# White Matter Integrity and Subclinical Depression: A Diffusion Tensor Imaging Study

**Nicole Huffman[1] and Ilana Bennett[2]**

*1 Department of Molecular, Cell and System Biology*

*2 Department of Psychology*

## ABSTRACT

Major Depressive Disorder (MDD) is characterized by the persistent presence of at least five depressive symptoms over a two-week period. These symptoms must include either depressed mood, or loss of interest or pleasure. Early identification, and ultimately treatment, of depression may be accomplished by identifying neural markers of individuals at risk for MDD, including those with subclinical depressive symptoms. Neuroimaging studies have shown that MDD is associated with impairments to integrity in white matter tracts such as the corpus callosum and internal capsule. However, it is unclear whether these same structures also are disrupted in subclinical depression. The present study sought to examine this question through utilizing diffusion tensor imaging to assess white matter integrity as a function of Geriatric Depression Scale Short Form (GDS-SF) scores. Using a median split of GDS-SF scores, statistical analyses revealed no difference in white matter integrity between low risk and high risk depression groups. However, there was a nonsignificant trend ($p=0.072$) such that higher GDS-SF scores were associated with decreased white matter integrity localized to the corpus callosum, right internal capsule, left cingulum, external capsule and fornix. This finding extends previous research on MDD by providing evidence for similar neural correlates of subclinical depression. This may provide insight into the development of MDD and ultimately aid diagnostic and treatment efforts with early identification and intervention.

**Keywords:** Major depressive disorder, diffusion tensor imaging, white matter integrity

**Nicole Huffman**

*Department of Molecular, Cell and Systems Biology*

Nicole Huffman is a fourth year neuroscience major who has studied white matter integrity in subclinical depression for almost two years under the advisement of Dr. Ilana Bennet. Nicole is a member of University Honors, and an editor for the Undergraduate Research Journal. Her passions include teaching, and conducting research in mood disorders. She plans to pursue a PhD in Psychology with an emphasis in Affective Science, followed by a faculty position.

## FACULTY MENTOR

**Dr. Ilana J. Bennett**

*Assistant Professor in the Department of Psychology*

Professor Bennett earned her doctorate in lifespan cognitive neuroscience from Georgetown University and her bachelor degree in cognitive science from the University of California, Irvine. Her research seeks to advance our understanding of neurocognitive aging by examining age-related differences in the way we acquire, retain, and retrieve information and identifying the neural substrates that underlie these learning and memory processes using a combination of diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI). Her work has attracted funding from the National Institute on Aging, including a current Pathway to Independence Award (K99/R00).

## INTRODUCTION

Major Depressive Disorder (MDD) is characterized by sad, empty, or irritable mood, and is accompanied by somatic and cognitive alterations that significantly affect an individual's ability to function (American Psychiatric Association, 2013). Diagnosis is made according to the persistent presence of at least five depressive symptoms over a two-week period. These symptoms must include either depressed mood, or loss of interest or pleasure. Other possible depressive symptoms are: significant changes to appetite, weight loss or sleeping patterns; fatigue or loss of energy; feelings of worthlessness and inappropriate guilt; diminished ability to think or concentrate; and recurring thoughts of death or suicide (American Psychiatric Association, 2013; Reynolds and Kamphaus, 2013). As of 2010, MDD was the second leading cause of years lived with disability, the leading cause of burden, and a contributor to the burden allocated to suicide and ischemic heart disease (Ferrari, Charlson, Norman, Patten, Freedman, Murray, Vos and Whiteford, 2013). An estimated 16.1 million adults over the age of 18 - representing 6.7% of the US population - had at least one major depressive episode in 2016 (Substance Abuse and Mental Health, 2017). Given this extensive impact of MDD on individuals and society, it is increasingly important to identify, and ultimately treat, depression early.

This goal may be addressed through identifying subclinical depression, which has been shown to increase an individual's risk of developing MDD (Wesselhoeft, Heiervang, Kragh-Sorensen, Sorensen and Bilenberg, 2016). Subclinical depression is characterized by the presence of clinically relevant depressive symptoms without meeting the criteria for MDD (Cuijpers, Koole, van Dijke, Roca, Li and Reynolds, 2014). It is highly prevalent, has its own serious consequences for an individual's quality of life, and is associated with increased economic costs and mortality rates (Cuijpers and Smit, 2008; Cuijpers, Koole, van Dijke, Roca, Li and Reynolds, 2014).

One method for identifying subclinical depression is the Geriatric Depression Scale Short Form (GDS-SF). This 15-item self-reported questionnaire evaluates the presence or absence of various depressive symptoms, such as a lack of energy and the inability to feel pleasure (Sheikh & Yesavage 1986). The GDS-SF has been demonstrated as a valid and reliable assessment in both young and old adults (Ferraro & Chelminski 1996; Sheikh & Yesavage 1986). Scores in the 0 to 4 point range indicate limited to no presence of depression, while scores in the 5 to 10 point range indicate subclinical depression, and scores from 11 to 15 indicate major depression (Cuijpers and Smit, 2008).

Another method with promise for identifying depression in the subclinical range is neuroimaging. For example, diffusion tensor imaging (DTI) is a structural magnetic resonance imaging (MRI) technique that measures the diffusion of water molecules in the brain. The rate and orientation of diffusion is constrained by the cellular environment and thus is thought to reflect the integrity of underlying white matter. That is, water will diffuse in all directions (isotropic diffusion) when there are no restrictive structures present, as seen in the ventricles, which only contain cerebrospinal fluid. In contrast, water diffusion is restricted (anisotropic diffusion) in the presence of neurons, diffusing faster along the myelinated axons of white matter tracts relative to the less coherent diffusion around cell bodies in grey matter.

DTI measures of diffusion are used to calculate multiple integrity metrics, including fractional anisotropy (FA) and mean diffusivity (MD). FA describes the degree of anisotropic diffusion, and is sensitive to fiber orientation. An FA value approaching one indicates that diffusion is anisotropic, or restricted, and suggests intact white matter integrity. MD measures the average rate of diffusion. Lower MD values indicate increased anisotropy, and suggest intact white matter integrity (Soares, et al., 2013; Alexander, Lee, Lazar & Field, 2007).

Recent DTI studies have shown that MDD is associated with decreased integrity in white matter throughout multiple brain regions, but especially in the corpus callosum and internal capsule, seen in ***Figure 1*** (see Chen, et al, 2016 for review). These studies primarily compared white matter integrity in individuals diagnosed with MDD to normal controls using tract-based spatial statistics (TBSS), in which integrity measures (FA, MD) are compared within a "skeleton" of white matter voxels, or volume elements, common to all participants. However, it remains to be

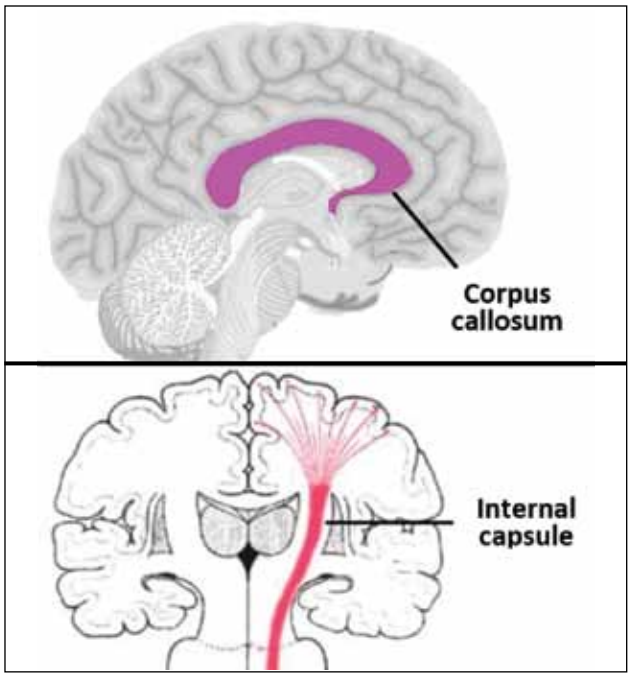


***Figure 1 - Regions of Interest***
*Diagrams showing the anatomical location of the corpus callosum (top, in purple) and internal capsule (bottom, in red).*

examined whether white matter tracts that are disrupted in MDD also are disrupted in subclinical depression.

To test the hypothesis that subclinical depression is associated with white matter integrity declines similar to those seen in MDD, the present study used TBSS to assess white matter integrity as a function of GDS-SF scores. Subclinical depression was assessed via group comparison between low depression risk and high depression risk groups based on a median split of the GDS-SF scores. Further analyses examined relationships between white matter integrity and GDS-SF scores within the FA and MD skeleton. Overall, it was predicted that higher GDS-SF scores would relate to worse integrity (lower FA, higher MD), particularly in the corpus callosum and internal capsule. Such a finding would support the notion that the white matter tracts impaired in MDD are also impaired in subclinical depression.

## 2. METHODS

### 2.1 Participants

A sample of 40 young adults (24 males) aged 18-24 years were recruited via the Psychology Department Research Pool at the University of California, Riverside. Participants were compensated with class credit. All procedures were approved by the University of California, Riverside Institutional Review Board.

Prior to participation, all individuals were screened for neurological disorders (stroke, epilepsy, brain tumor, etc.), psychiatric disorders (bipolar disorder, schizophrenia, etc.), other medical conditions (alcoholism, HIV, diabetes, etc.), and contraindications to MRI scanning (non-removable ferrous materials, current pregnancy, claustrophobia, and head or neck tattoos).

### 2.2 Depression measure

Participants completed a series of neuropsychological assessments that included the GDS-SF. The GDS-SF was scored as a total number of points out of a possible 15.

### 2.3 Diffusion Tensor Imaging

#### 2.3.1 Acquisition

Diffusion images were obtained using a 3T Siemens Prisma MRI fitted with a 32-channel head coil. Fitted padding was used to minimize head movements. Two diffusion-weighted echo-planar imaging sequence were acquired using separate anterior to posterior and posterior to anterior acquisition sequences with the following parameters: time repetition (TR)/time echo (TE) = 3500/102 ms, field of view (FOV) = 218×218 mm, 72 axial slices, and 1.7 mm3 spatial resolution. For each sequence, gradients (b = 1500 and 3000 s/mm2) were applied in 64 orthogonal directions, with six images having no diffusion weighting (b=0).

#### 2.3.2 Preprocessing and Quality Control

Diffusion-weighted data were separately processed for each participant using a combination of FSL (FMRIB Software Library; Behrens et al. 2003) and AFNI (Analysis of Functional NeuroImages; Cox 1996). To correct for head movement and eddy currents, all volumes were aligned to the b=0 image (eddycorrect). Diffusion tensors were independently fit to each voxel (DTIfit) using a binary mask to limit tensor fitting to brain space (3dSkullStrip). The output yielded voxel-wise diffusion images of FA and MD.

Before proceeding to analysis, each participant's data was manually assessed for quality. This process involved checking for precise image alignment, minimal head

motion, accurate brain extraction, good tensor fitting, and minimal voxels containing the theoretically impossible value of FA greater than 1. Quality control screening resulted in the exclusion of 3 participants.

### 2.3.3 Analysis

Tract-Based Spatial Statistics (TBSS) was utilized to perform exploratory skeleton-wise analyses (i.e., voxel-wise analyses within the mean skeleton) separately for each diffusion index (FA and MD) (Smith et al. 2006). The FA map of each participant was aligned nonlinearly to the FMRIB58_FA_1-mm template in MNI152 standard space. These aligned images were then averaged across all individuals to generate a mean FA image, which was used to produce a "skeleton" of white matter voxels common to all participants. Non-white matter voxels were excluded by thresholding FA at 0.2. The same nonlinear registrations used for FA images were then applied to each participant's MD image.

In order to enhance cluster-like structures without prior definition of a cluster forming threshold, threshold-free cluster enhancement (TFCE) was employed (Smith and Nichols, 2009), yielding statistical maps that were FWE-corrected for multiple comparisons across space (TFCE, P<0.05). Skeletonized data for both diffusion indices (FA, MD) were subjected to independent t-tests between low depression risk and high depression risk groups as determined by a median split at a value of 3, and to skeleton-wise correlations with GDS-SF scores.

## 3. RESULTS

### 3.1 Behavioral Data

GDS-SF scores ranged from 0 to 9 with a median of 3, which was used to split participants into separate low (n = 21, M = 1.4, SD = 1.2) and high (n = 19, M = 5.3, SD = 1.5) depression risk groups. An F-test revealed equal variances between groups, therefore an independent t-test assuming equal variances was conducted and revealed a statistically significant difference in GSD-SF scores between the two groups ($p < 0.01$). These behavioral results, along with the frequency of each score, are summarized in ***Figure 2***.

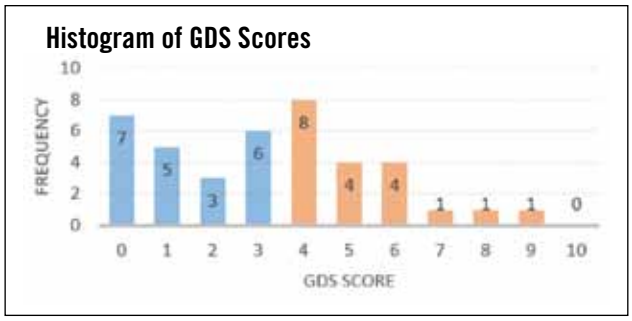


***Figure 2 - GDS Behavioral Data***
*The above histogram shows the frequency of each score. A median split at a score of three resulted in a low risk depression group (blue; N=21; M=1.4) and a high risk depression group (orange; N=19; M=5.3). An independent t-test between the two groups showed a statistically significant differnce between the means (p=5.98 x 10 ^-11).*

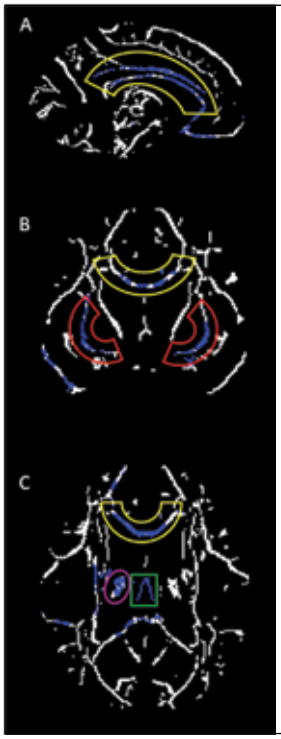


***Figure 3: Regions Exhibiting a Positive Correlation between MD and GDS***
*Blue areas show the nonsignificant positive trend between MD and GDS (p=0.072) within various white matter tracts of the brain, as noted below.*

*A) Right cingulum and corpus callosum (both in yellow)*

*B) Corpus callosum (in yellow) and external capsule (in red)*

*C) Corpus callosum (in yellow), fornix (in green) and the right internal capsul (in pink).*

### 3.2 Imaging Data

Group differences in white matter integrity were assessed using separate skeleton-wise t-tests between low risk and high risk depression groups for both FA and MD. No results approached significance ($p > 0.05$). The same pattern of null results was found when further analyses split participants at a GDS-SF score of 2 based on the bimodal distribution, and at a score of 5 based on the subclinical threshold reported in the literature.

To further assess whether white matter integrity is sensitive to subclinical depression symptoms, skeleton-wise correlations were conducted between GDS-SF scores

and each diffusion index. A nonsignificant positive trend ($p = 0.072$) was observed between MD and GDS-SF, such that the risk of depression increased as white matter integrity decreased. This effect was localized to the corpus callosum, internal capsule, external capsule, left cingulum, and fornix, as shown in ***Figure 3.***

No areas showed a negative correlation between MD and GDS-SF, and neither the positive or negative correlation between GDS-SF and FA approached significance ($p > 0.16$).

## 4. DISCUSSION

White matter tracts implicated in MDD have been extensively examined (Chen, at al, 2016; Kieseppa, et al, 2010; Liao, et al, 2013; Xiao, He, McWhinne & Yao, 2015). The present study sought to extend this work by examining whether similar impairments in white matter integrity are seen in subclinical depression. Results revealed three main findings. First, in partial support of our hypothesis, there was a nonsignificant positive trend between GDS-SF and MD. Second, there was no difference in white matter integrity between low and high depression risk groups. Third, the relationship between GDS-SF and FA was not significant.

Consistent with our hypothesis that similar declines in white matter integrity are seen in MDD and subclinical depression, we observed a non-significant trend between GDS-SF and MD in the corpus callosum, right internal capsule, external capsule, left cingulum, and fornix. This finding parallels, and expands upon, previous research in MDD which found significant decreases in white matter integrity in the corpus callosum and internal capsule of depressed patients relative to healthy controls (Chen, et al, 2016). Importantly, degradation of white matter in the aforementioned regions may be associated with particular symptoms of MDD. For example, the internal capsule, which connects the thalamus to prefrontal cortex, plays a role in executive functions such as the planning of complex behaviors. The corpus callosum is the largest commissure, connecting the cerebral lobes; and integrates motor, sensory and cognitive functions. Disruptions to these areas may account for previous reports of impaired cognitive control in MDD (Hertel, 1997). Similarly, the left cingulum connects the left cingulate gyrus to the entorhinal cortex, and is involved in the appraisal of pain and the reinforcement of behavior that reduces it. This may account for previous reports of comorbidity between pain and depression (Goesling, Clauw and Hasset, 2913). Finally, the fornix connects the hippocampus to the hypothalamus, septal nuclei and nucleus accumbens; and is involved in limbic functions and recall memory. This may account for the disturbances in affect and memory, which are assessed by the questions on the GDS-SF (i.e. Do you feel happy most of the time? Do you have more problems with memory than most?).

The observation that there were no group differences in white matter integrity between low and high depression risk groups was consistent across all three grouping methods - median split, bimodal spilt, and threshold split. This pattern of null results is at odds with previous reports of significant differences in white matter integrity in MDD patients (see Liao, et al, 2013 for review). This contradictory finding could be explained by two interpretations. First, collapsing subjects into high and low risk groups may obscure the individual differences in white matter integrity that are related to subclinical depression. Alternatively, the pathophysiology of subclinical depression may not be developed enough to be detectable in a group comparisons fashion. In partial support of these interpretations, our correlation analyses revealed a nonsignificant trend between white matter integrity (MD) and the presence of depressive symptoms (GDS-SF score).

In contrast, the positive correlation between GDS-SF and FA did not reveal the expected trend. This contradictory data may be explained by the fact that FA seems to be more sensitive to the organization and directionality of tissues, while MD tends to be more sensitive to non-directional measures such as the degree of myelination and the number of axons. Based on this interpretation, the present data may indicate that impaired white matter integrity in subclinical depression is a result of myelination or axon number, as opposed to fiber directionality and organization. However, there is still much more to be elucidated, as the characteristics of integrity measured by FA and MD overlap to a great extent.

The current study analyzed white matter integrity as a function of GDS-SF scores to examine subclinical depression in young adults. Findings indicate that there is no significant differences between low risk and high

risk depression groups; but that increased MD, and therefore impaired white matter integrity, shows a strong nonsignificant trend with subclinical depression. Notable limitations include sample size and GDS-SF score distribution. The relatively small number of subjects may have limited the power of the present analysis, while the number of participants who truly scored in the subclinical depression range was moderately limited. Future studies could overcome these limitations by recruiting a larger number of participants, with a higher percentage scoring in the subclinical depression range. Regardless of these limitations, the present study suggests that a potential relationship between subclinical depression and impaired white matter integrity in the same tracts implicated in MDD may exist. Such findings could provide insight into the development of MDD and ultimately aid diagnostic and treatment efforts with early identification and intervention.

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***Conflict of Interest:*** None declared.

## REFERENCES

Alexander AL, Lee JE, Lazar M, Field AS. (2007). Diffusion Tensor Imaging of the Brain. Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics, 4(3), 316–329.

American Psychiatric Association. (2013). Major Depressive Disorder. In Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC

Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med, 50, 1077–1088.

Bennett IJ, Huffman DJ, Stark CEL. (2015). Limbic tract integrity contributes to pattern separation performance across the lifespan. Cerebral Cortex, 25, 2988-2999.

Bessette KL, Nave AM, Caprihn A, Stevens MC. (2014) White matter abnormalities in adolescents with major depressive disorder. Brain Imaging Behavior, 8(4), 531-541.

Chen G, Hu X, Li L, Huang X, Lui S, Kuang W, … Gong Q. (2016). Disorganization of white matter architecture in major depressive disorder: a meta-analysis of diffusion tensor imaging with tract-based spatial statistics. Scientific Reports, 6, 21825.

Cox RW. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res, 29, 162–173.

Cuijpers P, Koole SL, van Dijke A, Roca M, Li J, Reynolds CF, III. (2014). Psychotherapy for subclinical depression: meta-analysis. The British Journal of Psychiatry, 205(4), 268-274.

Cuijpers P, Smit F. (2008). Subclinical depression: a clinically relevant condition? Tijdschr Psychiatr, 50(8), 519-528.

Ferrari AJ, Charlson FJ, Norman RE, Patten SC, Freedman G, Murray CJL, Vos T, Whiteford HA. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLOS Medicine, 10(11), 1-12.

Ferraro FR, Chelminski I. (1996). Preliminary normative data on the Geriatric Depression Scale-Short Form (GDS-SF) in a young adult sample. J Clin Psychol, 52(4), 443-447.

Goesling J, Clauw DJ, Hassett AL. (2013) Pain and depression: An integrative review of neurobiological and physiological factors. Current Psychiatry Reports, 15:421.

Hertel PT. (1997) On the contribution of deficient cognitive control to memory impairment in depression. Cognition and Emotion, 11(5-6), 569-583.

Hoogenboom WS, Perlis RH, Smoller JW, Zeng-Treitler Q, Gainer VS, Murphy SN, … Iosifescu DV. (2014) Limbic system white matter microstructure and long-term treatment outcome in major depressive disorder: a diffusion tensor imaging study using legacy data. World Journal Biological Psychiatry, 15(2), 122-134.

Kieseppa T, Eerola M, Mantyla R, Neuvonen T, Poutanen VP, Luoma K, … Isometsa E. (2010). Major depressive disorder and white matter abnormalities: a diffusion tensor imaging study with tract-based spatial statistics. Journal of Affective Disorders, 120(1-3), 240-244.

Liao Y, Huang X, Wu Q, Yang C, Kuang W, Du M, … Gong Q. (2013). Is depression a disconnection syndrome? Meta-analysis of diffusion tensor imaging studies in patients with MDD. Journal of Psychiatry & Neuroscience : JPN, 38(1), 49–56.

Phillippi CL, Motzkin JC, Pujara MS & Keonigs M. (2015). Subclinical depression severity is associated with distinct patterns of functional connectivity for subregions of anterior cingulate cortex. Journal of Psychiatric Research, 71, 03-111.

Reynolds CR, Kamphaus RW. (2013) DSM-5 Diagnostic Criteria Major Depressive Disorder. Pearson Clinical.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage, 31, 1487–1505.

Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. Frontiers in Neuroscience, 7, 31.

Substance Abuse and Mental Health Services Administration. (2017). Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

Wesselhoeft R, Heiervang ER, Kragh-Sorensen P, Sorensen MJ, Bilenberg N. (2016).Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort. Comprehensive Psychiatry, 70, 65-76.

Xiao J, He Y, McWhinnie CM, & Yao S. (2015). Altered white matter integrity in individuals with cognitive vulnerability to depression: a tract-based spatial statistics study. Scientific Reports, 5, 9738.

Yesavage JA, Sheikh JI. (1986). 9/Geriatric Depression Scale (GDS). Clinical Gerontologist, 5(1-2), 165-173.