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Genetic and behavioral determinants of hippocampal volume recovery during abstinence from alcohol

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A B S T R A C T

Alcohol-dependent individuals (ALC) have smaller hippocampi and poorer neurocognition than healthy controls. Results from studies on the association between alcohol consumption and hippocampal volume have been mixed, suggesting that comorbid or premorbid factors (i.e., those present prior to the initiation of alcohol dependence) determine hippocampal volume in ALC. We aimed to characterize the effects of select comorbid (i.e., cigarette smoking) and premorbid factors (brain-derived neurotrophic factor [BDNF] genotype [Val66Met rs6265]) on hippocampal volume in an ALC cohort followed longitudinally into extended abstinence. One hundred twenty-one adult ALC in treatment (76 smokers, 45 non-smokers) and 35 non-smoking light-drinking controls underwent quantitative magnetic resonance imaging, BDNF genotyping, and neurocognitive assessments. Representative subgroups were studied at 1 week, 1 month, and at an average of 7 months of abstinence. ALC had smaller hippocampi than healthy controls at all time points. Hippocampal volume at 1 month of abstinence correlated with lower visuospatial function. Smoking status did not influence hippocampal volume or hippocampal volume recovery during abstinence. However, only BDNF Val homozygotes tended to have hippocampal volume increases over 7 months of abstinence, and Val homozygotes had significantly larger hippocampi than Met carriers at 7 months of abstinence. These findings suggest that BDNF genotype, but not smoking status or measures of drinking severity, regulate functionally relevant hippocampal volume recovery in abstinent ALC. Future studies aimed at exploring genetic determinants of brain morphometry in ALC may need to evaluate individuals during extended abstinence after the acute environmental effects of chronic alcohol consumption have waned.

Introduction

Recent brain imaging in alcohol-dependent individuals (ALC) has focused on the degree to which hippocampal morphometry relates to the direct neurotoxic effects of chronic alcohol consumption. Structural neuroimaging in adult treatment-seeking ALC demonstrated smaller hippocampal volumes within the first month of abstinence compared to healthy controls (Agartz, Momenan, Rawlings, Kerich, & Hommer, 1999; Jarrard, 1995; Pfefferbaum et al., 1995; Sullivan & Pfefferbaum, 2005; Wrase et al., 2008). Adolescents with a short history of alcohol abuse also have smaller hippocampi than age-matched healthy controls (De Bellis et al., 2000; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005). Importantly, the literature is mixed on the association of measurements of alcohol consumption and hippocampal volume. De Bellis et al. (2000) found that hippocampal size correlated positively with age of onset of alcohol dependence and correlated negatively with alcohol use duration, but other studies have found no such associations (Agartz et al., 1999; Gazdzinski et al., 2008; Nagel et al., 2005) or did not report on such a relationship (Pfefferbaum et al., 1995; Wrase et al., 2008). Together, these findings suggest that the observed hippocampal atrophy in adult ALC may be related to environmental factors other than alcohol consumption (such as chronic smoking, for example) or that hippocampal volume

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differences exist prior to the development of alcohol dependence (i.e., are premorbid).

Approximately 60–90% of ALC smoke cigarettes chronically with significant health risks (Giovino, 2002; Romberger & Grant, 2004). In our previous magnetic resonance studies of a small patient cohort (Gazdzinski et al., 2008), chronically smoking ALC (sALC) had smaller hippocampi during the first month of abstinence than non-smoking ALC (nsALC). Furthermore, both groups had hippocampal volume increases over this period, but only in nsALC did these increases correlate with improvements in visuospatial memory. Both preclinical and clinical studies suggest the hippocampus is involved in visuospatial memory (Devenport, Stidham, & Hale, 1989; Grant, 1987; Jarrard, 1995; Matthews, Simson, & Best, 1995; Munro, Saxton, & Butters, 2000; Vandergriff, Matthews, Best, & Simson, 1996).

Only 2 studies have explored the potential effects of premorbid factors on hippocampal volume by comparing alcohol-naïve adolescents with and without a family history of alcohol problems, and they found no significant effects of family history on hippocampal volume (Hanson et al., 2010; Hill et al., 2001). Although genetic factors account for >50% of the variance in alcoholism liability (Goldman, Oroszi, & Ducci, 2005), and although the size of the hippocampus is hereditary (Sullivan, Pfefferbaum, Swan, & Carmelli, 2001), no study has explored specific functional genes that may affect hippocampal volume in ALC.

One candidate gene shown to affect brain morphology and cognition in other neurodegenerative diseases is brain-derived neurotrophic factor (BDNF). This neurotrophin is primarily active in the hippocampus and cerebral cortex (Hofer, Pagliusi, Hohn, Leibrock, & Barde, 1990); it supports survival of extant neurons and promotes neurogenesis (Ernfors, Kucera, Lee, Loring, & Jaenisch, 1995; Murer, Yan, & Raisman-Vozari, 2001). Carriers of the Val66Met (rs6265) single nucleotide polymorphism (SNP) (Met carriers) have impaired intracellular secretion and trafficking of BDNF relative to Val homozygotes (Chen et al., 2004; Egan et al., 2003). Healthy Met carriers have smaller hippocampi than Val homozygotes (Bueller et al., 2006; Molendijk et al., 2012; Ozsoy, Durak, & Esel, 2013). A recent quantitative neuroimaging study of adult recovering ALC from our laboratory (Mon et al., 2013) found no effect of BDNF genotype on neocortical gray matter cross-sectional volumes. However, cortical gray matter volume increased during the first month of abstinence in BDNF Val homozygotes only, not in Met carriers. The specific effects of BDNF genotype on hippocampal volume during abstinence from alcohol have not been investigated. The aims of this study were therefore to measure the effects of BDNF genotype and smoking on hippocampal structure and function in a large alcohol-dependent cohort followed further into abstinence than reported previously. We hypothesized that a) smoking ALC would demonstrate smaller hippocampi than non-smoking ALC up to 1 year into abstinence, b) BDNF Met carriers would exhibit less hippocampal volume recovery during abstinence than Val homozygotes, and c) hippocampal volume recovery would correlate with improvements in visuospatial memory.

Materials and methods

Participants

One hundred and twenty-one alcohol-dependent individuals (ALC) were recruited from the substance abuse treatment programs at the VA Medical Center and Kaiser Permanente in San Francisco, and 35 healthy non-smoking light drinkers (nsLD) were recruited from the San Francisco Bay Area Community as controls. The ALC group consisted of current smokers (sALC, $n = 76$) and non-smokers (nsALC, $n = 45$). As the primary focus of the study was to identify determinants of hippocampal recovery during abstinence from alcohol, ALC participants were preferentially recruited for the study. All participants provided written informed consent and all study procedures were approved by The Institutional Review Boards of the University of California San Francisco and the San Francisco VA Medical Center.

Of 121 ALC participants who received structural MRI, 117 also completed the neuropsychological assessment. The study design included 3 separate time points (TP): ALC participants were studied after 7 ± 3 days of abstinence (TP1), after 33 ± 9 days of abstinence (TP2), and after 213 ± 57 days of abstinence from alcohol (TP3). The sample was comprised of both "early starters" and "late starters." "Early starters" entered the study at TP1 and were then assessed at TP2 and TP3, unless they were lost to follow-up or relapsed to drinking any amount of alcohol prior to their next assessment. Given the realities of clinical research and recruitment constraints, some individuals did not enter the study at TP1 (i.e., within 7 ± 3 days of stopping drinking) and instead entered the study at TP2 (i.e., within 33 ± 9 days of stopping drinking). These participants were classified as "late starters" and were then re-assessed at TP3, unless they were lost to follow-up or relapsed to drinking any amount of alcohol prior to TP3. Thus, individual participants could have data for any combination of TP1, TP2, and TP3, with the sample size at each TP determined by time of enrollment, ability to remain abstinent from alcohol, and attendance at follow-up assessments. The number of participants by group at each TP and the proportion of "early starters" and "late starters" can be found in Table 1. The sample did not differ on demographics or drinking severity measure at TP1, TP2, and TP3. The number of days abstinent at TP1, TP2, and TP3 were not different for nsALC and sALC (all $p > 0.3$). Of the 35 nsLD participants, 16 were re-studied at 290 ± 49 days after baseline assessments to confirm stability of imaging outcome measures over time.

All inclusion and exclusion criteria were reported previously (Durazzo, Gazdzinski, Banys, & Meyerhoff, 2004). Briefly, all ALC individuals met DSM-IV criteria for alcohol dependence, and had consumed >150 standard alcohol-containing drinks (i.e., 13.6 g of pure ethanol) per month for >8 years prior to enrollment into the study for males and >80 drinks for >6 years for females. All participants were free of general medical, neurologic, and psychiatric conditions known to influence hippocampal volume and neurocognition (e.g., schizophrenia, PTSD, dementia), except unipolar mood disorders, hypertension, and hepatitis C due to the high

Table 1
Number of participants present at each time point (TP).

Time point	nsALC			sALC			ALC (nsALC + sALC)	nsLD
	Early starters	Late starters	Combined cohort	Early starters	Late starters	Combined cohort		
TP1	35	0	35	49	0	49	84	35
TP2	29	16	45	38	38	76	121	0
TP3	19	7	16	11	10	21	37	16

nsLD, non-smoking light drinking participant; nsALC, non-smoking alcohol-dependent participant; sALC, smoking alcohol-dependent participant.
"Early Starters" entered the study at TP1 after 7 ± 3 days of abstinence from alcohol; "Late Starters" entered the study at TP2 after 33 ± 9 days of abstinence.