnormalities caused by AUD are in corticostriatal-limbic circuits whose dysfunctions may involve in craving and observed functional deficits.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.03.034
0149-7634/

1. Introduction

Alcohol-use disorder (AUD) is a highly prevalent neuropsychiatric disorder with a maladaptive pattern of alcohol consumption, which is manifested by symptoms leading to clinically significant impairment or distress, and can shorten lifespans of affected people. AUD is estimated to account for approximately 4% of all global deaths and 4.5% of disability-adjusted life-years worldwide. The historical classifications of the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders DSM-III (DSM-III, APA, 1980), DSM-IV (DSM-IV, APA, 1994), and DSM-IV-TR (DSM-IV-TR, APA, 2000) differentiated between alcohol abuse and alcohol dependence as two discrete disorders. Considering the misconception of the boundary between abuse and dependence, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders—DSM-5 (DSM-5, APA, 2013) combines diagnostic criteria for abuse and dependence into a single unitary diagnosis of AUD, suggesting continuity, rather than discontinuity, in the likelihood of substance-related problems being related to substance dependence (Hasin, 2012).

With the fast development of brain-imaging techniques, we can fully understand the effects of alcohol abuse and dependence on structural alterations in the human brain. In humans, long term and excessive alcohol consumption results in a variety of somatic and central nervous system impairments that must be parsed from the normal growth of the brain. Alcohol dependence is marked by widespread gray matter and white matter loss in selective constellations of neuro-circuitry, including the fronto-cerebellar, frontostriatal, and limbic systems (Jang et al., 2007). Several MRI morphometric studies have provided evidence of reduced volume in cortical and subcortical cerebral structures in alcohol-dependent patients (Chanraud et al., 2009; Chanraud et al., 2007; Demirakca et al., 2011; Fein et al., 2013) and nonhuman primates AUD models (Kroenke et al., 2014). These findings are consistent with post-mortem studies, which have demonstrated that neuronal loss is primarily located in the dorsolateral frontal cortex, hypothalamus, and cerebellum, but not in hippocampus which shows glial rather than neuronal loss in AUD (Kril and Halliday, 1999). Furthermore, several studies have reported that the degree of brain atrophy is correlated with the rate and amount of alcohol consumed over a lifetime (Brooks et al., 2014; Harding et al., 1996; Segobin et al., 2014) as well as the degradation of neuropsychological performance, especially executive functions (Chanraud et al., 2009). These studies may explain the biological processes occurring in brain regions that are correlated with the psychological experiences manifested in AUD. The alcoholism-related gray matter alterations in different brain regions that occur in AUD are consistent with those identified in previous functional MRI studies. After a prolonged period of alcohol consumption, the neurotoxic effects of alcohol may impede the functional integrity of these regions, which are involved in cognitive/behavioral control and emotion regulation, and may result in an increased allostatic load on key neural circuits (Seo et al., 2013). A number of task-related fMRI analyses have dominantly reported that in response to alcohol-related stimuli, altered activities occur in brain regions involving the ventromedial prefrontal cortex/anterior cingulate cortex (ACC) and striatum; these functional changes are significantly associated with alcohol consumption and alcohol craving. The impairment of functional connectivity (FC) and brain network topology (i.e., global efficiency and local efficiency) has also been consistently found in several research studies (Courtney et al., 2013; Sjoerds et al., 2015; Zhu et al., 2015a; Zhu et al., 2015b). A recently published study reported that greater alcohol dependence severity is associated with weaker functional connectivity between the putamen and prefrontal regions during response inhibition (Courtney et al., 2013). It implicated that the fronto-striatal pathway underlying response inhibition is weakened as alcoholism progresses. Taken together, these structural and functional findings strengthen the notion that the corticostriatal-limbic circuits might play a crucial role in the pathophysiology of AUD.

Although there is evidence for structural brain abnormalities in AUD, the findings of current studies have been somewhat inconsistent. For example, the dopaminergically rich structures of the striatum and related structures have been identified as critical nodes underlying addiction and craving in alcohol dependence. Despite the marked volume reductions found in the striatum (Makris et al., 2008; Sullivan et al., 2005), volume increases have also been reported (Howell et al., 2013). Howell and colleagues found that compared to controls, patients with alcoholism have increased gray matter volume in the striate (Howell et al., 2013). Interestingly, Fein and colleagues found that AUD males had smaller putamen volumes and females had larger putamen volumes, thus confirming the gender-specific effects on striatum changes (Fein et al., 2013). Furthermore, the alcohol-related brain structures are not limited to the corticostriatal-limbic circuits. Thinning of the corpus callosum (Pfefferbaum et al., 1996) and reduced volume in the cingulate cortex (Grodin et al., 2013) and in the cerebellar anterior–superior vermis (Sullivan et al., 2000) (the ALC had gray but not white matter cerebellar hemisphere volume deficits) were also reported in previous studies. Furthermore, the relationship between volume losses and clinical measurements is variable in many studies. The heterogeneity of subjects, variability of outcome measures used, and other fundamental problems of research design have led to discrepancies in describing the etiology of the disorder.

However, studies of alcohol exposure have been confounded by age, psychiatric comorbidity and treatment status. In contrast to studies of adults, some researchers have found that in adolescents with alcohol exposure but without comorbidities, the differences of gray matter density between AUD patients and healthy controls were limited to regions in the left lateral frontal, parietal and temporal lobes (Fein et al., 2013), whereas the significant brain atrophy in children was found in the bilateral superior temporal gyrus (Brooks et al., 2014). The results of these studies must be interpreted with caution based on the unique effects of alcohol consumption on the developing brain. Comorbidity may act as another confounding factor because several psychiatric conditions are also associated with volumetric alterations. For example, cigarette smoking among alcoholics exacerbates alcohol-induced structural and metabolic changes (Gazdzinski et al., 2008; Luhar et al., 2013; Mason et al., 2006). The prefrontal cortical regions and their associated functions might be commonly affected in both depression and alcoholism (Miguel-Hidalgo and Rajkowska, 2003). Furthermore, brain shrinkage and partial recovery with continuous abstinence are commonly observed in individuals with AUD. Brain volume increase has been reported to recover significantly within only a few weeks of sobriety in alcoholics (Gazdzinski et al., 2005). Besides, variability of outcome measures used, and other fundamental problems of research design will also lead to discrepancies in describing the etiology of the disorder. Identifying consistent results from VBM studies of AUD individuals through meta-analysis is therefore of particular importance.

Currently, a newly developed signed differences method called effect-size signed differential mapping (ES-SDM) has enabled the identification of the most spatially consistent brain changes reported in the literature through the use of the coordinate information reported in each study. While both peak-probability and signed differences methods have enabled investigators to conduct exhaustive whole-brain meta-analysis of neuroimaging studies and to determine the most prominent and replicable brain areas (Rubia et al., 2014). Whole-brain analyses are not restricted to manual