Published in final edited form as:

Am J Geriatr Psychiatry. 2009 January ; 17(1): 24–29. doi:10.1097/JGP.0b013e318180056a.

Modulation of a Human Memory Circuit by Subsyndromal Depression in Late Life: An fMRI Study

Shoshana L. Woo, BS¹, Steven E. Prince, PhD², Jeffrey R. Petrella, MD², Caroline Hellegers, MA¹, and P. Murali Doraiswamy, MD¹

¹ Department of Psychiatry, Center for Study of Aging, and School of Medicine Duke University Medical Center, Duke University, Durham, NC, USA

² Department of Radiology (Alzheimer Imaging Research Laboratory) Duke University Medical Center, Duke University, Durham, NC, USA

Abstract

Objective: Functional deactivation of the posterior medial cortex (PMC) appears to be a physiologic process underlying normal memory. We examined whether older subjects with subsyndromal depressive symptoms show impaired PMC deactivation.

Design: Subjects underwent 4T fMRI scanning while performing a novel and familiar face-name associative encoding task. The Beck-II Depression Inventory (BDI) was used to self-rate depression symptoms. A novel-minus-familiar encoding contrast was built into a simple regression model showing brain activation magnitudes that co-varied with BDI score. A region-of-interest (ROI) mask was applied to isolate the PMC and other midline structures of the default-mode network.

Setting: The study was conducted at a university-based medical center.

Participants: Participants included 62 non-demented subjects aged 55–85, with and without mild memory deficits. BDI scores ranged from 0 to 17.

Results: Analysis revealed a distinct PMC cluster confined to the dorsal posterior cingulate cortex (BA 31) whose activity correlated significantly with BDI score. A multiple regression model further showed that BDI score, as well as a history of depression and current use of antidepressants, had a significant effect on cluster variance, while age, education, gender and MMSE scores did not.

Conclusions: Our findings raise the hypothesis that subsyndromal depressive symptoms in late life may impair physiological PMC deactivation in the dorsal posterior cingulate cortex. A prospective study of a full spectrum of depressed patients may be warranted.

Keywords

subsyndromal depression; memory; functional deactivation; default network; fMRI

Objective

The past decade has witnessed a progressively heightened recognition of subsyndromal depression as a significant problem afflicting the older population [1]. Generally, patients with minor, dysthymic, or otherwise “subthreshold” depression have been incorporated under the umbrella term of *subsyndromal depression*, as is done here. As such, subsyndromal depression

has a collective point prevalence greater than that of major depression and is consistently associated with considerable functional and medical morbidity in primary care elders [1].

The exact mechanisms by which depression of any form impacts human memory are not fully known. However, we do know that memory complaints often arise in patients with depression, even if their symptoms are subsyndromal. Studies have further shown that depression may not only masquerade as pseudodementia but may also serve as a prodrome or risk factor for Alzheimer's disease (AD) [2].

Recent functional MRI studies have focused on the role of the posteromedial cortex (PMC) in cognition. The PMC is a distinct brain region consisting of the precuneus (BA7), posterior cingulate (BA 23/31), and retrosplenial cortex (BA 26/29/30). Together, these areas effectively form the posterior portion of a greater *default-mode* cognitive network that is thought to be involved in a diverse range of cognitive processes including self-awareness and reflection, consciousness, environmental monitoring, and various forms of undirected thought [3,4]. Other major regions of the default-mode network that are consistently cited in the literature include midline structures such as the anterior cingulate (BA 24/32), subgenual (BA 25), orbitofrontal (BA 11), and anterior prefrontal (BA 10) cortices.

Normal memory has been strongly associated with a physiological decrease in signal, or *functional deactivation*, in the PMC. Lustig et al., for example, demonstrated PMC deactivation in young healthy adults during a semantic classification task, while older patients with AD displayed impaired PMC deactivation or even activation [4]. Recent evidence provided by our group further confirmed decreased PMC deactivation or activation in AD subjects compared to normal controls while performing a face-name associative encoding task [5,6]. It is believed that PMC deactivation is not specific to any particular type of memory encoding. Instead, it likely represents an efficient and advantageous reallocation of neurocognitive resources that supports the activation of other brain regions specific to the particular cognitive task at hand [7].

Prior fMRI studies in major depression have mostly focused on emotional pathways, though recently some have begun to explore the effects of depression on cognitive circuits [8-11]. Indeed, Greicius et al. published the first study to investigate *resting-state* default-mode functional connectivity in subjects with major depression, showing abnormally increased signals in the thalamus and subgenual cingulate cortex [11]. We build on their contribution in the current fMRI study by exploring midline default-mode activity in relation to subsyndromal depression during an *active* memory task.

Methods

The study of memory and aging was approved by the Duke University Medical Center Institutional Review Board and was conducted in compliance with the Health Insurance Portability and Accountability Act.

Enrollment & Screening

All subjects, ages 55 to 85, were recruited from the local community through advertisements and referrals. All were fluent in English, completed at least 8 years of formal education, and gave written informed consent prior to participation. Subjects prospectively underwent a clinical interview, focused neurological and physical exam, and demographic inventory (age, gender, education). Subjects further underwent a detailed neuropsychological screening battery, including the Mini-Mental State Exam (MMSE) [12] and the Clinical Dementia Rating (CDR) interview with subject and informant [13]. Depression self-ratings were scored using the Beck-II Depression Inventory (BDI) [14]. Because the primary study focused on memory

and aging, it was not intended to enroll subjects with a current major depressive episode. Subjects with treated major depression or those with subsyndromal or minor depressive symptoms were eligible to enroll. Subjects with a past history of depression were also permitted to enroll. All subjects meeting criteria for dementia per NINCDS-ADRDA [15] or DSM-IV-TR criteria [16] were excluded from this study, leaving a total of 62 subjects.

Recruitment in our original cohort was stratified based in part on the CDR global score in order to recruit two groups of subjects: cognitively normal individuals and subjects meeting research criteria for mild cognitive impairment of the amnesic type (aMCI). The full criteria used to define aMCI are described elsewhere [18], but in essence they had impaired delayed memory performance, a CDR global score of 0.5, and near normal independent and global cognitive function. Cognitively normal controls had a global CDR of 0 and essentially normal delayed recall and function. For this report, we pooled both groups together.

Paradigm

This study employed a face-name associative memory encoding task [17]. Prior to fMRI scanning, subjects extensively studied 2 different photographs, each with a face-name pair. These 2 face-name pairs were assigned to the “familiar” condition. During the fMRI scan, subjects viewed a series of face-name pairs in a blocked experimental design. The series was composed of both familiar photographs as well as new photographs that the subjects had never seen before, comprising the “novel” condition. For the task, subjects were asked to associate each familiar or novel face with the respective name given (with the intention of remembering the face-name pairs for later). Behavioral responses (i.e. “Yes,” this name suits this face; or “No,” this name does not suit this face) were monitored with a fiber-optic button box within the scanner. Fixation cross-hairs were presented in between each face-name pair and between blocks. Each run consisted of 20 novel and 20 familiar face-name pairs. A total of 3 runs were performed in 6 minutes. All face-name pairs were drawn from the AR Face Database [18].

Imaging

Subjects underwent 4.0 Tesla fMRI scanning (GE Medical Systems, Milwaukee, WI) while performing the memory task using an audio-visual goggle system (Resonance Technology, Northridge, CA). For each of the 3 runs per subject, functional scans consisting of a time series of 164 T2*-weighted isotropic image volumes (inverse spiral echo-planar imaging [EPI]; repetition time [TR] 2500ms; echo time [TE] 31ms; flip angle [FA] 60°; matrix 64 × 64; field of view [FOV] 240mm) were acquired in 44 continuous, 3.75-mm-thick coronal slices. All functional images were screened for quality using center-of-mass plots to detect excessive motion or slice acquisition errors.

Statistical Processing

Statistical Parametric Mapping (SPM2) software was used for spatial preprocessing and to perform voxel-wise data analysis. For each subject, a contrast map was created to represent magnitude differences in fMRI signal between the novel and familiar encoding conditions across the entire brain. This contrast was built into a simple regression model to determine areas of brain activation magnitudes that co-varied with BDI score across subjects. Finally, a region-of-interest (ROI) mask encompassing BA 7, 10, 11, 23, 24, 25, 26, 29, 30, 31, and 32 from WFU PickAtlas [19] was applied to isolate the posteromedial cortex (PMC) and other midline structures of the default-mode network. For this ROI analysis, the uncorrected voxel-wise threshold was set at $p < 0.01$, with an extent threshold $k = 15$ voxels. Small volume correction [20] at the same $p < 0.01$ was applied in SPM2 to an identified cluster, with all voxels surviving this procedure. Next, two contrast maps were created to represent the magnitude differences in fMRI signal for the novel-encoding condition versus baseline (cross-hair fixation) as well as for the familiar-encoding condition versus baseline. For each contrast,

activation magnitudes were extracted from the previously identified cluster in order to clarify the underlying difference in brain activity.

Statistical Analysis

SPSS software (Version 12.2, 2004, SPSS Inc., Chicago, IL) was used for the statistical analysis of demographic and behavioral variables, as well as to reanalyze and confirm the SPM2-generated correlation between BDI score and brain activity. A p-value of <0.05 was considered statistically significant. BDI scores were not a primary outcome variable in our original study; as such, this was an exploratory analysis of data originally collected to study fMRI changes associated with early memory loss [5,6].

Results

Demographic and Behavioral Analysis

Our sample consisted of 30 males and 32 females. Mean (SD) age was 72.81 (7.23). The average number of years of education was 15.69 (2.71). Twenty-eight subjects had a global CDR score of 0, while 34 subjects had a score of 0.5. Mean MMSE score was 27.39 (1.86). BDI scores ranged from 0 to 17, with a mean of 5.23 (4.16). Thirty-four percent of subjects had a history of depression, and 29% of subjects were taking antidepressant or anxiolytic medications at the time of scanning.

In a multiple regression model with BDI as the dependent variable (Model $R^2_{adj} = 0.171$, $F_{5, 56} = 3.52$, $p = 0.008$), there was no significant relationship with age ($t_{56} = -1.27$, $p = 0.21$), gender ($t_{56} = 1.95$, $p = 0.06$), education ($t_{56} = -1.19$, $p = 0.24$) or CDR ($t_{56} = -1.80$, $p = 0.08$). However, BDI score did correlate significantly with MMSE score ($t_{56} = -3.34$, $p = 0.002$).

fMRI Cluster Analysis

ROI analysis revealed a distinct 63-voxel cluster ($t_{60} = 2.39$, $p_{uncorrected} < 0.01$, $k = 15$ voxels) correlating with BDI score, with a maximum at MNI coordinates {8, -46, 36} or Talairach {8, -43, 34}. All voxels survived small volume correction at $p < 0.01$. Notably, the cluster was confined to the dorsal posterior cingulate cortex (BA 31) within the PMC. The cluster is illustrated in Figure 1.

In a multiple regression model with cluster activity as the dependent variable (Model $R^2_{adj} = 0.289$, $F_{8, 53} = 3.52$, $p = 0.001$), cluster activity significantly correlated with BDI score ($t_{53} = 3.41$, $p = 0.001$), past history of depression ($t_{53} = -2.30$, $p = 0.025$) and current use of antidepressant or anxiolytic medications ($t_{53} = 3.08$, $p = 0.003$). The correlation between cluster activity and BDI score is demonstrated in Figure 1 (scatter plot). Variables that did not correlate with cluster activity were age ($t_{53} = 1.43$, $p = 0.16$), gender ($t_{53} = -1.74$, $p = 0.09$), education ($t_{53} = 1.14$, $p = 0.26$), CDR ($t_{53} = -0.10$, $p = 0.92$), and MMSE score ($t_{53} = -0.74$, $p = 0.46$).

Mean cluster activity levels against baseline cross-hair fixation were {-0.347} for the novel-encoding condition and {-0.236} for the familiar-encoding condition, as depicted in Figure 1 (bar graph). A paired t-test revealed that the difference between these two conditions was statistically significant ($t_{61} = -3.09$, $p = 0.003$).

Conclusions

The current fMRI analysis sought to explore the relationship between subsyndromal depressive symptoms and brain activity in the posteromedial cortex (PMC), a discrete portion of the default-mode network that undergoes task-related functional deactivation in healthy young adults. Our region-of-interest analysis revealed a distinct cluster within the PMC whose activity

co-varied with depression variables, including BDI score, past history of depression, and current use of antidepressants or anxiolytics. In this cluster, we verified that both the novel and familiar encoding task conditions elicited functional deactivations (negative activity levels) compared to baseline cross-hair fixation. Furthermore, novel encoding elicited a greater mean deactivation magnitude than familiar encoding - a phenomenon that likely reflects the need for a more extensive reallocation of neurocognitive resources in order to perform a more difficult cognitive task [7].

It is interesting to note that this cluster was completely confined to the dorsal portion of the posterior cingulate cortex (BA 31). Not only is this region recognized as part of the default-mode cognitive network, but it is also a well-known region of the limbic system, the brain's emotion processing center. For example, glucose metabolism in the dorsal posterior cingulate cortex has been positively correlated with major depressive symptoms in positron emission tomography studies [21]. Our finding thus raises the hypothesis that a common node may exist between the default cognitive network and the limbic mood circuit at the level of the dorsal posterior cingulate cortex – a structural “crossing” where these circuits might exert influences on one another. Of note, the PMC cluster identified here is distinct from, yet adjacent to a larger PMC cluster previously reported in MCI and AD patients [6].

As this was an exploratory pilot analysis, our findings should be viewed as hypothesis-generating rather than definitive. Limitations of this study include its cross-sectional nature and relatively narrow range of depression severities. Furthermore, we intended only to use BDI as an indicator of current mood near time of scanning and to simply correlate present mood with brain activity, regardless of history of depression or current use of medications. Studies in which subjects undergo a lifetime depression structured interview, as well as longitudinal studies in more severely depressed individuals with a range of memory performances, may be needed to investigate the prognostic implications of our findings.

Acknowledgements

This study was funded by the NIA. Ms. Woo is a medical student at Duke University and was funded by the 2007-2008 Ewald W Busse Fellowship in Late-Life Mood Disorders. Dr. Doraiswamy has received research grant support and/or honoraria for consulting or speaking from several pharmaceutical or diagnostic companies and owns equity in Sonexa Therapeutics. Duke University and Dr. Doraiswamy hold a use patent for an unrelated treatment indication in children; that patent is unlicensed and he derives no income from it. Dr. Petrella has received research support from Eisai/Pfizer and AVID for other pilot studies. Ms. Hellegers has received salary support from several pharmaceutical companies for other studies. Dr. Prince and Ms. Woo have no conflicts to disclose.

Funding Sources: This study was supported by NIA R01AG019728. Ms Woo was supported by the Ewald W Busse Fellowship in Late Life Mood Disorders at Duke.

References

1. Lyness JM. Naturalistic outcomes of minor and subsyndromal depression in older primary care patients. *Int J Geriatr Psychiatry*. 2008
2. Ownby RL, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and meta-regression analysis. *Arch Gen Psychiatry* 2006;63(5):530–8. [PubMed: 16651510]
3. Raichle ME, et al. A default mode of brain function. *Proc Natl Acad Sci U S A* 2001;98(2):676–82. [PubMed: 11209064]
4. Lustig C, et al. Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A* 2003;100(24):14504–9. [PubMed: 14608034]
5. Petrella JR, et al. Cortical deactivation in mild cognitive impairment: high-field-strength functional MR imaging. *Radiology* 2007;245(1):224–35. [PubMed: 17885190]
6. Petrella JR, et al. Prognostic value of posteromedial cortex deactivation in mild cognitive impairment. *PLoS ONE* 2007;2(10):e1104. [PubMed: 17971867]

7. McKiernan KA, et al. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci* 2003;15(3):394–408. [PubMed: 12729491]
8. Kyomen HH, et al. Greater depression severity in elderly patients with memory complaints is associated with decreased left temporal-parietal dominance indicated by dynamic susceptibility contrast magnetic resonance imaging cerebral blood volume measures. *Am J Geriatr Psychiatry* 2007;15(7):604–10. [PubMed: 17586784]
9. Takami H, et al. Attenuated anterior cingulate activation during a verbal fluency task in elderly patients with a history of multiple-episode depression. *Am J Geriatr Psychiatry* 2007;15(7):594–603. [PubMed: 17353296]
10. Walsh ND, et al. A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. *Biol Psychiatry* 2007;62(11):1236–43. [PubMed: 17601497]
11. Greicius MD, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry* 2007;62(5):429–37. [PubMed: 17210143]
12. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189–98. [PubMed: 1202204]
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43(11):2412–4. [PubMed: 8232972]
14. Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck Depression Inventory-II. Psychological Corporation; San Antonio, TX: 1996.
15. McKhann G, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939–44. [PubMed: 6610841]
16. First, MB., et al. American Psychiatric Press, Inc.; Washington, DC: 1997. Structured Clinical Interview for DSM-IV-TR Axis I Disorders - Patient Edition (SCID-I/P, 2/2001 Revision).
17. Petrella JR, et al. Mild cognitive impairment: evaluation with 4-T functional MR imaging. *Radiology* 2006;240(1):177–86. [PubMed: 16684919]
18. Martinez AM, Benavente R. The AR Face Database, in CVC Technical Report #24. 1998
19. Maldjian JA, et al. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage* 2003;19(3):1233–1239. [PubMed: 12880848]
20. Worsley KJ, et al. A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping* 1996;4(1):58–73.
21. Milak MS, et al. Neuroanatomic correlates of psychopathologic components of major depressive disorder. *Arch Gen Psychiatry* 2005;62(4):397–408. [PubMed: 15809407]

Figure 1.

Three orthogonal views of the identified PMC cluster (blue) superimposed on a canonical T1-weighted brain template image. Scatter plot illustrates correlation between brain parameter estimate (cluster activity) and BDI score. Bar graph demonstrates cluster activity level against baseline for both novel- and familiar-encoding conditions. Statistical details are described in the text.