

Anomalous Temporoparietal Activity in Individuals with a Family History of Alcoholism: Studies from the Oklahoma Family Health Patterns Project

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Background: Individuals with a family history of alcoholism (FH+) are at enhanced risk of developing alcohol or other substance use disorders relative to those with no family history (FH−). Alcoholics and FH+ subjects have greater interference scores on the Stroop color-word task, suggesting these impairments may be a component of the cognitive phenotype of at-risk individuals.

Methods: In this study, we examined whole-brain activations in 24 FH+ and 28 FH− young adults performing the counting Stroop task, a variant of the Stroop task adapted for neuroimaging studies.

Results: Across all subjects, incongruent versus congruent comparisons showed activations in regions including parietal lobe areas, frontal eye fields, premotor areas, the anterior cingulate cortex, dorsolateral prefrontal cortex, and bilateral insula, indicating typical regions of activation involved in conflict resolution tasks. Compared with FH− participants, FH+ participants had greater activations in the left superior parietal lobule and precuneus (BA 7 and 19), inferior parietal lobule (BA 40), and middle temporal gyrus (BA 39 and 19), indicating a predominance of greater left hemisphere activity among FH+ in temporoparietal regions. There were no regions showing greater activations in the FH− group compared with the FH+ group.

Conclusions: These results are consistent with less efficient cognitive functioning potentially due to poorer communication over long pathways connecting temporoparietal regions to prefrontal brain regions that participate in a distributed network involved in cognitive processing and working memory necessary for conflict resolution.

Key Words: Cognition, Counting Stroop Task, Family History, Temporoparietal, Vulnerability.

INDIVIDUALS WITH A family history of alcohol and other drug use disorders (FH+) are at increased risk of developing these same disorders compared with those with no such history (FH−; Finn et al., 1990; Lieb et al., 2002; Merikangas et al., 1998). Although the FH+ associated risk has a strong genetic component (Cloninger et al., 1981; Merikangas, 1990; Reich et al., 1998; Slutske et al., 2002), the specific biological mechanisms mediating this risk remain elusive. In real-world settings, FH+ is linked with a pattern of “behavioral undercontrol” (Sher and Trull, 1994; Sher

et al., 2004) or “neurobehavioral disinhibition” (Tarter et al., 2003), patterns that include increased sensation seeking, risk taking, aggressiveness, and antisocial behaviors. Similarly, laboratory behavioral assessments reveal that FH+ is associated with subtle deficits on measures of executive functioning, impulse control, decision making, and attention (e.g., Acheson et al., 2011a,b; Corral et al., 2003; Deckel, 1999; Lovallo et al., 2006; Stevens et al., 2003). Emerging functional imaging research indicates that FH+ appear to have altered patterns of brain activity during such tasks (e.g., Acheson et al., 2009; Cservenka et al., 2012; Glahn et al., 2007; Heitzeg et al., 2010; Schweinsburg et al., 2004; Silveri et al., 2011). Improved understanding of how neural functioning is altered in FH+ individuals could substantially advance our understanding of underlying biological vulnerabilities to alcohol and other substance use disorders.

We have shown in a large sample study that FH+ subjects have modest performance impairments relative to FH− on the traditional Stroop color-word task, as indicated by their greater interference scores (longer times to name text colors in incongruent word-color pairings vs. reading words; Lovallo et al., 2006; Stroop, 1935). Given that Stroop deficits are also seen in alcoholics and other populations with addictive disorders (Vadhan et al., 2007), these impairments may be a component of the cognitive phenotype of at-risk individuals. Recently, Silveri and colleagues (2011) reported brain activa-

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tion differences within a frontolimbic region of interest in FH+ versus FH- adolescents while performing the classic Stroop color-word task. However, by restricting the analyses to these regions, this study was not able to examine other brain regions implicated in Stroop task performance such as the parietal cortex and precuneus (BA 7; Bush et al., 1998; Matthews et al., 2004). In this study, we sought to extend these findings by examining whole-brain activations in FH+ and FH- young adults performing a counting version of the Stroop task (Bush et al., 1998). This task induces comparable activation patterns as traditional Stroop tasks; however, it is less prone to data loss due to excessive head movement from speaking. We hypothesized that FH+ individuals would also show altered activity in both forebrain as well as nonforebrain regions known to be involved in Stroop task performance.

MATERIALS AND METHODS

Subjects

Twenty-eight FH- individuals and 24 FH+ were recruited from a larger cohort of 450 volunteers participating in the Oklahoma Family Health Patterns (OFHP) project intended to identify cognitive, psychological, behavioral, and physiological characteristics of healthy young adults at elevated risk of alcoholism. Characteristics of the FH groups are given in Table 1.

Inclusion and Exclusion Criteria. Prospective volunteers were excluded if they had a history of alcohol or drug dependence; met criteria for substance abuse within the past 2 months; failed a urine drug screen or a breath alcohol test on days of testing; or who had a history of any Axis I disorder other than past depression (>60 days), as defined by the Diagnostic and Statistical Manual of Mental disorders, 4th ed. (APA, 2000). Subjects were also excluded if they met criteria for an Axis II disorder in clusters A or C. Cluster B diagnoses were not exclusionary due to the known overlap between risk of alcoholism and antisocial tendencies. Psychiatric history was obtained by the computerized Diagnostic Interview Schedule-IV conducted by a certified research assistant under the direction of a licensed clinical psychologist, and through the Beck Depression Inventory II (Beck et al., 1996). Women were required to have a negative urine pregnancy test on each day of testing. All participants were in good physical health, had a body mass index <30, were not taking prescription medications, had no reported history of serious medical disorder, and were right handed as assessed with the Toronto Handedness Scale. Smoking and smokeless tobacco use were not exclusionary.

All participants signed consent forms approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City, OK and at the University of Texas Health Science Center (UTHSCSA), San Antonio, TX, and were paid for their participation.

Family History of Alcohol and Other Drug Use Disorders

Family history classification was established using the Family History Research Diagnostic Criteria (FH-RDC; Andreasen et al., 1977). The FH-RDC has a high degree of inter rater reliability (0.95) for reports of substance use disorders (Andreasen et al., 1977; Zimmerman et al., 1988). In the neuroimaging studies emerging from the OFHP, family history reports by volunteers were all confirmed by parent report. All FH+ participants reported that at least 1 biological parent met at least 2 of the possible 6 criteria for alcohol

Table 1. Sample Characteristics

Family history	FH-	FH+	<i>p</i> -Values
<i>N</i> (M/F)	28 (12/16)	24 (5/19)	
Age (years)	24.0 (2.6)	23.6 (4.0)	0.7
Education (years)	15.6 (1.4)	15.4 (2.1)	0.6
SES	51 (12)	42 (13)	0.01
Shipley vocabulary	31 (4.2)	31 (3.5)	0.5
Ethnicity			
Caucasian	28	18	0.006
African-American	0	6	
Other	0	0	
Hispanic	1	2	0.6
CPI-So	31.6 (4.2)	30.8 (4.0)	0.5
BDI	4.4 (5.8)	4.0 (4.4)	0.8
EPI neuroticism	5.5 (4.1)	4.0 (3.5)	0.8
Narcissism	1	1	0.9
Histrionic	0	0	—
Borderline	1	0	0.9
Antisocial	0	3	0.09
AUDIT	4.9 (3.0)	4.0 (2.6)	0.4
Age at first drink	16.8 (2.8)	15.2 (4.0)	0.1
Alcohol intake (oz/mo)	34 (47)	19 (30)	0.2
Past depression	3	2	0.7
Past alcohol buse	2	1	0.6
Caffeine (mg/day)	167 (177)	167 (255)	0.9
Tobacco (<i>N</i> using weekly)	1	1	0.9

Entries (mean \pm SD) unless given otherwise. SES scores shown are considered "middle class." FH-, negative family history; FH+, positive family history; M, male; F, female; SES, Hollingshead and Redlich Socioeconomic Status Score (Hollingshead, 1975); Shipley Vocabulary, Shipley Institute of Living Vocabulary Score (Tamkin and Jacobsen, 1987); CPI-So, California Personality Inventory Sociability Scale (Gough, 1994); BDI, Beck Depression Inventory (Beck et al., 1996); EPI, Eysenck Personality Inventory (Eysenck and Eysenck, 1964); AUDIT, Alcohol Use Disorders Identification Test (Babor et al., 1992).

or substance abuse. Participants were excluded if either they or the parent reported possible fetal exposure to alcohol or other drugs.

Procedure

Stroop Task. We used a counting version of the Stroop task that did not require reading aloud and that was adapted for use in the magnetic resonance imaging (MRI) environment administered as a block design task (Bush et al., 1998). This version consisted of a 6-second welcome screen with task instructions followed by 5 congruent trial blocks alternating with 5 incongruent trial blocks. Each trial block had 20 trials, and each trial lasted 1.5 seconds. Each trial in congruent trial blocks showed 1 to 4 semantically related words (e.g., "lion, tiger, cheetah"), and the subject pressed a button indicating how many words appeared. Trials on the incongruent trial blocks were identical except that the words presented were incompatible number words (e.g., the word "one" printed 2 times).

Imaging Acquisition. Imaging was carried out on a research-dedicated Siemens 3T MRI (Siemens, Munich, Germany) housed in the Research Imaging Institute at UTHSCSA. Functional imaging used a gradient-echo, echo-planar sequence, acquiring 30 slices (4 mm thick, 1 mm gap) parallel to the anterior commissure-posterior commissure plane (repetition time/echo time [TR/TE] = 3,000/30 ms, 128 \times 128 \times 5 mm, and field of view = 256 mm). For anatomical reference, we acquired a high-quality 3-dimensional image (TR/TE = 2,200/2.83 ms, and flip angle = 13°, 0.8 mm isotropic). The imaging session was completed in 1 hour.

Analysis of Functional MRI Data. Analysis of functional MRI (fMRI) images was carried out using FEAT (FMRI Expert Analy-

sis Tool) version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Prior to statistical modeling, data were motion corrected (Woolrich et al., 2001), nonbrain tissue was removed (Jenkinson and Smith, 2001; Jenkinson et al., 2002), and spatially smoothed with a Gaussian kernel of FWHM 5 mm, and a high-pass temporal filtering was applied (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 seconds). Time-series statistical analysis was carried out using local autocorrelation correction (Beckmann et al., 2003; Woolrich et al., 2004). Registration to high resolution and/or standard images was carried out using FLIRT (Worsley et al., 1992). Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) with a mixed-effects model (Beckmann et al., 2003; Woolrich et al., 2004) to generate *z* statistical images for the incongruent versus congruent conditions. Group maps for all subjects and FH- versus FH+ were generated using conservative cluster thresholds (corrected *p* < 0.05, *z* ≥ 1.96; Woolrich et al., 2005).

RESULTS

Behavioral Results

The FH groups' performances on the congruent and incongruent trial blocks over the course of the task were not significantly different (Table 2).

Imaging Results

Across all subjects, incongruent versus congruent comparisons showed activations in regions including parietal lobe areas (BA 7, 19, and 40 including bilateral precuneus, left inferior parietal lobule, and right superior parietal gyrus), frontal eye fields (precentral gyrus, BA 6), premotor areas (BA 8 and 9), the anterior cingulate cortex (BA 24, 32, 33), dorsolateral prefrontal cortex (BA 46), and bilateral insula (BA 13; Fig. 1, Table 3). This pattern indicates significant involvement in parietal regions, anterior cingulate, and dorsolateral prefrontal cortex in accord with the demands of the task, involving resolution of response competition during incongruent trial blocks.

We next examined statistical activation maps contrasting FH+ versus FH- groups. These contrasts demonstrated relatively greater activations for FH+ in the left superior parietal lobule and precuneus (BA 7 and 19), inferior parietal lobule (BA 40), and middle temporal gyrus (BA 39 and 19; Fig. 2, Table 4). This pattern shows a predominance of

greater left hemisphere activity among FH+ in temporoparietal regions. There were no regions showing greater activations in the FH- group compared with the FH+ group. Cohen's *d* effect sizes were calculated for the *z*-scores of the significant clusters from the group differences.

DISCUSSION

In the present study, we observed that a family history of alcoholism (FH+ vs. FH-) was positively related to greater activation in the left parietal lobe and a closely associated extension of the left temporal lobe. The FH groups did not significantly differ on reaction time change during incongruent trials or in reduced percent correct, suggesting that the greater parietal and temporal lobe activations in this group may imply a lower level of efficiency in performing the task. The results for the whole group indicated that the pattern of cerebral activation is consistent with other imaging studies of the Stroop task, suggesting that the task activations were typical for the demands imposed by the interference condition (Laird et al., 2005). The differences in activation patterns in the FH groups suggest potential for future work on functional differences associated with risk of alcoholism.

Table 2. Performance on the Stroop Task

	FH+	FH-	<i>p</i> -Value
Reaction time (ms)			
Interference	1,437 (391)	1,362 (144)	0.4
No interference	1,260 (350)	1,227 (144)	0.7
Difference	176 (228)	135 (162)	0.5
Accuracy (% correct responses)			
Interference	78 (22)	86 (14)	0.2
No interference	82 (23)	90 (13)	0.1
Difference	-3.17 (6)	-3.89 (4)	0.6

FH-, negative family history; FH+, positive family history. Entries show *M* ± SD.

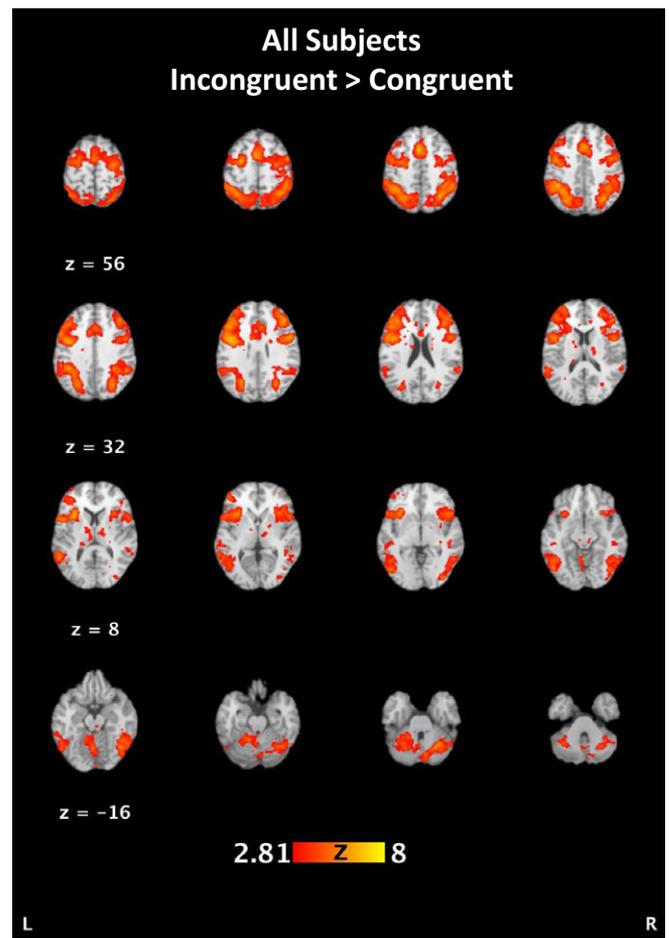


Fig. 1. Areas activated across all subjects map for the incongruent versus congruent contrast. See Table 3 for details.

Table 3. Activation Across All Subjects

Talairach space (mm)			Region	Brodmann area	z-Score	Cohen's <i>d</i>
X	Y	Z				
			Left hemisphere			
-22	-62	40	Precuneus	7	6.22	1.73
-38	-44	38	Inferior parietal lobule	40	6.71	1.86
-56	-46	10	Superior temporal gyrus	22	5.42	1.50
-42	-58	6	Fusiform gyrus	37	5.66	1.57
-8	6	28	Anterior cingulate gyrus	24	4.95	1.37
-2	10	46		32	6.8	1.89
-50	12	32		9	6.24	1.73
-16	4	60		6	4.8	1.33
-24	-4	58		6	5.15	1.43
-24	-8	56		6	5.19	1.44
-26	-6	48		6	6.23	1.73
-34	-10	40		6	5.51	1.53
-36	32	22		46	6.41	1.78
-40	38	14		46	5.29	1.47
-44	44	2	Inferior frontal gyrus	-	4.66	1.29
-34	-2	30	Precentral gyrus	6	7.19	1.99
-40	0	28		6	7.16	1.99
-48	6	6	Insula	13	5.52	1.53
-42	14	6		13	5.97	1.66
-28	20	-4		47	5.65	1.57
-30	12	8		-	6.35	1.76
-14	-59	-24	Cerebellum	-	5.37	1.49
			Right hemisphere			
32	-60	42	Superior parietal lobule	7	6.42	1.78
26	-66	54		7	5.32	1.48
16	-72	48	Precuneus	7	4.72	1.31
30	-72	32		19	5.94	1.65
44	-76	14	Fusiform gyrus	19	5.5	1.53
50	6	26	Inferior frontal gyrus	9	6.24	1.73
44	32	26	Middle frontal gyrus	9	6.36	1.76
40	0	28	Precentral gyrus	6	5.21	1.44
44	-2	38		6	5.33	1.48
50	2	36		6	4.99	1.38
0	2	48	Anterior cingulate gyrus	24	5.99	1.66
4	22	30		32	5.37	1.49
32	16	10	Insula	13	5.69	1.58
0	-64	-16	Cerebellum	-	5.23	1.45
12	-74	-26		-	5.36	1.49
26	-64	-30		-	5.83	1.62
32	-58	-28		-	5.89	1.63
42	-62	-16		-	5.63	1.56

$p < 0.0001$, $z \geq 4.00$.

The classic Stroop color-word interference effect on incongruent trials reflects the time required to suppress a prepotent response (reading the word) and choosing the correct response modality (ink color) and then providing that response (speaking the ink color; Stroop, 1935). Smith and Jonides (1999) have shown that the executive processes necessary for overcoming Stroop interference engage the anterior cingulate gyrus and dorsolateral prefrontal cortex. The counting Stroop (Bush et al., 1998) is a variation of the task developed for neuroimaging studies that avoids the use of speech and induces similar activation contrasts on incongruent versus congruent trial blocks, including the anterior cingulate cortex (BA 24 and 32), dorsolateral prefrontal cortex

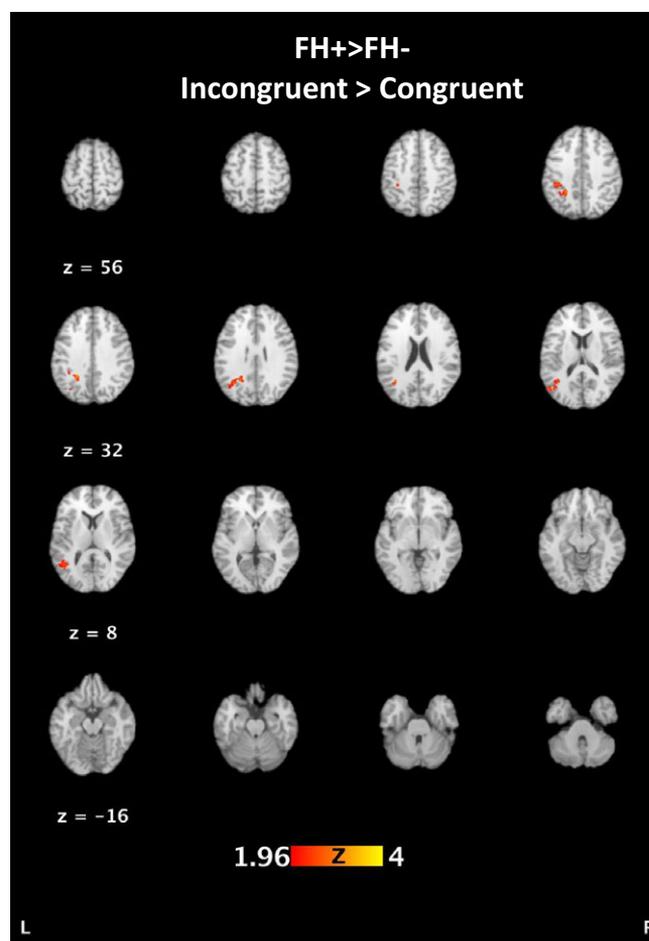


Fig. 2. Activation differences in FH- and FH+ individuals for the incongruent versus congruent contrast. FH+ participants had greater activations in the left superior parietal lobule and precuneus (BA 7 and 19), inferior parietal lobule (BA 40), and middle temporal gyrus (BA 39 and 19; see Table 4). FH-, negative family history; FH+, positive family history.

(BA 9 and 46), frontal eye fields (BA 6 and 8), higher-level visual association cortex (BA 19), and the superior parietal lobule and precuneus (BA 7; Bush et al., 1998; Matthews et al., 2004). Our findings in the present study also accord with findings from imaging studies of other conflict tasks, indicating that the dorsal anterior cingulate is involved with conflict identification and engages the dorsolateral prefrontal cortex to resolve the conflict (Carter and van Veen, 2007; Peterson et al., 1999).

To date, 1 previous neuroimaging study has examined Stroop task activations in FH groups. Silveri and colleagues (2011) compared activations within a frontolimbic region of interest in adolescents performing a variant of the color-word Stroop and found that FH+ adolescents averaging 13 years of age had greater activation in left middle frontal gyrus (BA 6) and insula (BA 13). In contrast, in the present study, our whole-brain analysis of counting Stroop activations in young adult FH groups revealed that FH+ adults, averaging 24 years of age, had greater activity in temporoparietal regions (BA 7, 19, 39, 40). It is possible that Silveri and

Table 4. Group Activation Differences, FH+ > FH-

Talaraich space (mm)			Region	Brodmann area	z -Score	Cohen's <i>d</i>
X	Y	Z				
-24	-58	42	Left superior parietal lobule	7	2.16	0.60
-20	-58	40	Precuneus	7	2.18	0.61
-22	-50	40		7	2.98	0.83
-24	-46	38		7	3.05	0.85
-32	-70	30		19	2.16	0.60
-30	-36	40	Left inferior parietal lobule	40	3.07	0.85
-32	-52	40		40	2.09	0.58
-36	-36	38		40	2.93	0.81
-38	-68	28	Left middle temporal gyrus	39	2.29	0.63
-34	-58	22		39	3.25	0.90
-50	-68	14		39	2.69	0.74
-40	-66	14		39	2.59	0.72
-36	-56	12		19	2.83	0.79
-40	-60	10		19	2.90	0.80

FH-, negative family history; FH+, positive family history.
 $p < 0.05, z \geq 1.96$.

colleagues may have observed results similar to ours had they also examined structures outside of their region of interest. Alternatively, these differences in the studies may result from the age differences in the subject samples and specific differences in task requirements, as the Silveri and colleagues (2011) task called for spoken responses and the use of colored words, while ours avoided the use of speech and but required tracking numbers of objects appearing on the screen and manual responding. A number of studies show that the precuneus and superior parietal lobule become engaged in tasks calling for hand-eye coordination and object matching and grasping (Culham and Kanwisher, 2001).

While both our and the Silveri and colleagues (2011) study found increased activations in FH+ individuals during Stroop task performance, studies of brain activity during Stroop interference comparing controls to persons with impulse control and substance use disorders have shown hypoactivations in regions such as parietal areas and anterior cingulate gyrus, along with dorsolateral and ventromedial prefrontal cortex (Barros-Loscertales et al., 2011; Bush et al., 1999; Potenza et al., 2003). The lack of significant hypoactivations in FH+ individuals may be due to excluding individuals with comorbid psychiatric conditions and thus examining individuals with more normative brain functioning. The left parietal and temporoparietal hyperactivations we observed in the present study do suggest that circuits involving processing the language components of the task were affected, perhaps due to less efficient regulation of these circuits by frontal cortical regions.

The present study and the Silveri and colleagues (2011) study implicate a constellation of temporoparietal and prefrontal areas seen as encompassing a network of regions involved in control of attention, decision making, and working memory necessary for successful Stroop performance. In an influential review of the primate literature involving anatomical tracing techniques, Goldman-Rakic (1998) showed

that cognitive processing utilizes a network of regions with the parietal association cortex at the center of a reciprocal distributed network including visual association cortex, superior temporal gyrus, parahippocampal gyrus, anterior and posterior cingulate cortex, and dorsolateral prefrontal cortex (terms translated into human neuroanatomical features). The foregoing review of the Stroop imaging literature encompasses this same set of regions. We may speculate that in both our study and the Silveri and colleagues' study, FH+ individuals had less efficient functioning within given regions or poorer communication across the distributed cognitive network as described by Goldman-Rakic. It is noteworthy that the concept of cognitive efficiency has been used to account for neuropsychological performance deficits in studies of abstinent alcoholics (Lawton-Craddock et al., 2003; Nixon et al., 2002). The potential for poorer efficiency in carrying out tasks of working memory in both substance abusers and nonabusing FH+ suggests the possible conclusion that some cognitive deficits seen in alcohol and other substance abusers may represent a risk factor rather than a consequence of the disorders.

There are strengths and limitations to the present study. Strengths include a well-characterized subject population with confirmed family histories, no current comorbid conditions, and little problem drinking as indicated by the low Alcohol Use Disorders Identification Test scores. Limitations include that we were only able to scan a subset of participants from the full cohort of subjects of the OFHP project due to constraints in budget and subject availability. Furthermore, both subject groups contained more women than men, and there were socioeconomic and racial differences between the groups as well. Controlling for socioeconomic status in preliminary analyses did not affect the FH group differences; however, attempting to control for race and gender did affect these outcomes. We did not attempt to model the influence of race and gender in our final analyses because we were not adequately powered to examine the contributions of these factors. While we do not feel that race would influence our findings beyond that accounted for by socioeconomic differences, it is possible that gender effects such as influences of sex hormones may have affected our results. Additionally, given evidence for altered default mode activity in FH+ individuals (Spadoni et al., 2008), it is possible that differences in baseline brain activity may have influenced our outcomes. Finally, we did not observe Stroop task performance differences, but the Stroop task differences we reported previously were of modest effect size and unlikely to be detected with the sample size of the present study (Lovallo et al., 2006). Additionally, while the differences observed between groups were not statistically significant, they were all in the same direction with our previously observed findings in the larger sample and suggest a tendency toward poorer Stroop task performance for FH+ adults.

At present, it is difficult to tightly relate the brain activation differences seen here to FH classification and to a behavioral phenotype associated with the risk of

alcoholism. Although Stroop performance was similar for the 2 FH groups, we were able to detect impairments in FH+ subjects on Stroop performance in a much larger sample of subjects (Lovallo et al., 2006), and the activation differences seen here may relate to these relatively subtle behavior differences. Furthermore, differences in processing information that call for greater cerebral resource utilization by FH+ may indicate a reduced level of cognitive control over behavior or the potential for greater lapses in attention that may result in a long-term pattern of disinhibited behavior. Studies replicating the present one are therefore called for as well as studies of white matter integrity in pathways connecting distant brain regions involved in the distributed network of regions involved in cognition generally. We have consistently found a pattern of antisocial and disinhibitory behavior in FH+ persons in the OFHP cohort (Acheson et al., 2011b; Saunders et al., 2008; Yechiam et al., 2006), and these differences in temperament may similarly reflect a less tightly regulated pattern of behavior, again involving a need for greater allocation of effort to maintain behavioral control.

In conclusion, we report that while undergoing fMRI scanning, FH+ adults relative to FH– controls showed greater activations in temporoparietal regions while performing a counting Stroop task. These results are consistent with less efficient cognitive functioning or poorer communication over long pathways connecting these posterior regions to more anterior brain areas that participate in a distributed network of regions involved in cognitive processing and working memory.

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