The Effects of Obesity on Brain Structure and Size

By Majid Fotuhi, MD, PhD and Brooke Lubinski

Obesity is defined as having a body mass index (BMI) of 30 or higher. In the United States, the prevalence of obesity among adults is 35.7 percent, and 17 percent among adolescents ages 2-19.1 The rate of obesity is also on the rise worldwide with over 400 million adults who are considered obese. The number of obese adults is expected to nearly double by 2015.2 These findings are disturbing in that they indicate the rise of an epidemic, in which the global population is becoming obese at an exceedingly rapid rate.3 Traditionally, obesity has been linked to numerous health conditions including cardiovascular disease, type II diabetes, and hypertension. In recent years, however, obesity has been attributed to significant brain atrophy and cognitive impairment. In this review, we examine both the pathophysiology of the link between obesity and brain injury, and available strategies that may be able to reverse it.

Obesity can cause a clear and distinct reduction in brain size without additional contributing factors. A 2.4 percent decrease in brain parenchymal volume is observed for obese individuals compared to those with a normal BMI (p=.010).4 Brain areas particularly vulnerable to obesity-related atrophy include the hippocampus, cingulate gyrus, and frontal lobes.4-8 As would be expected, a BMI of 30 or higher has been linked with a decline in executive function over a ten-year period (p=0.035).5 Moreover, an elevated BMI is significantly correlated (p < 0.01) with a reduction in neuronal fiber bundle length (FBL), which is believed to contribute to brain atrophy. The reduction of FBL throughout the brain was correlated with increasing age and BMI. However, in the temporal lobe, shorter FBL was independent of age and uniquely associated with a high BMI.9 Several studies of cognitive testing demonstrate that extensive cerebral atrophy noted in overweight and obese individuals impairs the cognition of individuals with a higher BMI.6 Additional evidence suggests the effects of obesity on cognitive function increase with age.10

Central Obesity

A subset of obesity, central obesity, has a distinct association with vascular and metabolic disease. Also known as abdominal obesity, central obesity is determined by a waist-hip ratio (WHR). A high risk waist circumference is classified as >40 inches in men and >34 inches in women.11 Increasing evidence shows a significant positive correlation between WHR and brain atrophy.12, 13 Greater WHR (p = 0.02) is associated with a smaller hippocampal volume. WHR accounts for 4 percent variability in hippocampal volume. The distribution and amount of body fat per individual is also related to the amount of white matter hyperintensities (WMHs). While a 1-SD increase in WHR is associated with a 27 percent increase in WMHs compared to individual baseline measurements obtained previously.13 Central obesity is related to an increased risk of memory loss and dementia 30 years later. In a longitudinal study, participants were divided into normal, overweight, and obese categories, as determined by their BMI, and were evaluated for three decades to determine whether abdominal obesity was independent of total obesity in influencing the risk of developing dementia. Those in the highest quintile of abdominal diameter had a 2.72-
fold increased risk of developing dementia compared to those in the lowest quintile. Those who were overweight or obese, and had central obesity had a 2.34-fold and 3.60-fold increase in dementia risk, respectively. Even those in the normal BMI category were at a higher risk (89 percent more likely) of developing dementia if they had a large abdominal area, than their normal BMI counterparts without abdominal obesity.12

Additionally, abdominal obesity is associated with lowered immediate memory. In individuals with abdominal obesity and associated metabolic syndrome, there is a 15 percent reduction in mean gray matter cerebral blood flow when compared to controls. This reduction is believed to impair immediate memory function.14

The exact mechanisms through which obesity leads to brain atrophy and cognitive decline are complex and may involve a number of factors such as associated diabetes, genetic vulnerability, brain metabolites, and cytokines. Although, extensive research has revealed the degree to which these factors are linked with obesity, further analysis is required to understand the way these elements interact with each other.

TYPE II DIABETES MELLITUS

Obesity and type II diabetes mellitus (T2DM) are two interlinked conditions that have been attributed to brain atrophy. Recent studies indicate that T2DM significantly reduces the volume of the hippocampus and other brain structures. Brain MRIs of individuals with T2DM and a high BMI show significant atrophy (p<0.001) in the frontal lobes (r = -0.24), prefrontal cortex, the genu and splenium of the corpus callosum (r = -0.17 and r = -0.21, respectively), middle cingulate gyrus, superior parietal lobe, the occipital lobe, and the cerebellum. The study also showed a reduction in the white matter volumes (WMVs) of the frontal lobes.6

An increase in the size of the temporal horn of the brain ventricles can be used as an indirect measure of atrophy in the hippocampus. Midlife diabetes is associated with a significant increase in temporal horn volume, suggesting a reduction in hippocampal volume (p=0.017) less than 10 years after initial measurements. As would be expected, this reduction is associated with a decline in memory with aging.5 Those with T2DM have more temporal lobe atrophy (p=0.004) than those not afflicted by the disease.16

The brain atrophy found in patients with diabetes could be due to stroke. T2DM individuals are 1.7 times more likely to have brain infarcts.16 In one study, the brains of those in the obese group appeared 16 years older, while the brains of the overweight subjects appeared 8 years older in comparison to the normal BMI control group. The obese group had 8 percent lower brain volume than the normal BMI group, while the overweight group had 4 percent lower brain volume.6, 17

Obesity and diabetes have severe consequences for adolescents too. In the past three decades, obesity rates have nearly tripled in children and adolescents, and with this increase, the prevalence of T2DM among adolescents has increased dramatically.18 According to a recent study, obese adolescents with T2DM have atrophy in the hippocampus and frontal lobe in parallel with their poor glycemic control, a trait generally seen in adults with T2DM. In the study, obese adolescents with T2DM underwent brain imaging to compare the sizes of various brain structures with those in adolescents without T2DM. T2DM adolescents had prefrontal lobe and global cerebral atro-
### TABLE 1.

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<tr>
<td>Ward et al. 2005</td>
<td>Cross-sectional study</td>
<td>Between the ages of 40 and 66 and had no current major Axis I psychiatric disease or history of a severe medical problem. They were required to have normal cognitive functioning. Individuals on medications that altered cerebral perfusion or cognition were excluded.</td>
<td>Determine whether affected the total brain volume of individuals 40-66 using T1-weighted #D volumetric MRI.</td>
<td>BMI and age are correlated with decreased total brain volume. A 2.4% decrease in brain parenchymal volume is observed in obese individuals compared to normal individuals. BMI did not show a strong association with cognition.</td>
<td>Obese individuals are more susceptible to brain atrophy with aging than normal individuals.</td>
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<td>Debette et al. 2011</td>
<td>Prospective cohort study</td>
<td>Individuals of the Framingham Heart Study who did not have a history of stroke, or neurological disorders that may affect brain volume were selected to participate.</td>
<td>Examine midlife vascular risk factors to determine their influence on brain volume and cognitive function.</td>
<td>Midlife diabetes and smoking were attributed to a reduction in hippocampal volume (p=0.017 and p=0.008, respectively). Obesity and hypertension were correlated to decreased executive functioning (p=0.012 and 0.035, respectively.) Central obesity was associated with a significant reduction in total brain volume (p=0.021).</td>
<td>Midlife hypertension, diabetes, smoking, and obesity, including central obesity, significantly reduce brain volume and cognitive function within a decade.</td>
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<td>Raji et al. 2010</td>
<td>Longitudinal study</td>
<td>Participants from the Cardiovascular Health Study (1998-1999).</td>
<td>Use tensor-based morphometry to examine GMV and WMV differences in elderly patients that had remained normal for at least 5 years after their initial scan.</td>
<td>BMI and T2DM are negatively correlated with brain atrophy (p&lt; 0.001). T2DM was not significant when BMI was controlled. Obese individuals showed the most drastic change in brain structure (r &gt; 0.50), but atrophy was evident in overweight individuals too (</td>
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phy associated with increasing HbA1c (p=0.007 and p=0.027, respectively). It is important to note that a control group of adolescents with type I diabetes mellitus did not display similar atrophy. HbA1c has been implicated as a direct factor responsible for brain atrophy. Significant brain atrophy is correlated with a higher HbA1c. One study found that other than age, the most significant indicator of brain atrophy is HbA1c. Individuals with an HbA1c higher than median level (5.6 percent) experienced rates of atrophy that were twice as high as those in the lowest quartile (Hb1Ac 4.4 to 5.2 percent). Those above the median HbA1c had annual brain volume changes of −0.49 ± 0.25%, while those in the lowest quartile saw a change of -0.24 ± 0.17% (p=0.0001).7

Hyperinsulinemia has been identified as a major contributor to brain atrophy. Hyperinsulinemia affects the brain through vasoactive effects on cerebral arteries, neurotoxicity because of diminished clearance of amyloid from the brain, and stimulation of the formation of neurofibrillar tangles. High levels of insulin are associated with atrophy in the hippocampus (left: r= -0.31; right: r= -0.33), the splenium of the corpus callosum (r= -0.27), and the orbital frontal cortex (r= -0.33).6

T2DM also causes damage through excessive glycation of key brain structural proteins. The production of advanced glycosylation end products (AGEs) contributes to the development

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<td>Enzinger et al. 20057</td>
<td>Longitudinal study</td>
<td>Participants from the Austrian Stroke Prevention Study whose MRI scans were available at baseline and at a 6-year follow-up. Participants were employed white subjects of European origin.</td>
<td>Assess brain parenchymal fraction over 6 years as well as examined vascular risk factors that may affect brain structure and cognition.</td>
<td>Individuals with a higher HbA1c experienced greater brain atrophy (p=0.0001). A significant correlation of brain atrophy was also associated with higher BMI (p=0.02) and severe WMH (p=0.03).</td>
<td>Brain volume loss is associated with aging. Those with a higher HbA1c experience brain atrophy at a greater rate.</td>
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<td>Pannacciulli et al 20068</td>
<td>Cohort study</td>
<td>Caucasian males and females who are non-diabetic. Obese individuals required a BMI ≥ 30.</td>
<td>Utilize voxel-based morphometry to compare neuroanatomical differences between participants.</td>
<td>Obesity is associated with lower gray matter volume in the post-central gyrus, frontal operculum, putamen and middle frontal gyrus (p&lt;0.01).</td>
<td>BMI is negatively correlated with gray matter density in several areas of the brain. There are key structural differences between the brains of obese and lean individuals.</td>
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<td>Bolzenius et al. 20139</td>
<td>Cohort study</td>
<td>English-speaking participants with no evidence of a medical or psychiatric condition that may affect cognition or mental state. Exclusion criteria included history of neurological disease or an Mini-Mental State Examination score below 24. No history of diabetes, head injury, drug or alcohol abuse, or Axis I psychiatric condition.</td>
<td>Assess fiber bundle length throughout the brain using quantitative tractography based on diffusion tensor imaging.</td>
<td>BMI, independent of age, was correlated with shorter fiber bundle length in the temporal lobe (p=0.002). BMI and age are attributed to shorter fiber bundle length throughout the brain.</td>
<td>BMI uniquely reduces the length of fiber bundles which can be attributed to atrophy within the temporal lobe.</td>
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<td>Whitmer et al. 2008 12</td>
<td>Longitudinal study</td>
<td>Continual members of Kaiser Permanente Medical Care Program of Northern California who participated in Multiphasic Health Checkups, between 1964 and 1973 when they were 40-45 years old.</td>
<td>Evaluate the association between midlife central obesity and risk of dementia 30 years later.</td>
<td>Those in the highest quintile of abdominal diameter had a 2.72 fold increased risk in developing dementia compared to those in the lowest quintile. Individuals who were overweight or obese had a 2.34-fold and 3.60-fold increase in dementia risk, respectively.</td>
<td>Individuals with a larger abdominal area, even if they had a normal BMI had an increased risk of developing dementia later in life.</td>
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<tr>
<td>Jagust et al. 2005 13</td>
<td>Cross-sectional study</td>
<td>Age 60 or older and participating in a separate cohort study of cognitive and functional decline in 1789 older Latino individuals</td>
<td>Magnetic resonance images at baseline were analyzed to determine the volume of the right and left hippocampus and the percentage of white matter.</td>
<td>Greater WHR is associated with a reduction in hippocampal volume (p=0.02). A 1-SD increase in WHR is associated with 0.2-SD decrease in hippocampal volume and a 27% increase in WMHs.</td>
<td>The distribution and amount of body fat is associated with the significance of atrophy observed in the hippocampus and the amount of WMHs.</td>
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<td>Birdsill et al. 2012 14</td>
<td>Cohort study</td>
<td>Individuals from the Wisconsin Registry for Alzheimer’s Prevention with or without a family history of late onset Alzheimer Disease. Required normal cognitive function, normal MRI scan and no current diagnosis of major medical or psychiatric disorder or head trauma.</td>
<td>Patients receive comprehensive neuropsychological assessment, blood tests, and magnetic resonance images in order to test the relationship between metabolic syndrome, white matter hyperintensity burden, and gray matter volume.</td>
<td>Evidence of metabolic syndrome was associated with a 15% reduction in gray matter cerebral blood flow when compared to controls. These individuals experienced reduced immediate memory function attributed to the lowered cerebral blood flow.</td>
<td>Metabolic syndrome is correlated with a reduction in cerebral blood flow in gray matter. There is associated lowered memory function related to this reduction.</td>
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<tr>
<td>Bruehl et al. 2009 22</td>
<td>Cohort study</td>
<td>Normal cognition with normal IQ scores. All participants at least had a high school education. Participants were excluded if they had any neurological conditions or active psychiatric conditions.</td>
<td>Examine association between T2DM, cognition and brain volume while accounting for diabetes associated factors.</td>
<td>The mean IQ of a diabetic group (104.25±11.88) was significantly lower than the IQ of the control group (114.23±8.44, p ≤ 0.001). Notable impairments in verbal declarative memory and multiple cognitive domains.</td>
<td>Hippocampus has a high vulnerability to metabolic insults; therefore with aging and disease progression, additional impairments may appear.</td>
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<tr>
<td>den Heijer et al. 2003 16</td>
<td>Cohort study</td>
<td>Ages 60 to 90 without dementia and who didn’t have MRI contraindications.</td>
<td>Using MRI, investigate correlation between diabetes mellitus, insulin resistance on atrophy in hippocampal and amygdalar regions.</td>
<td>Those with T2DM were 1.7 times more likely to develop brain infarcts. T2DM individuals had more amygdalar (p=0.042) and temporal (p=0.004) lobe atrophy.</td>
<td>T2DM significantly reduced hippocampal and amygdalar brain volume.</td>
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<td>Bruehl et al. 2011¹⁹</td>
<td>Cohort study</td>
<td>Individuals with severe medical problems other than T2DM were excluded from the study. Adolescents were excluded with development Tanner stage less than 4, mental retardation or significant learning disability, or if they had a psychiatric diagnosis and used psychoactive medications.</td>
<td>Investigate whether adolescents have atrophy in the hippocampus or frontal lobe that is associated with glycemic control.</td>
<td>Adolescents had atrophy in the prefrontal lobe (p=0.007) and global cerebral (p=0.027) that was associated with increasing HbA1c. Cognitive domains were also subjected to damage in adolescents. Individuals with type I diabetes mellitus did not display similar atrophy.</td>
<td>When controlling for hypertension, individuals with higher levels of HbA1c had more significant reductions in the prefrontal lobe and global cerebral volumes.</td>
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<td>Frayling et al. 2007²⁴</td>
<td>Population based study</td>
<td>White European adults who resided in the U.K. that participated in the Wellcome Trust Case Control Consortium.</td>
<td>Determine the effects of having an A allele at SNP rs9939609 within FTO through a genome-wide association study.</td>
<td>Each additional copy of the A allele is significantly associated (p=3X10-35) with an increase of ~0.4kg/m². On average, a copy of the A allele accounted for 1.2kg higher weight and a 1-cm greater waist circumference.</td>
<td>Having an A allele at SNP rs9939609 within FTO is associated with a significant chance to be overweight or obese.</td>
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<tr>
<td>Ho et al. 2010²⁶</td>
<td>Cohort study</td>
<td>Caucasian (non-Hispanic) with normal cognition.</td>
<td>Determine if there are structural differences in the brains of individuals who carry obesity-related risk alleles that are correlated to a higher BMI.</td>
<td>Carrying a risk allele is associated (p=1.31x10-3) with reductions in regional brain volume. For every 1-SD in BMI there was an associated 1-1.5% reduction in the frontal, parietal, temporal and occipital lobes. Atrophy was also noted in the brain stem and cerebellar regions.</td>
<td>There is a significant association between carrying a risk allele and having brain atrophy.</td>
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<tr>
<td>Gazdzinski et al. 2008²⁷</td>
<td>Population based cohort study</td>
<td>Middle aged (mean age, 41.7±8.5 years) without a history of HIV and who were free of any medical problems that may affect brain morphology and metabolism.</td>
<td>Examine correlation between BMI to mean concentrations of NAA, choline, creatine metabolites and myo-inositol.</td>
<td>A Higher BMI yields reduced NAA in the frontal (p=.0001), parietal (p=.006), and temporal (p=.008) white matter. It reduced NAA in the frontal grey matter (p=.001) and choline in frontal white matter (p=.05).</td>
<td>Reduced concentrations of NAA and choline suggest axonal and myelin abnormalities throughout the white matter, especially in the frontal lobe. White matter in the frontal lobe is more susceptible to the effects of aging.</td>
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of atherosclerosis in individuals with T2DM due to increased oxidative stress. The interaction of AGEs with their receptors elicits drastic vascular cell changes such as alterations in vascular tone control. The extensive damage caused by these species on the vasculature of patients with diabetes, in turn substantially increases their risk of stroke.21

T2DM's detrimental effect on hippocampal integrity in adults is evident in cognitive testing. In one study, the mean IQ of a diabetic group (104.25 ± 11.88) was significantly lower than the IQ of the control group (114.23 ± 8.44, p ≤ 0.001). The impairments were generally restricted to verbal declarative memory. Elderly individuals, however, showed additional impairments in multiple cognitive domains. This is attributed to the hippocampus' high vulnerability to metabolic insults, or hypoxia.22 Additionally, a meta-analysis of the effects of diabetes found a 1.5-fold increased risk of developing mild cognitive impairment in individuals with diabetes.23 The cognitive impairments attributed to T2DM atrophy are evident even in adolescents. A T2DM group demonstrated that cognitive domains in the prefrontal cortex were subject to damage even though the subjects were adolescents and not more mature. Within the group, the obese teens with T2DM performed poorly on tests of verbal memory and processing speed.18, 19

**FAT MASS AND OBESITY-ASSOCIATED GENE**

In recent years, a genetic component of obesity has been identified within variants of the fat mass and obesity-associated (FTO) gene. One allele for the FTO gene that is associated with obesity is a base-pair substitution at single-nucleotide polymorphism (SNP) rs9939609 with an A allele. Each additional copy of the A allele is significantly associated (p = 3 x 10-35) with an increase of ~0.4 kg/m². This accounts for an average 1.2 kg higher weight gain and a 1-cm greater waist circumference.24 Similarly, a meta-analysis of 1729 ado-

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<tr>
<td>Soreca et al. 200928</td>
<td>Longitudinal study</td>
<td>Women participating in the Pittsburgh Healthy Women Study who were not menopausal, between 42 and 50 years old, were not receiving thyroid or hormone replacement therapy, or psychotropic medication, and were not hypertensive.</td>
<td>Determine whether GMV is correlated with BMI between pre- and postmenopausal periods.</td>
<td>Observed, on average, a 15% reduction in GMV for obese women from pre- to post-menopause.</td>
<td>An increase in BMI during this transitional period is associated with a reduction in GMV.</td>
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<tr>
<td>Marsaland et al. 200829</td>
<td>Population based study</td>
<td>No history of severe medical problems. Women were excluded if they were pregnant.</td>
<td>Determine if there is an association between plasma IL-6 levels and hippocampal GMV.</td>
<td>There was a negative correlation between IL-6 and GMV in the left hippocampus (p=0.02). IL-9 seems to account for 19% of the variance in the left hippocampal GMV and 6% of the right hippocampal GMV.</td>
<td>A reverse correlation exists between levels of IL-6 and hippocampal GMV.</td>
</tr>
<tr>
<td>Colcombe et al. 200331</td>
<td>Population based study</td>
<td>Participants were excluded if they were younger than 55 years old, scored below 20 on the Mini-Mental State Examination, had a history of stroke or other brain dysfunction, or had metallic implants or pacemakers that may interfere with the MRI scan.</td>
<td>Use voxel-based morphometric technique to determine the impact of cardiovascular fitness on age-related differences in brain tissue density.</td>
<td>There was a negative association between gray and white matter densities and age (p&lt;0.002). Also, there was a significant increase in density as a result of cardiovascular fitness (p&lt;0.002).</td>
<td>Age reduced brain density in many areas of the brain however, cardiovascular exercise significantly increased density in these same brain areas.</td>
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FTO-gene was significantly associated with higher total body fat \( (p=0.002) \).\(^{25}\)

FTO is expressed at the highest level in the cerebral cortex of the human brain. Knowing that FTO is related to variances in BMI, a study was designed to determine if there were structural differences in the brain of individuals who carried the obesity-related risk alleles that were correlated to higher BMI. Two SNPs associated with obesity are a C allele for rs1421085 and a G allele for rs17817449.

There is an association between BMI and carrying at least one copy of the risk allele at a predetermined FTO tagging SNP. Carrying a risk allele is also associated with statistically significant differences in regional brain volumes \( (p=1.31\times10^{-3}) \). For every 1-unit increase in BMI there was an associated 1-1.5 percent average brain tissue reduction in the frontal, parietal, temporal and occipital lobes. There were also signs of atrophy in both the brain stem and cerebellar regions.\(^{26}\)

In order to confirm that these changes were not attributed to microvascular damage in white matter, a measure of white matter burden (WMB) was regressed against brain structure. WMB did not explain the brain atrophy related to FTO because WMB affected different brain regions than the FTO risk allele. With a unit increase in WMB, there was approximately a 10 percent reduction in the frontal lobe.

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<th>Effect on Brain (excluding Hippocampus)</th>
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| Obesity: A BMI of 30 or higher\(^{1}\) | 5 | 5 | • Among middle age individuals between the ages of 40-66, obesity was associated with a 2.4% decrease in parenchymal volume.\(^{4}\)  
• BMI over 30 is linked to cognitive decline over a ten-year period.\(^{6}\)  
• Higher BMI is associated with shorter FBL which contributes to brain atrophy.\(^{5}\) |
| Central Obesity  
WHR: >102cm in men >88cm in women\(^{9}\) | 5 | 5 | • Greater WHR \( (p = 0.02) \) is associated with reduction in hippocampal volume. A 1-SD increase in WHR is associated with a 0.2-SD decrease in hippocampal volume.\(^{13}\)  
• A 1-SD increase in WHR is associated with a 27% increase in WMHs compared to baseline.\(^{13}\)  
• Individuals who are overweight or obese, and had central obesity had a 2.34-fold and 3.60-fold increase in dementia risk, respectively.\(^{12}\)  
• Individuals who are normal weight but have a large abdominal area are 89% more likely of developing dementia.\(^{12}\)  
• Gray matter cerebral blood flow is reduced by 15% in individuals with abdominal obesity.\(^{14}\) |
| Type II Diabetes Mellitus (HbA1c) | 3 | 5 | • Adults with T2DM showed significant atrophy \( (p < 0.001) \) throughout the brain.\(^{6}\)  
• T2DM individuals have amygdalear \( (p=0.042) \) and temporal \( (p=0.004) \) lobe atrophy.\(^{16}\)  
• Those with T2DM are 1.7 times more likely to have brain infarcts.\(^{16}\)  
• T2DM adolescents had prefrontal lobe and global cerebral atrophy associated with increasing HbA1c \( (p = 0.007 \) and \( p = 0.027, \) respectively).\(^{18}\)  
• T2DM subjects had a mean IQ of 104.25±11.88 compared to a mean IQ of 114.23±8.44, \( p \leq 0.001 \) for the control group.\(^{15}\)  
• Diabetes increases the risk of mild cognitive impairment 1.5-fold.\(^{22}\) |
and precuneus brain region (p=0.0016). Also, an observed 15-20 percent increase in ventricular volume was attributed to WMB.

On average, carriers of the obesity-related risk allele had an 8 percent reduction in brain tissue in the bilateral frontal lobe, and a 12 percent reduction in the bilateral occipital lobe compared to non-carriers. These results suggest that BMI does affect brain structure and FTO exerts a significant additive effect.26 The meta-analysis of adolescents also determined that carrying an obesity-related risk allele reduced total brain volume (p=0.005).25

### BRAIN METABOLITES

Gazdzinski and colleagues further examined the mechanisms by which adiposity alters the brain by examining the concentration of metabolites throughout the brain and their association with atrophy. The study focused on the concentrations of N-acetylaspartate (NAA), choline-containing compounds, creatine-containing metabolites, and myo-inositol (m-Ino). NAA is a marker for neuronal viability. Choline is utilized as an indicator of cell membrane deterioration and synthesis, while m-Ino is used as a marker for glial cells. A higher BMI was significantly correlated with three distinct features: (1) reduced NAA...
concentration in the frontal (p=.0001), parietal (p=0.006), and temporal (p=0.008) white matter; (2) reduced NAA concentration in frontal GM (p=0.001); and (3) a reduced concentration of choline in the frontal white matter (p=0.05).

The reduced concentrations of NAA and choline suggests axonal and myelin abnormalities throughout the white matter, especially in the frontal lobe. The researchers deduced that because the white matter in the frontal lobe is more susceptible to the effects of aging these results may reflect accelerated aging in overweight and obese individuals. This accelerated aging poses an increased risk for cognitive decline and the development of Alzheimer’s disease.27

**CYTOKINES AND OTHER PEPTIDES**

In 2009, Isabella Soreca led a longitudinal study to determine whether a change in BMI during midlife would predict the total volumes of gray and white matter in the brain later in life. In the study, researchers examined whether an increase in BMI for women, during their premenopausal and postmenopausal period, would be associated with gray matter volume (GMV) reduction. They noted an increase in BMI during this transition was uniquely associated with a reduction in GMV. On average, there was a 15 percent reduction in GMV for obese women from pre- to post-menopause.28

The changes observed in the women were determined to be independent of microvascular disease, hypertension and stress, conditions generally associated with brain atrophy. It was suggested that the changes were a result of interactions between neuropeptides because the degree of reduction in GMV has only been associated with the transition from pre- to post-menopause. It is possible that circulating inflammatory cytokines may explain the results of the study.28

Adipocytes produce inflammatory cytokines, like interleukin-6 (IL-6), in which higher levels are associated with being overweight or obese. IL-6 production in adipocytes is stimulated by the proinflammatory mediators released in the tissue. It is believed that IL-6 may affect glucose homeostasis and thereby produce similar outcomes to increased cortisol production. Increased levels of IL-6 are also associated with a reduction in hippocampal volume in both women and men.29, 30 There was a significant reverse relationship between IL-6 and GMV in the left hippocampus (p=0.02). It appears that IL-6 explains for about 19 percent of the variance in left hippocampal GMV and approximately 6 percent of the right hippocampal GMV.29

Additionally, neuropeptides such as leptin and insulin, both regulators of eating, may have influenced the results. Leptin, a neuropeptide produced by adipocytes, is positively correlated to weight gain, and thereby may influence brain structures.31 Elevated levels of leptin in obese individuals are believed to be a consequence of reduced sensitivity to endogenous leptin, caused by inefficient leptin receptors in the brain. Although it is unclear how exactly leptin is related to insulin, research has demonstrated that increased levels of insulin elevate the level of leptin.32 Many of the neurochemical systems that regulate eating behavior are implicated in psychiatric disorders as well. Serotonin, dopamine, norepinephrine and other compounds are all involved in receiving information from the hypothalamus as well as regulating mood and behavior. A commonality among these compounds may account for an increase in ventricular volume in both obesity and mood disorders.31 The correlations between obesity and psychiatric disorders described here are imperative in future research to determine whether the changes observed in the brain are related to mood disorders rather than obesity.

**SUMMARY**

Obesity, as well as numerous related factors, is associated with significant atrophy throughout the brain. The reduced brain volumes are associated with impaired performance on cognitive testing. The extensive volume reduction attributed to a high BMI is concerning, but evidence suggests that these effects may be reversible.

For example, exercise and improved cardiovascular fitness may reverse some of the obesity-related brain atrophy. Several studies have shown that better fitness is associated with an increase in brain volume.4 33-35 This may be secondary to the increased production of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1).33 These factors appear to stimulate neurogenesis. Moreover, in a placebo-controlled study, individuals who walked 40 minutes three days a week showed an increase in GMV in the prefrontal, parietal, and lateral temporal regions and an increase in WMV in the genu of corpus callosum. Increased cardiovascular fitness improves blood flow to the brain and thus reduces the vascular

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Neurologic Tremor Disorders: Causes, Therapies, and Possible Future Treatments

Treatment options for tremor range from pharmacotherapy to possibly deep brain stimulation.

BY NADER POURATIAN, MD, PhD

Tremor is one of the most common and debilitating neurologic conditions in the world, affecting more than 10 million people in the US alone. In an era in which the burden of neurologic disease on society is increasing rapidly, diseases with tremors are amongst the leading causes of disability-adjusted life years lost (DALY). Optimal management of patients with tremor hinges on understanding the causes of tremor, making the right diagnosis, prescribing first-line medical therapies, and referring patients for surgical intervention when appropriate.

Tremor is defined as the involuntary, alternating, rhythmic contractions of opposing muscles. It is not a diagnosis in and of itself, but a symptom. While tremor most commonly affects the arms and hands, it can also affect the head, voice, trunk, and legs. Besides location, tremor is classified with respect to amplitude, rate, and position. The position in which a tremor occurs is one of the most important characterizing features, occurring either at rest, with posture, or with action (i.e., kinetic).

CAUSES AND DIAGNOSES

Essential tremor (ET) is the most common cause of tremor, affecting four to five percent of people over the age of 40 years and up to nine to 10 percent of people over the age of 60 years—a prevalence approximately 10 times that of Parkinson’s disease. A diagnosis of ET is based on the presence of bilateral postural tremor (8-12 Hz) with or without a kinetic (or action) tremor involving the hands and forearms. The tremor usually emerges either in adolescence or after the age of 50, affects men and women equally, should be gradual in onset, and has a variable progression. ET generally has a very strong family history; it is not uncommon to hear of multiple relatives with similar tremor. Although often referred to as “benign” essential tremor, many patients with ET argue the disease is anything but “benign” and that the tremors interfere with even the most basic functions and activities of life, like drinking, eating, and brushing teeth.

Although not the most common cause of tremor, for many, the term “tremor” is synonymous with Parkinson’s disease (PD). The tremor of PD and ET however are vastly different. PD tremor is slow (3-6 Hz), is predominantly at rest, almost always has an asymmetric onset, and is most often associated with other neurologic symptoms of bradykinesia (slowness) and rigidity (stiffness). While Parkinson’s disease is considered a movement disorder, one must be cognizant of a host of other problems these patients have, including depression, anxiety, constipation, sleep disorders, and cognitive problems later in disease. In fact, more than 80 percent of patients who have suffered from PD for 20-plus years will eventually meet diagnostic criteria for dementia, an incidence which is approximately four times that of the general population.

While PD is most often diagnosed after the age of 65, affecting one to two percent of people over 65 and men twice as often as women, it can also be diagnosed in patients under the age of 40 (so called “young onset Parkinson’s disease”) which is associated with a slower rate of disease progression but greater psychosocial complications. Having a relative with PD increases the risk of developing PD by about threefold. Diagnosis is based on the constellation of symptoms described, but also on response to levodopa or dopamine agonists and the absence of atypical parkinsonism (e.g., early cognitive deficits, incontinence, apraxia, autonomic dysfunction, etc.). Challenging diagnostic cases can be facilitated by DOPA PET scans or DaTscan, which can demonstrate decreased dopamine metabolism in the basal ganglia, but such studies are not diagnostic and must be interpreted in a clinical context. Unlike ET, which does not have a clear
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Pathologic etiology, PD is hallmarked by degeneration of the substantia nigra, pars compacta with deposition of Lewy Bodies containing alpha-synuclein. Before rendering a diagnosis of ET or PD, secondary causes of tremor need to be excluded. Drug-induced tremors, especially in the setting of lithium, valproate, antipsychotic medications, and antidepressants, should be considered, especially when onset of tremor coincides temporally with initiation or changes in dosing of such medications. Medical causes of tremor including hyperthyroidism and exogenous and endogenous stimulants, such as caffeine and hormone producing tumors should be included in the differential diagnosis. Other neurologic causes of tremor include cerebellar disease, multiple sclerosis, and stroke. Abrupt onset may suggest a cerebellar, midbrain, or thalamic stroke and should prompt detailed neuroimaging assessment. Finally, an astute practitioner will consider the possibility of an enhanced physiologic tremor, which is an exaggeration of a normal physiologic tremor that can emerge in stressful situations.

Symptom Directed Therapy

The goals of treatment for patients with tremor are to reduce tremor severity, improve daily functioning, and improve quality of life. Because therapy is symptom directed, the threshold for intervention will vary by patient and by the degree of impairment. In general, but especially in the case of Parkinson’s disease in which medical therapies can result in complications, therapy is delayed until symptoms are clearly interfering with quality of life.

For ET, two medications are considered first-line therapies: propranolol and primidone. In many cases, these medications can reduce tremor by as much as 50 percent and may obviate the need for further intervention. Combining the two therapies may result in an additional 10-15 percent in improvement in tremor control and function. In many cases, these therapies are not tolerated due to dose limiting side effects of low blood pressure and drowsiness. Second line treatment options can include gabapentin, topiramate, atenolol, alprazolam, sotalol, and clonazepam. In addition to medical therapies, occupational therapies are helpful to provide assistance with adaptive devices such as weighted utensils, plate guards, and other specially designed devices for patients with tremor.

First line therapies for patients with PD largely depend on patient age and degree of functional impairment. There is a different threshold for intervention for every patient. While younger patients (less than 70 years) are generally started with dopamine agonists and MAO-B inhibitors (which may provide a neuroprotective effect), older patients are usually treated with levodopa as a first line agent. The goal

Figure 1. Radiographic images of deep brain stimulator leads implanted in the brain with wires extending down the neck to a generator which transmits electrical impulses to the brain (Sample 1). Coronal (Sample 2) and Sagittal (Sample 3) CT reconstructions of a patient’s brain after deep brain stimulator implantation, demonstrating placement of the leads in the globus pallidus.
is to delay levodopa use as much as possible in younger patients because of the possibility of developing levodopa-induced dyskinesia with prolonged use of this drug. While dopamine agonists can delay use of levodopa, an important dose-limited side effect that must be recognized is impulse control disorders (ICD) which can manifest, amongst other possibilities, as impulsive gambling and spending or hypersexuality. Other classes of medications that can be used to prolong the action of dopamine within the synaptic cleft include COMT inhibitors (such as entacapone or tolcapone) or MAO-B inhibitors (such as selegiline and rasagiline). Amantadine can be used to treat motor fluctuations as well, but its benefit is often limited in time and it can be associated with hallucinations. In patients with tremor dominant disease, tremor often does not respond to any of these medications and may be best managed with anticholinergic medications (e.g., trihexyphenidyl). Because of the complexity of managing multiple medications with varying doses and schedules, such complex patients are ideally managed by a movement disorders specialist with extensive experience with such management.

LIMITATIONS AND COMPLICATIONS OF MEDICAL THERAPY
While medications and lifestyle modifications can be more than sufficient for most patients with ET to cope with tremor, in some cases, tremor persists or progresses, does not respond to medical therapy, and significantly interferes with function, either at home or at work. In the setting of ET, lack of response to medical therapies does not affect the diagnosis of ET but may warrant consideration of other therapeutic modalities.

In contrast to ET, lack of response to PD medications in a patient suspected of having PD calls into question the diagnosis. In such cases, metabolic imaging, such as DOPA PET or DaTscan should be considered. More often, however, the complications of medical therapy are not a lack of response but the development of motor fluctuations, which include dyskinesia (or excess uncontrolled movements) when taking medication, rapid wearing off of medication effects, and dystonia when medications are subtherapeutic. These motor fluctuations, which usually require patients to take medications every two to four hours, are thought to be due to the pulsatile nature of taking drugs and are therefore considered a complication of medical therapy. It is nearly impossible to predict when patients will develop such complications, with some developing motor fluctuations within just a few years of initiating therapy and others not developing such fluctuations after using medical therapies for over a decade. The onset of motor fluctuations are complicated by the simultaneous progression of the underlying disease, such that patients develop gait problems including shuffling and freezing of gait as well as balance difficulties.

SURGICAL CONSIDERATIONS
The surgical management of tremor is deeply rooted within neurosurgery and centers on manipulation and modulation of the thalamus (the ventral intermediate nucleus). The indication for surgical intervention is the presence of tremor that is refractory to medication and is impairing quality of life regardless of tremor amplitude. While historically, tremor was treated with invasive lesioning procedures (i.e., thalamotomy), contemporary therapy is based on modulating the thalamus with deep brain stimulation (DBS) therapy. Rather than creating a lesion, a DBS electrode is precisely and stereotactically implanted in the thalamus and connected to a pulse generator that is implanted in the chest. Just like a cardiac pacemaker resets rhythms in the heart, the DBS system resets pathologic brain rhythms to restore a more normal pattern of activity and level of function. The advantage of DBS over thalamotomy is the ability to modulate the therapy over time.

Figure 2. Precise and careful implantation of deep brain stimulator leads demands an intricate understanding of neuroanatomy, especially of the structures surrounding the DBS targets. Advanced imaging using MR diffusion tractography can be used to illustrate and define white matter tracts, such as the internal capsule, that surround the DBS target, such as the subthalamic nucleus. In this illustration, the lead (green line) is targeted around and inside of the internal capsule (depicted in colorful vertical streamlines).
using a wireless remote device and the ability to reverse the therapy at any time.

For patients who may not be medically fit for, or who may absolutely refuse surgery, consideration can be given to stereotactic radiosurgery (SRS) thalamotomy. SRS is a method by which to deliver a very high dose of focused radiation to a specific target in the brain. SRS can be delivered with one of three technologies, including Gamma Knife, linear accelerator (LINAC), or proton beam therapy. SRS is most often used for the management of cerebral metastases, but was originally designed for functional stereotactic procedures, such as thalamotomies. While this approach is appealing because it is non-invasive and because studies have shown it to be effective (at least 50 percent tremor reduction) in up to 90 percent of patients, it actually has a greater risk profile than DBS (four percent vs. one percent risk of stroke) and is therefore considered second line. The risk is largely attributable to the inability to accurately select the precise target for lesioning based on current imaging technology. Innovations in current imaging strategies and brain mapping techniques, however, may minimize these risks.

Surgical consideration is given to patients with PD who have advanced PD and demonstrate a good response to levodopa, but have motor fluctuations, including wearing off of medications and medication-induced dyskinesia. Response to levodopa is the most critical component of the history. Patients should expect that DBS therapy will allow them “to spend more time in their best on condition.” In fact, several controlled trials have now demonstrated the superiority of DBS therapy compared to best medical therapy in patients with motor fluctuations. In general, patients can expect to spend up 4-6 more hours per day in their best “on condition.” Interestingly, studies now find that DBS targeting the subthalamic nucleus (STN) and globus pallidus internus (GPi) are equally efficacious with respect to controlling the motor complications of PD. While DBS of the STN is associated with greater medication reduction, it is also associated with an increased trend for neurocognitive complications. GPi DBS, on the other hand, is associated with greater control of dyskinesia. STN however may be particularly preferable in patients with tremor-dominant disease. The recent EARLYSTIM trial concluded that patients should be treated with DBS after the diagnosis of motor fluctuations in order to maximize the benefits of DBS and patients’ quality-of-life.

**DEEP BRAIN STIMULATION: THE PROCESS AND THE RISKS**

A critical component to DBS therapy is managing patient and provider expectations. DBS is a symptomatic adjunctive treatment that has been shown in multiple clinical trials to improve motor control and quality of life. It is not however disease modifying and it does not eliminate the need for medications. Workup and assessment for DBS in a comprehensive program will require neurosurgical evaluation, formal on- and off-medication videotaped assessment by a movement disorders neurologist, formal neuropsychological assessment, and general medical examination. Stereotactic implantation of the DBS electrodes and generators can be done in as little as one procedure in one day or may be spread out over 4 procedures over a 6-12 month period, depending on the individual patient’s health and specific medical needs. Surgery is most often done with the patient awake to facilitate intraoperative neurophysiological testing to confirm optimal electrode placement that optimizes the therapeutic window for stimulation, including minimization of side effects of stimulation. Programming requires at a minimum a 3-6 month commitment of return visits for both initial programming and adjustments of both stimulation parameters and medications in order to optimize benefits of stimulation. Patients will then need to return on a semi-annual or annual basis for generator interrogations and possible generator replacement every 3-7 years.

While the benefits of DBS are clear, patients must be aware of the most important risks of DBS surgery. The risk patients are most concerned about is risk of hemorrhage or stroke, which is estimated at approximately 0.6 percent chance of permanent neurological deficit per electrode implanted. The greater risk is that of infection, which can occur in up to 5-10 percent of patients undergoing surgery, which in most cases requires removal of the implant and prolonged antibiotic therapy. Because this is major brain surgery, other medical complications can occur as well including heart attack, deep vein or pulmonary thrombosis, and urinary tract or pulmonary infections. These complications are rare, however. Finally, patients must be aware that implanting a device can be associated with discomfort, skin erosion, and other complications. These types of complications have become more rare with improvements in technology.

The most important factor to safeguard patient safety and maximizing outcomes is the development and implementation of evidence-based protocols for patient management, which ensure providers systematically consider all factors that can minimize complications and optimize benefits.

**FUTURE PROMISING THERAPIES**

While DBS is a state-of-the-art proven therapy, recognized limitations include the risk of stroke associated with the surgical procedure (albeit low), the invasive nature of the procedure, and the need for frequent physician visits for programming. To address these shortcomings, several new technologies and approaches are being investigated.
The most promising technology is the non-invasive treatment of magnetic resonance guided focused ultrasound therapy (MRgFUS). MRgFUS is currently beginning a Phase III randomized clinical trial for the treatment of ET and a Phase I safety trial for management of PD. Like SRS, MRgFUS uses focused energy to create a lesion in a precise area of the brain. Instead of using radiation energy, MRgFUS uses ultrasonic energy that allows the physician to create test lesions to ensure the efficacy and safety of the final target before making a final lesions. This adds a level of safety to current SRS technology, which is critical. Phase I trial results in ET have been reported in conference proceedings, demonstrating greater than 50 percent tremor reduction in almost all patients with few side effects.

Other innovations are occurring in the domain of DBS therapy, with new technologies being investigated and developed to create “closed loop” systems. While current DBS technology requires the physician to assess patients to determine how to modify stimulation, several academic centers are working on intelligent DBS systems that can detect brain signals and modify stimulation parameters based on intrinsic patterns of brain activity. One device manufacturer has developed such a sensing device and is collaborating with multiple centers to develop novel approaches and methods for closed loop neuromodulation.

Finally, in the interest of avoiding brain surgery altogether, duodopa is a method of delivering a continuous infusion of levodopa directly into the gastrointestinal tract to reduce motor fluctuations associated with pulsatile drug delivery. While the concept holds promise, early reports suggest equal efficacy relative to DBS but with increased procedural complications. Further studies and experience are necessary to better define its role in the management of PD patients.

**SUMMARY**

Tremor is prevalent and can be associated with an array of medical and neurologic diagnoses. Characterizing the tremor and associating it with the correct diagnosis is key to guiding medical and surgical therapies. In all instances, therapy is symptom directed and aims to improve function and quality-of-life. When first line medical therapies fail, attention should be given to surgical therapies, which have a proven track record in clinical trials of providing greater benefit than best medical therapy. Surgical therapy, however, is not a standalone therapy and is optimally delivered in the context of a comprehensive multidisciplinary program. ■

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(Continued from page 29) injury secondary to obesity and related conditions.35 Therefore there is hope that brain volume reduction with obesity, though severe, can be reversed over time with interventions such as exercise. Such interventions may also minimize the risk of late-life dementia secondary to midlife obesity. ■

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