Reduced memory in fat mass and obesity-associated allele carriers among older adults with cardiovascular disease

Michael L. ALOSCO,1 Andreana BENITEZ,3 John GUNSTAD,1,2 Mary Beth SPITZNAGEL,1,2 Jeanne M. MCCAFFERY,4 John E. MCGEARY,4,5 Athena POPPAS,6 Robert H. PAUL,7 Lawrence H. SWEET4 and Ronald A. COHEN4

1Department of Psychology, Kent State University, Kent, 2Department of Psychiatry, Summa Health System, Akron, Ohio, 3Mary S. Easton Center for Alzheimer’s Disease Research, UCLA, Los Angeles, California, 4Department of Psychiatry and Human Behavior, Brown Medical School, 5Research Service, Providence VA Medical Center, 6Department of Cardiology, Rhode Island Medical Center, Providence, Rhode Island, and 7Department of Psychology, University of Missouri, St. Louis, Missouri, USA

Correspondence: Mr Michael L. Alosco BA, Department of Psychology, Kent State University, Kent, OH 44240, USA. Email: malosco@kent.edu
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Abstract

Background: Much attention has been paid to the prevalence and predisposition of the fat mass and obesity-associated (FTO) gene to obesity, although only a few studies have characterized the extent to which this affects cognitive function. This study examined differences between risk allele carriers (i.e. FTO-AC/AA) and non-carriers (i.e. FTO-CC) on indices of attention/executive function/psychomotor speed, memory, language, and visual-spatial ability in a sample of older patients with cardiovascular disease.

Methods: We recruited 120 older adults from an outpatient cardiology clinic who underwent blood draw and completed neuropsychological testing. Participants were classified into two groups: one for those who were homozygous for the non-risk-conferring allele (i.e. FTO-CC) (n = 49) and the other for those who had at least one copy of the obesity risk-conferring A allele (i.e. FTO-AC/AA) (n = 71).

Results: MANCOVA analyses adjusting for age and years of education revealed the FTO-AC/AA group performed significantly worse on indices of memory (λ = 0.94, F(2, 115) = 3.58, P = 0.03, partial η² = 0.06). Follow-up tests revealed a significant effect for the FTO-AC/AA group, relative to the non-carrier group, on encoding (i.e. California Verbal Learning Test Total Learning) and California Verbal Learning Test long-delay free recall (P < 0.05). No such differences between FTO carriers and non-carriers emerged on tests of attention/executive function/psychomotor speed, language, or visual-spatial ability (P > 0.05 for all).

Conclusions: These findings suggest that the FTO risk allele is associated with reduced memory performance, particularly on aspects of memory encoding and delayed recall. To elucidate underlying mechanisms, these findings will need to be replicated in larger samples that utilize neuroimaging.

Key words: cardiovascular disease, cognitive function, FTO risk allele, memory, obesity.

INTRODUCTION

Obesity produces significant public health and economic burdens worldwide, through both independent effects and its promotion of conditions such as cardiovascular disease, diabetes and stroke. As such, much attention has been paid to genetic contributors to obesity, most notably the fat mass and obesity-associated gene (FTO), which is associated with obesity across ethnicities and nationalities, as confirmed by meta-analyses of genome-wide studies. Through its effects on obesity, carriers of the FTO obesity risk A allele are at greater risk for diabetes and subsequent cardiovascular disease – both of which are linked to poor outcomes including cognitive impairment.
FTO is highly expressed and known to act in the central nervous system. Recent findings identified volumetric and functional central nervous system deficiencies among risk allele carriers. In their analysis of healthy elderly enrolled in the Alzheimer’s Disease Neuroimaging Initiative study, Ho et al. identified that carriers of the FTO risk allele demonstrate ~8% and 12% lower brain volume in the frontal and occipital lobes, respectively, than non-carriers. A separate study showed that individuals who have both copies of the risk allele are at an increased risk for dementia, particularly those with the Alzheimer’s disease risk allele apolipoprotein E (APOE) ε4. To our knowledge, only one published study has corroborated these findings using a common neuropsychological test of executive function. Benedict et al. found that risk allele carriers among overweight and obese elderly men demonstrated diminished verbal fluency compared to non-carriers; they concluded that FTO modulates cognition depending upon an individual’s body weight. The extent to which FTO carriers also exhibit reductions on other neuropsychological measures of frontal function and other cognitive domains is unknown.

The current study examined attention/executive function/psychomotor speed, memory, language, and visual-spatial ability among FTO risk allele carriers and non-carriers. We hypothesized that carriers of the FTO risk allele would have poorer functioning across multiple cognitive domains.

METHODS

Participants
Participants included 120 older adults enrolled in a longitudinal study of neurocognitive consequences of cardiovascular disease. Participants were recruited from outpatient cardiology clinics and were eligible for the study if they had had one or more of the following: myocardial infarction, cardiac surgery, heart failure, coronary artery disease, or hypertension. Individuals were excluded from the study if they had a history of a major neurological (e.g. Alzheimer’s disease, stroke) or psychiatric disorder (e.g. schizophrenia, bipolar disorder, current substance abuse). Participants were classified into two groups: one for those who were homozygous for the non-risk-conferring allele (i.e. FTO-CC) (n = 49) and one for those who had at least one copy of the obesity risk-conferring A allele (i.e. FTO-AC/AA) (n = 71). Of these carriers, 23% (n = 27) were homozygous for the A allele. Demographic and medical characteristics of the FTO groups are presented in Table 1.

Measures

Neuropsychological tests
Neuropsychological tests were grouped into one of four neuropsychological domains to facilitate interpretation. Raw scores for each test were used in primary analyses. See Table 2 for neuropsychological test performance. All neuropsychological tests used in the current study demonstrate strong psychometric properties, including excellent reliability and validity. The domains and neuropsychological tests administered are as follows:

- attention/executive function/psychomotor speed: Trail Making Test A, Trail Making Test B, Digit Symbol Coding, Similarities
- memory: California Verbal Learning Test (CVLT) Total Learning and Long-Delay Free Recall
- language: Boston Naming Test, Animal Naming
- visual-spatial: Block Design, Hooper Visual Organization Test

Procedures
This study was approved by the institutional review board at Brown University (Providence, RI, USA) and all participants gave written informed consent. Participants provided medical history information through self-report, which was corroborated by medical records wherever possible. Participants underwent blood draw and completed neuropsychological testing.

Following neuropsychological testing, blood samples were collected in tubes and refrigerated within 10 min of collection. FTO single nucleotide polymorphism determinations were performed using the fluorogenic 5’ nuclease (TaqMan; Applied Biosystems, Foster City, CA, USA) method, with reagents (VIC- and FAM-labelled probes and TaqMan Universal PCR Master Mix without AmpErase UNG) obtained from Applied Biosystems. Reactions were performed in an Applied Biosystems Prism 7300 Sequence Detection System using both absolute quantification and allelic discrimination modes as described in the instrument documentation. In our sample, 59% were identified as A-allele carriers of the FTO rs8050136 single nucleotide polymorphism, which is consistent
with population-based prevalence estimates. However, the genotype distributions did differ from Hardy–Weinberg Equilibrium ($\chi^2 = 15.6, P < 0.001$) with fewer heterozygotes found than expected.

### Statistical analysis

Independent samples $t$-tests and $\chi^2$ analyses were used to explore potential differences between the FTO-CC and FTO-AC/AA groups on relevant demographic and medical variables. MANCOVA analyses were conducted to ascertain an omnibus difference between the raw scores of the two groups on the indices of attention/executive function/psychomotor speed, memory, language, and visual-spatial ability. Given that raw scores of neuropsychological tests were used as dependent variables, age and years of education were controlled for.
education were included as covariates to account for the known contribution of these variables to test performance. Follow-up univariate analyses were conducted to clarify significant omnibus tests.

RESULTS

No differences were found between the carrier groups on relevant demographic and medical variables (Table 1). As such, no other covariates or moderators except for age and education were included in the models.

MANCOVA analyses yielded an omnibus between-groups difference for memory ($\lambda = 0.94, F(2, 115) = 3.58, P = 0.03$, partial $\eta^2 = 0.06$). The FTO-AC/AA group demonstrated significantly reduced performance on encoding (i.e. CVLT Total Learning) and CVLT Long-Delay Free Recall compared to the non-carrier group ($P < 0.05$). No between-group differences emerged for other domains, including attention/executive function/psychomotor speed ($\lambda = 0.97, F(4, 113) = 1.03, P = 0.40$, partial $\eta^2 = 0.04$), language ($\lambda = 0.97, F(2, 115) = 1.83, P = 0.17$, partial $\eta^2 = 0.03$) or visual-spatial ability ($\lambda = 0.96, F(2, 115) = 2.22, P = 0.11$, partial $\eta^2 = 0.04$) (Table 2).

DISCUSSION

Previous work has shown that carriers of the FTO risk allele may be at risk for reduced volume and function of frontal brain regions. The current study extends these findings by demonstrating that carriers of the FTO risk allele also have significantly reduced memory functioning on neuropsychological testing. Therefore, several aspects of these findings warrant further discussion.

The current study demonstrated that carriers of the FTO risk allele had significantly reduced memory functioning. Previous work has linked FTO with increased risk for Alzheimer’s disease, further supporting the possible adverse effects of the FTO risk allele on memory functioning. Interestingly, recent work has also shown the risk of Alzheimer’s disease among FTO risk allele carriers was even greater in the presence of APOE $\varepsilon 4$. There is extant evidence linking APOE $\varepsilon 4$ with memory dysfunction and corresponding neuroimaging abnormalities, including atrophy and decreased white matter integrity of the temporal lobe. Given these findings, further work examining the negative effects of FTO on memory functioning and temporal lobe structures of the brain is needed, particularly as this may introduce adverse effects over and above deficits already observed in individuals with obesity and cardiovascular disease.

Although not examined in the current study, the influence of APOE $\varepsilon 4$ on cognitive function, especially in the context of FTO, deserves additional discussion. APOE $\varepsilon 4$ significantly increases cardiovascular disease risk by disrupting cholesterol transport and homeostasis. Interestingly, past work has shown that APOE $\varepsilon 4$ interacts with vascular factors (i.e. stroke, myocardial infarction, hypertension) to influence the progression of cognitive decline and subsequent Alzheimer’s disease. FTO has also been linked with elevated risk of cardiovascular disease through its effects on obesity, and the current findings further suggest that FTO is also associated with cognitive dysfunction. Based on such findings, future work should examine whether FTO and APOE $\varepsilon 4$ may produce synergistic effects on cognitive function in addition to cardiovascular disease risk.

The current study failed to find between-group differences on measures assessing frontal function. Although past work has demonstrated that FTO risk allele carriers have reduced frontal functioning, such findings reflect cognitive test performance based on a single task of verbal fluency. Thus, our study is the first to examine the effects of the FTO risk allele with multiple neuropsychological measures that are sensitive to frontal lobe functions. Despite our non-significant findings, frontal deficits are common in obesity and cardiovascular disease populations, and further work clarifying the effects of the FTO risk allele on frontal functions is strongly encouraged. Moreover, exploration of the possible incremental impact of FTO risk allele status on the frontal lobes is imperative, as characterization of the involvement of the frontal lobes in FTO risk allele carriers may have significant implications for the pathogenesis and treatment of obesity. For instance, much work has been dedicated to the importance of intact frontally mediated executive functions to the success of weight loss strategies. In turn, it is possible that the FTO risk allele confers risk for obesity through both its physiological and behavioural effects.

Some limitations must be considered when reviewing these results. First, although the groups had similar demographics and medical histories, we did not employ markers of cardiovascular (e.g. stress test)
or metabolic functioning (e.g. Homeostatic Model Assessment-Insulin Resistance), which could have moderated our results. Second, the current study did not examine body mass index within the sample. Body mass index has been shown to be associated with cognitive deficits in some studies, but findings are inconsistent. Future work examining obese and non-obese FTO risk allele carriers are needed to clarify the independent effects of the FTO gene on cognitive function. Additionally, our sample was relatively small and exclusively composed of patients with cardiovascular disease. Confirmation of these findings is necessary in larger, population-based samples in order to promote generalizability and increase statistical power. Also, the current sample was noteworthy for a departure from Hardy–Weinberg Equilibrium, though the exact aetiology of this pattern is unclear. We believe that genotyping error is unlikely given the standardized assay and 100% reliability with rerun samples. The possibility of unmeasured substructure or association of FTO variability with cardiovascular disease cannot be discounted, particularly given the recent report by Lappalainen et al. that found the FTO risk allele to be associated with a two-fold increased risk of cardiovascular disease. Future work is needed to clarify this possibility.

Finally, the current study did not examine variations in the polymorphisms of the FTO gene. Meta-analytic studies have identified up to five polymorphisms of the FTO gene that are associated with obesity risk, some of which are also associated with diabetes (i.e. the rs8050136 FTO polymorphism examined in the current study). In turn, it is likely that variations in polymorphisms of the FTO gene not only increase risk for obesity, but for other various cardiovascular disease risk factors as well. Moreover, such effects appear to differ according to race and ethnicity. Larger and more diverse sample sizes are needed to elucidate the differential effects of FTO polymorphisms on obesity risk, among other cardiovascular disease risk factors. Future work should also examine the interaction between FTO gene polymorphisms with other genetic markers such as kidney and brain protein, which has been linked with enhanced memory and hippocampal processing and may be protective against the effects of genes such as FTO or APOE ε4.

In conclusion, the current study shows that the FTO risk allele is associated with reduced memory functioning. Subsequent research can extend our findings by using neuropsychological and functional neuroimaging methods in larger, more representative samples.

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REFERENCES


