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Serum Brain-Derived Neurotrophic Factor Mediates the Relationship between Abdominal Adiposity and Executive Function in Middle Age

Sonya Kaur,[1] Mitzi M. Gonzales,[1] Takashi Tarumi,[2] Astrid Villalpando,[1] Mohammed Alkatan,[2] Martha Pyron,[2,3] Hirofumi Tanaka,[2] AND Andreana P. Haley[1,4]

[1]Department of Psychology, Austin, Texas
[2]Department of Kinesiology and Health Education, Austin, Texas
[3]Medicine in Motion, Austin, Texas
[4]Imaging Research Center, The University of Texas at Austin, Austin, Texas

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Abstract

Objectives: Excessive adipose tissue, especially in the abdominal area, is associated with increased risk of dementia in older adults. However, the mechanisms underlying this relationship are poorly understood. As increased adiposity is also associated with lower circulating levels of brain-derived neurotrophic factor (BDNF), a key molecule modulating brain plasticity and neuronal regeneration, we hypothesized that the changes in cognition that occur as a result of excessive abdominal adiposity would be driven by lower levels of circulating BDNF. **Methods:** Fasting blood samples were obtained from 60 participants aged 40–60 years (mean $\pm$ *SD* = 52.3 $\pm$ 5.6) and BDNF levels were assessed with an enzyme linked immunosorbent assay. Abdominal adiposity was measured using a ratio of waist circumference to hip circumference (WHR). Participants also completed a neuropsychological assessment battery to assess executive function. Statistical mediation was assessed using traditional causal steps and nonparametric bootstrapping. **Results:** Higher WHR was significantly associated with poorer performance on the Controlled Oral Word Association (COWA) letter fluency test ($\beta = -0.489$; $p = .003$) and lower levels of circulating BDNF ($\beta = -0.345$; $p = .006$). Linear regression and bootstrapping methods indicated that BDNF fully mediated the relationship between WHR and performance on the COWA ($\beta = 0.60$; 95% confidence interval [−3.79, −0.26]). **Conclusions:** The relationship between higher WHR and verbal fluency was fully statistically mediated by circulating BDNF levels. The BDNF pathway is thus a useful probable mechanism through which executive function decline occurs in individuals with high abdominal adiposity. BDNF enhancing interventions (physical exercise and dietary restriction) could thus be used to improve executive function in these individuals. (*JINS*, 2016, *22*, 493–500)

Keywords: Central obesity, Cognitive decline, Cardiorespiratory fitness, Executive function, Visceral fat, Brain derived neurotrophic factor

INTRODUCTION

The number of people being classified as obese or overweight has doubled in the past 20 years in the United States, encompassing almost two-thirds of the adult population (NCHS, 2006), rendering it the fifth leading cause of mortality worldwide (World Health Organization, 2009). Despite concerted governmental efforts to combat obesity in the United States (Khan et al., 2009), prevalence remains high (Ogden, Carroll, Kit, & Flegal, 2014). Obesity contributes to the manifestation of several adverse health outcomes, including diabetes, cardiovascular and gall bladder diseases, cancer, and overall mortality (Kopelman, 2000). Recent evidence has shown similar adverse effects of obesity on the brain (Gustafson et al., 2004). Being classified as obese is linked to increased risk of dementia (Gustafson et al., 2003) and poorer performance on cognitive tasks (Stingl et al., 2012), particularly tasks that evaluate executive function (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Waldstein et al., 2006).

Executive function is an umbrella term that refers to a cluster of functions such as planning, working memory, processing speed, mental flexibility, and the initiation or monitoring of action (Lezak, Howieson, Loring, Hannay, & Fischer, 2004).

Correspondence and reprint requests to: Andreana P. Haley, Department of Psychology, The University of Texas at Austin, 108 East Dean Keeton, Stop A8000, Austin, TX 78712. E-mail: haley@austin.utexas.edu

Data from the Framingham Heart Study highlight deficits in working memory and verbal fluency in obese middle-aged and older men (Elias et al., 2003). The combination of obesity and hypertension is associated with poorer performance on the Stroop interference test (Waldstein et al., 2006). In children and adolescents, obesity is linked to poorer mental flexibility by Cserjesi, Molnar, Luminet, & Lenard (2007) and complex attention, mental flexibility, and disinhibition by Lokken, Boeka, Austin, Gunstad, & Harmon (2009). However, the mechanisms that lead to this cognitive decline are poorly understood. As dementia treatments are limited at present, and no cures are available, it is crucial to identify the mechanisms underlying this relationship so that targeted preventative measures may be developed and launched.

The distribution of adipose tissue appears to selectively impact cognitive function (Cereda, Sansone, Meola, & Malavazos, 2012). In particular, abdominal adiposity is a more salient predictor of cognitive decline and dementia compared with whole-body adiposity as assessed by body mass index (BMI) (Cereda et al., 2007; Kanaya et al., 2009; Kerwin et al., 2011). Higher levels of abdominal fat have been correlated with insulin resistance (Raji, Seely, Arky, & Simonson, 2001), a phenomenon that has been shown to affect cerebral glucose metabolism (Doyle, Cusin, Rohner-Jeanrenaud, & Jeanrenaud, 1995), and mediate the inverse relationship between BMI and working memory-related functional activation (Gonzales et al., 2010). Insulin resistance is also positively correlated with levels of circulating brain-derived neurotropic factor (BDNF) (Levinger et al., 2008), a key neurotrophin crucial for neuronal regeneration and survival (Mattson, Maudsley, & Martin, 2004). Infusion of BDNF into the lateral ventricles of diabetic mice normalizes glucose regulation (Nakagawa et al., 2002). Mouse models have also depicted higher levels of obesity and hyperactivity as a result of conditional deletion of BDNF in the brain (Kernie, Leibl, & Parada, 2000; Rios et al., 2001). There is thus a plausible link between the BDNF and insulin regulation mechanisms, and central adiposity could cause disruption in BDNF production and distribution in the central nervous system.

BDNF has been consistently linked to brain health. BDNF is found in high levels in hippocampal pyramidal cells (Gall & Lauterborn, 1992; Lang et al., 2009). Furthermore, treatment with BDNF enhances hippocampal long-term potentiation in BDNF knockout mice (Patterson et al., 1996). Postmortem research has revealed reduced BDNF levels in the hippocampi of donors with diagnosed Alzheimer's disease (Phillips et al., 1991). Exercise also induces increases in BDNF mRNA expression in rat hippocampi (Oliff, Berchstold, Isackson, & Cotman, 1998) and hippocampal volume in older adults (Erickson et al., 2011). Recent work by Beckinschtein et al. highlights the importance of hippocampal BDNF for long-term memory storage by transforming a non-lasting long-term memory trace into a persistent one (Bekinschtein, Cammarota, Igaz, et al., 2007; Bekinschtein, Cammarota, Katche, et al., 2007).

In addition to the documented effects of BDNF on hippocampal function and memory, BDNF is also associated with poorer performance in executive function tasks. Serum BDNF levels mediate the positive effects of exercise interventions on task switching in older adults (Leckie et al., 2014). Presence of the Met allele in the val66met polymorphism, a genetic marker linked with lower levels of peripheral and cortical BDNF (Chen et al., 2004; Ozan, Okur, Eker, Gonul, & Akarsu, 2010), is associated with poorer performance on tasks of processing speed (Miyajima et al., 2008) in older adults and higher levels of perseverative responses on the Wisconsin Card Sorting Test (Marques-Iturra et al., 2014) in participants aged between 12 and 40 years.

However, some researchers have reported no relationship between serum BDNF and genetic risk in patients with prodromal Alzheimer's disease (Langbaum et al., 2012). Furthermore, the literature on the relationship between genetic risk for low BDNF and executive function has been inconsistent, with recent meta-analytic work showing no effect of the polymorphism on most measures of cognition (Mandelman & Grigorenko, 2012). It would thus be necessary to use a direct measure of BDNF to examine the relationship between adiposity driven low BDNF and executive function. However, to our best knowledge, no studies have directly addressed this hypothesis. As BDNF levels can be modified through dietary restriction (Duan, Lee, Guo, & Mattson, 2001) and regular exercise (Wrann et al., 2013), it is vital to tease out the impact of BDNF on central nervous system functioning before neurodegeneration. This knowledge could promote the development of targeted interventions involving BDNF infusion and incorporation of non-pharmacological interventions that increase BDNF into existing cognitive rehabilitation programs.

In the present study, we used a ratio of waist circumference to hip circumference (WHR) as a proxy for central adiposity. The Framingham Heart Study revealed that individuals with high central obesity performed poorly the Trail Making Test, Part B, a measure of cognitive flexibility, switching, and working memory. Others have also highlighted a relationship between high visceral fat and poorer executive function (Schwartz et al., 2013). Previous work has highlighted a relationship between circulating BDNF and performance on several executive function tasks, such as task switching (Leckie et al., 2014) and perseveration (Marques-Iturra et al., 2014).

Based on the above literature, we hypothesized that individuals with higher abdominal adiposity would demonstrate poorer performance on cognitive tests that evaluate different aspects of executive function. We further hypothesized that these relationships would be accounted for (statistically mediated by) by serum levels of BDNF. A successful statistical mediation would suggest that central adiposity-related declines in executive functioning occur primarily in the context of lower levels of circulating BDNF.

MATERIALS AND METHODS

Sixty-one adults between the ages of 40 and 60 years were recruited from the community through electronic and print

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advertisements. All potential participants underwent a telephone screening carried out by trained research assistants and completed a medical history questionnaire to establish eligibility. Exclusionary criteria (Gonzales et al., 2013) included a positive medical history for overt coronary artery disease, neurological disease (e.g., stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., schizophrenia, bipolar disorder), and substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse). All participants were nonsmokers. Participants who passed the initial screen were enrolled in the study after providing written consent. The ethnic distribution of the participants was 82.0% Caucasian, 6.6% Hispanic, 4.9% African-American, and 6.5% Other/Did Not Specify.

Procedures

This study was conducted in accordance with the Helsinki Declaration and with approval from the local Institutional Review Board. All volunteers provided written informed consent before enrollment. Participants underwent three separate study visits: a general health assessment, a neuropsychological assessment, and a cardiorespiratory fitness assessment.

General Health Assessment

Participants abstained from caffeine and exercise for at least 24 hr and fasted for at least 4 hr before assessment. Waist circumference was measured at the midpoint between the iliac crest and lower rib during exhalation as recommended by the World Health Organization (World Health Organization, 2008). Hip circumference was measured at the broadest portion around the buttocks. Brachial systolic and diastolic blood pressure was assessed with a semi-automated device (VP – 1000plus, Omron Healthcare, Bannockburn, IL) after 15 min of rest. A fasting blood sample was also collected from the antecubital vein by venipuncture. Serum was separated within 2 hr of the collection, and aliquots were stored at −80°C until later analysis. Fasting levels of glucose, total cholesterol, and triglycerides were measured using the standard enzymatic techniques. Serum concentration of BDNF was measured using high sensitivity enzyme linked immunosorbent assays (ELISA kits, R&D Systems Inc., Minneapolis, MN).

Neuropsychological Assessment

Participants completed a battery of standard clinical neuropsychological assessments with established reliability and validity (Lezak et al., 2004), details of which have been described elsewhere (Gonzales et al., 2013). Based on published literature linking obesity (Schwartz et al., 2013) and BDNF (Leckie et al., 2014; Marques-Iturra et al., 2014) to executive function decline, several tests that tap specific domains of executive function were selected for this analysis: Trail Making Test (TMT) Part B time to completion, corrected for processing speed by subtracting time to completion for TMT Part A (Reitan, 1958), a measure of working memory, cognitive flexibility, and set shifting; Controlled Oral Word Associations test (COWA) (Ruff, Light, Parker, & Levin, 1996), a measure of verbal fluency; and Wechsler Adult Intelligence Scale III Digit Span Forward and Backward Subtests (Weschler, 1997), measures of working memory and attention. Global cognitive function was screened using the Wechsler Test of Adult Reading and the Mini-Mental State Examination (Lezak et al., 2004).

Cardiorespiratory Fitness Assessment

Participants abstained from caffeine and physical exercise for 24 hr and fasted for at least 12 hr before the visit. Maximal oxygen consumption (VO2 max) was assessed with a graded treadmill exercise test during a modified Bruce protocol. Following a 5-min warm-up period, participants ran or walked at a speed that corresponded to 60–70% of their age-predicted maximal heart rate. The treadmill slope was increased 2% every 2 min until volitional exhaustion. Oxygen consumption (indirect calorimetry *via* respiratory gas measurements; Physio-Dyne, Quogue, NY) and heart rate were measured throughout the protocol. At the end of each 2-min stage, participants rated their perceived exertion using the original Borg scale (Borg, 1982).

Statistical Analyses

Statistical analyses were conducted in three steps: first, associations between WHR and performance on each executive function test were examined using linear regressions. Clinically relevant covariates (age, years of education, systolic and diastolic blood pressure, total concentrations of glucose, total cholesterol, and cardiovascular fitness) were included in these analyses because of their published relationships with obesity (Alberti et al., 2009) and brain health (Gonzales et al., 2013; Haley et al., 2010). To control for multiple comparisons, a Sidak-adjusted two-tailed α-level of 0.01 was used (Sidak, 1967) here. Associations between performance on the one executive function test with significant adiposity effects (COWA) and serum BDNF levels were then assessed using linear regression. Finally, a mediation analysis was performed to test if the association between central adiposity and performance on the COWA is attenuated when considering the role of serum BDNF. For the single mediation analysis, a less conservative α-level of 0.05 was used.

Mediation was assessed using both the traditional causal steps approach and non-parametric bootstrapping procedures (Preacher & Hayes, 2004). The causal steps approach posits that four conditions must be met to determine mediation: (1) a significant relationship between the independent variable (WHR) and the dependent variable (executive function), (2) a significant relationship between the independent variable and the potential mediator (BDNF),

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Table 1. Selected demographic and physiological characteristics

Characteristic	Mean ± *SD*
N (men and women)	60 (40 & 20)
Age, years	52.3 ± 5.61
Education, years	16.9 ± 2.1
BMI, kg/m^2	24.9 ± 4.6
Systolic blood pressure, mmHg	119 ± 12
Diastolic blood pressure, mmHg	72 ± 6
Blood glucose, mg/dL	91.1 ± 10.7
Total cholesterol, mg/dL	199.2 ± 35.3
Maximal oxygen consumption, mL/kg/min	36.8 ± 11.8
Waist to hip ratio, U	0.85 ± 0.08
Serum BDNF, ng/mL	25.0 ± 5.9

BMI = body mass index; BDNF = brain-derived neurotrophic factor.

(3) a significant relationship between the potential mediator and the dependent variable, and (4) a non-significant relationship between the independent variable and the dependent variable after controlling for the potential mediator. While traditional causal steps are a parsimonious method for examining statistical mediation, it is no longer deemed necessary to establish indirect effects (Hayes, 2009). An additional assessment on the significance of the mediation model was conducted by using confidence intervals obtained through Preacher and Hayes bootstrapping method for assessing indirect effects (Preacher & Hayes, 2004). A 95% confidence interval that does not include 0 was used as the criterion for significance. All statistical analyses were carried out using IBM SPSS 22.0 software (SPSS Inc.). We further performed secondary analyses assessing the effects of WHR and BDNF on memory [as assessed by long delay free recall score on the California Verbal Learning Test (CVLT-II)].

RESULTS

Mean values for demographic and physiological characteristics as well as standard deviations are presented in Table 1. Table 2 presents all raw neuropsychological test scores. Descriptive statistics revealed a highly educated and cognitively intact sample (mean education = 16.87 years; *SD* = 2.1); mean estimated Full Scale Intelligence Quotient = 112.11; *SD* = 6.25). Participants had a mean WHR of 0.848 (*SD* 0.076) and mean serum BDNF of 24.99 ng/mL (*SD* 5.91).

Linear regression models examining the association between WHR and scores on each executive function neuropsychological test were completed, with age, years of education, systolic and diastolic blood pressure, blood concentrations of glucose and total cholesterol, and cardiovascular fitness entered as covariates. Higher WHR was only significantly associated with poorer performance on the COWA ($\beta = -0.55$; $R^2 = 0.25$; $p = .001$). WHR was not significantly associated with corrected time to completion on Trails B ($\beta = 0.09$; $p = .47$) as well as performance on Digit Span forward and backward ($\beta = 0.04$; $p = .79$ for digits forward, & $\beta = -0.18$, $p = .16$ for digits backward). These results are depicted in Table 3.

Table 2. Raw scores on neuropsychological assessment measures

Measure	Mean ± *SD*
Global cognition	
Mini-Mental State Examination (MMSE)	29.0 ± 1.2
WTAR predicted FSIQ	112.1 ± 6.3
Memory	
CVLT-II	
Long Delay Free Recall	11.6 ± 3.0
Recognition Discriminability	2.9 ± 0.8
Executive Function	
TMT	
Part A (s)	29.8 ± 8.6
Part B (s)	60.0 ± 17.4
Part B – Part A (s)	30.16 ± 15.12
COWA (number of words)	45.4 ± 10.5
WAIS-III	
Digit Span Forwards	11.3 ± 2.04
Digit Span Backwards	7.4 ± 2.5

MMSE = Mini-Mental State Examination; WTAR = Wechsler Test of Adult Reading; FSIQ = Full Scale Intelligence Quotient; CVLT = California Verbal Learning Test II; TMT = Trail Making Test; COWA = Controlled Oral Word Association; WAIS = Wechsler Adult Intelligence Scale III.

As a secondary analysis, we also looked at the relationships between WHR and performance on all other cognitive tests. These results are presented in Table 4. WHR was also significantly associated with memory performance after a 20-min delay ($\beta = -0.40$; $R^2 = 0.15$; $p = .001$). As age ($t = 1.46$; $p = 0.15$), education ($t = 1.22$; $p = .22$), systolic blood pressure ($t = 1.03$; $p = .31$), diastolic blood pressure ($t = -0.75$; $p = .45$), total cholesterol ($t = 0.34$; $p = .73$), and cardiorespiratory fitness, as measured by maximal oxygen consumption ($t = -0.31$; $p = .76$) were not significantly associated with performance on the COWA, these variables were not included in subsequent analyses.

Table 3. Linear regression statistics for waist to hip ratio and executive function measures

Test	β	*p*-Value
COWA	–0.49	.01*
TMT part B (time to completion)	0.09	.45
TMT part A (time to completion)	0.03	.79
TMT part B- part A (time to completion)	0.09	.46
WAIS III Digit Span forwards score	0.04	.79
WAIS III Digit Span backwards score	–0.18	.16

Note. Asterisks indicate values that are statistically significant at the Sidak-adjusted two-tailed α-level of 0.01.
COWA = Controlled Oral Word Association; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale.

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Table 4. Linear regression statistics for waist to hip ratio WHR and cognitive measures.

Test	β	*p*-Value
MMSE total score	–0.05	.72
WTAR predicted FSIQ	–0.16	.23
CVLT II long delay free recall	–0.40	.001*
CVLT II recognition discriminability	–0.38	.003*

Note. Asterisks indicate values that are statistically significant at the Sidak-adjusted two-tailed α-level of 0.01.
MMSE = Mini-Mental State Examination; WTAR = Wechsler Test of Adult Reading; CVLT = California Verbal Learning Test.

Blood glucose concentration was significantly linked with better performance on the COWA ($t = 2.16$; $p = .036$). However, because this association did not survive correction for multiple comparisons (Sidak, 1967), it was also excluded from subsequent analyses. None of the covariates were significantly correlated with BDNF ($r = -0.01$, $p = .94$ for systolic blood pressure; $r = -0.02$, $p = .84$ for diastolic blood pressure; $r = 0.03$, $p = .82$ for total cholesterol; $r = -0.02$, $p = .87$ for fasting blood glucose; $r = -0.21$, $p = .13$ for cardiorespiratory fitness; $r = -0.06$, $p = .67$ for years of education; and $r = -0.16$, $p = .23$ for age).

Higher WHR was significantly associated with lower levels of serum BDNF ($\beta = -0.345$; $R^2 = 0.12$; $p = .006$). Lower levels of serum BDNF successfully predicted poorer scores on the COWA ($\beta = 0.41$; $R^2 = 0.17$; $p = .001$). However, lower levels of serum BDNF did not predict poorer performance on the CVLT-II long delay free recall and recognition discriminability subtests ($ps > .05$). The relationship between higher WHR and poorer performance on the COWA was completely attenuated when serum BDNF was included in the model ($\beta = -0.20$; $p = .099$), thus fulfilling the requirements of Baron & Kenny's traditional causal steps approach for statistical mediation (Baron & Kenny, 1986). The results of these analyses are depicted in Figure 1. The significance of the mediation model was further confirmed by the 95% confidence interval range (–3.79, –0.26), derived by the Preacher and Hayes bootstrapping procedure for detecting indirect effects (Preacher & Hayes, 2004).

DISCUSSION

To our knowledge, this is the first study to highlight BDNF as a possible mediator for the relationship between abdominal adiposity and a classic executive function task. Functional magnetic resonance imaging research on cognitively intact young adults has revealed significant deactivation in the posterior cingulate gyrus during a verbal fluency task (Schlosser et al., 1998). Interestingly, we have recently reported changes in cortical thickness in the same region among middle-aged adults with high visceral fat (Kaur et al., 2015). Verbal fluency performance has also been consistently linked with cardiovascular risk factors (Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001), and in cases of post-stroke cognitive decline and vascular dementia, verbal fluency is disproportionately impaired compared with other cognitive functions such as memory (Lafosse et al., 1997; Starkstein et al., 1996; Wolfe, Linn, Babikian, & Albert, 1990).

Verbal fluency thus appears to be an area of executive functioning uniquely burdened by high cardiovascular risk. Individuals with high central adiposity also tend to have significantly higher risk of cardiovascular events such as coronary heart attacks, stroke, and mortality caused by cardiovascular events (Kannel et al., 1991; Ritchie, & Connell, 2007). It is thus possible that high central adiposity drives cardiovascular disease induced declines in verbal fluency that lead to more generalized cognitive impairment. Direct examination of this is, however, beyond the scope of this study.

Based on our results, the BDNF pathway is a plausible mechanism through which abdominal adiposity impinges upon the cognitive function. BDNF stimulates cell differentiation and proliferation by reducing inhibitor proteins and increasing the expression of neuronal nitric oxide synthase (nNOS) in adult mice (Cheng, Wang, Cai, Rao, & Mattson, 2003). Examination of cell cultures of rat embryonic neurons deprived of BDNF reveals increases in nNOS and motor neuron apoptosis (Estevez et al., 1998). In addition, BDNF infusion has resulted in neurogenesis in mouse hippocampi (Rossi et al., 2006) as well as improvements in long-term memory in mice (Bekinschtein, Cammarota, Katche, et al., 2007), thus further highlighting BDNF as a credible target for intervention.

However, small studies involving BDNF infusion in humans with neurologic conditions such as Parkinson's

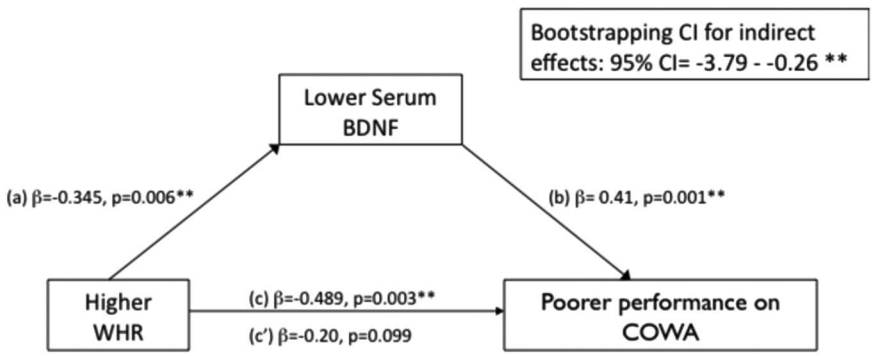

Fig. 1. Multiple linear regression analyses for full statistical mediation model.

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disease and amyotrophic lateral sclerosis have not reported significant effects on cognition thus far (Kordower, Palfi, Chen, & Shuang, 2001; Ochs et al., 2000). Thus, BDNF is likely to act in synergy with other disease states in humans and the interaction between BDNF and adiposity hormones likely drives the results of our study.

BDNF can also act on central nervous system functioning through N-methyl-d-aspartate (NMDA) receptors. BDNF infusion induces NMDA-dependent long-term potentiation in the insular cortices of adult mice (Escobar, Figuera-Guzman, & Gomez-Palacio-Schjetnan, et al., 2003). The NMDA receptor is the primary molecular device for controlling synaptic plasticity as well as a variety of neurocognitive declines, including verbal fluency (Krystal et al., 1994). Thus, BDNF could have a significant effect on cortical activity by acting on NMDA receptors in the left prefrontal cortex, resulting in higher performance on verbal fluency.

A critical next step would be to determine the moderators of BDNF expression in the central nervous system to develop useful targeted interventions. In addition to abdominal adiposity, BDNF levels are modulated by acute and chronic stress (Murakami, Imbe, Morikawa, Kubo, & Senba, 2005). Pharmacological interventions aimed at acute stress reduction such as sertraline increased BDNF levels and promoted neurogenesis in Huntington's disease mouse models (Peng et al., 2007). Furthermore, chronic stress is associated with higher levels of oxidative stress (Aschbacher et al., 2013), which interacts with BDNF to ameliorate the deleterious cognitive effects of high fat diet in mice (Wu, Ying, & Gomez-Pinilla, 2004). Direct examination of stress-related brain vulnerability mechanisms is beyond the scope of the current study but would be a critical next step in understanding how BDNF affects cognitive function in humans.

The main limitation of this study was the small sample size ($N = 61$), which limited the number and types of analyses. Larger sample sizes would allow us to examine the possible synergistic effects of stress, insulin resistance, and BDNF on cognitive function *via* moderated mediation or mixed models. The reported effect represents the effect of a statistical mediation procedure and may not be indicative of cause and effect. While higher levels of BDNF may be responsible for better performance on the COWA, it is also possible that both may be driven by genetic factors or developmental factors not examined in the present study. Confidence in the reported mechanism can be gained through longitudinal studies where temporal precedence between elevated BDNF levels and improvement in performance on the COWA can be clearly established. Furthermore, our sample consisted of relatively healthy individuals, with a mean BMI of 24.9. It is possible that including more overweight or obese individuals would lead to stronger cognitive effects seen across a larger variety of measures.

In summary, higher central adiposity significantly predicted poorer performance on the COWA, a measure of verbal fluency. Higher central adiposity was also linked to significantly lower levels of circulating BDNF. Finally, circulating BDNF significantly mediated the relationship between central adiposity and cognitive performance on the COWA. Despite the above-mentioned limitations, this study is a crucial first step in directly identifying a mechanistic pathway through which central adiposity uniquely impinges upon central nervous system functioning.

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