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Detection of Altered Hippocampal Morphology in Multiple Sclerosis-Associated Depression Using Automated Surface Mesh Modeling

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Abstract: Depression is very common in multiple sclerosis (MS) but the underlying biological mechanisms are poorly understood. The hippocampus plays a key role in mood regulation and is implicated in the pathogenesis of depression. This study utilizes volumetric and shape analyses of the hippocampus to characterize neuroanatomical correlates of depression in MS. A cross-section of 109 female patients with MS was evaluated. Bilateral hippocampi were segmented from MRI scans (volumetric T_1-weighted, 1 mm^3) using automated tools. Shape analysis was performed using surface mesh modeling. Depression was assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale. Eighty-three subjects were classified as low depression (CES-D 0–20) versus 26 subjects with high depression (CES-D $\geq$ 21). Right hippocampal volumes ($P = 0.04$) were smaller in the high depression versus the low depression groups, but there was no significant difference in left hippocampal volumes.

Stefan M. Gold and Mary-Frances O'Connor contributed equally to the manuscript

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Surface rendering analysis revealed that hippocampal shape changes in depressed patients with MS were clustered in the right hippocampus. Significant associations were found between right hippocampal shape and affective symptoms but not vegetative symptoms of depression. Our results suggested that regionally clustered reductions in hippocampal thickness can be detected by automated surface mesh modeling and may be a biological substrate of MS depression in female patients. *Hum Brain Mapp 35:30–37, 2014.*

Key words: depression; autoimmunity; hippocampus; cornu ammonis; magnetic resonance imaging

INTRODUCTION

Depression often coexists with chronic diseases and the comorbid state of depression incrementally worsens health compared with either disorder alone [Moussavi et al., 2007]. Depression is particularly frequent in patients with multiple sclerosis (MS): In a large population-based study, the 12-month prevalence for major depressive disorder (MDD) in MS has been estimated at 25% [Patten et al., 2003]. The underlying cause for the high frequency of depression is unknown but likely involves biological and psychological factors [Feinstein, 2011].

The neuroanatomical correlates of MS depression are poorly understood. However, smaller volumes in several brain areas have been reported in psychiatric patients with MDD including well-documented reductions in hippocampal volumes [Koolschijn et al., 2009]. Interestingly, hippocampal damage has also been described in a number of in vivo and post-mortem studies in MS [Dutta et al., 2011; Geurts et al., 2006, 2007; Roosendaal et al., 2010; Sicotte et al., 2008] as well as in its animal model [Ziehn et al., 2010]. Several papers have reported associations between MS-associated depression and decreased regional gray matter volumes, in particular in the temporal lobe [Feinstein et al., 2004; Zorzon et al., 2001, 2002]. Structural abnormalities of normal-appearing white and gray matter as measured by diffusion tensor imaging in frontal and temporal regions have also been linked to depression in MS [Feinstein et al., 2010]. Within the temporal lobe, recent evidence points to hippocampal volume reductions as a potential substrate of MS depression [Gold et al., 2010; Kiy et al., 2011]. Thus, damage to temporal structures involved in mood regulation such as the hippocampus may contribute to the high frequency of depression in MS.

Importantly, depression is characterized by a cluster of symptoms comprised of affective (such as depressed mood and loss of interest), vegetative (such as psychomotor slowing, fatigue, changes in sleep pattern), and interpersonal components. Patients with MS often suffer from disease-related fatigue [Stuke et al., 2009], which may resemble vegetative symptoms of depression. Fatigue itself has been linked to lower regional volumes in basal ganglia and frontal or parietal cortical regions in MS [Leocani et al., 2008]. Thus, the overlap of vegetative symptoms of depression and MS-related fatigue may potentially impede the identification of anatomical substrates. However, precise analyses of neuroanatomical correlates of affective versus vegetative aspects of depression in MS have not been done so far.

In the present cross-sectional study, we sought to characterize the role of hippocampal substructures in MS-associated depression using automated volumetric and shape analyses in a large sample of patients with MS. In addition, we aimed to dissect the affective, vegetative, and psychosocial components of MS depression and their relative association with hippocampal subregions.

MATERIALS AND METHODS

Subjects

Patients with MS were recruited from three sites at the University of California San Francisco (UCSF), Evergreen Hospital Medical Center in Seattle Washington (Evergreen), the Feinberg School of Medicine at Northwestern University (NU), and through local chapters of the National Multiple Sclerosis Society. Recruitment began in May 2005 and was completed in January 2008. Eligible patients had to be diagnosed with MS according to the revised McDonald criteria [Polman et al., 2005]. All participants were at least 18 years of age, and were able to speak and read English. Patients were excluded if they had received a corticosteroid treatment in the past 28 days, or were treated with a cytotoxic agent (e.g., mitoxantrone, cyclophosphamide, azathioprine, methotrexate) or natalizumab. Patients were excluded if they had other autoimmune or endocrine disorders, were pregnant or planning pregnancy, diagnosed with any serious psychiatric pathology or dementia, or were currently receiving or planning to begin psychotherapy.

Standard Protocol Approvals, Registrations, and Patient Consent

The research reported in this article was conducted in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Institutional review boards at each participating center approved the protocol, and signed consent was obtained from each participant. Subjects were enrolled as part of the Stress Intervention in MS (SIMS) study (ClinicalTrials.gov identifier:

NCT00147446). All data used in the current study were obtained during the baseline visit of the SIMS study, prior to randomization and intervention. From initially screened $n = 777$ patients, $n = 638$ were not consented ($n = 362$ did not meet inclusion criteria, $n = 205$ declined to participate in the study, mostly due to demands of MRI and stress intervention protocols and/or distance to the study centers, $n = 48$ could not be reached, and $n = 23$ did not participate for other reasons).

Clinical Measures

During the neurological examination, we obtained standard disability rating (Expanded Disability Status Scale [EDSS]) [Kurtzke, 1983], disease course and duration, and current medication.

Magnetic Resonance Imaging

Lesion quantification and whole brain fraction

"Dummy" scans were performed at each site prior to first subject enrollment and subsequent images were sent to a primary central MRI reading unit (UCSF, San Francisco) for quality control. Magnetic resonance imaging (MRI) of the brain ($T2/T1$-weighted images) with injection of a single-dose of gadolinium was performed according to a standardized protocol using a 3.0-Tesla magnet at each site. T_2 lesion volume analysis was performed using a semi-automated thresholding method and manual editing with simultaneous view access to both T_2 and proton density weighted slices. Normalized whole brain fraction values were derived from the output of the SIENAX analysis. All MRI analyses were performed by an expert rater blind to clinical characteristics of the subject.

Hippocampal volume and shape analysis

For hippocampal analyses, we analyzed T_1-weighted images obtained from volumetric high-resolution (1 mm^3, 160 slices) gradient-echo pulse sequences (Echo Time (TE) 2.0, Repetition time (TR) 15.0, Flip angle 22, Field of View (FOV) 26 cm, matrix 256) on a 3.0-Tesla magnet at each site. Volumetric images were then electronically transferred to UCLA for post-processing. The right and left hippocampi were auto-segmented using FIRST, a component of FSL tools [Patenaude et al., 2011] and volumes corrected for head size using the SIENAX generated volume scaling factor prior to statistical analysis. For the shape analysis, surface maps of the extracted right and left hippocampal volumes were constructed using a surface mesh procedure previously described [Shi et al., 2007]. Averages were constructed from individual surface maps for group comparisons and differences assessed using Laplace–Beltrami eigen-features derived from software developed in-house [Shi et al., 2009]. Briefly, we first generated a regular mesh representation of the group atlas surface with 2,000 vertices. Using the maps computed, we projected the triangular mesh of the atlas onto the generated surfaces for subsequent statistical analysis. This method uses spectral geometry to model hippocampal geometry and is reliable from the first principle since the Laplace–Beltrami eigenfunctions are "isometry invariant," which means our method is invariant to pose and scale differences, and robust to deformation [Shi et al., 2007, 2009].

Assessment of Depression

Depression was assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale, a scale with excellent validity and reliability for measuring depressive symptoms [Radloff, 1977], especially in medical settings. The sample was split into two groups: low depression (CES-D 0–20), and high depression (CES-D score 21 or higher). Although the cut-off of 16 is sometimes used with the CES-D for probable depression, scores tend to be higher in a population with chronic health problems because the CES-D includes somatic symptoms [Knight et al., 1997]. It has been demonstrated that a cut-off score of 21 is a better predictor of MDD in patients with co-morbid medical illness [Schulberg et al., 1985]. This was also shown in a study of 739 patients with MS [Chwastiak et al., 2002]. Therefore, we split our sample based on Chwastiak and coworkers use of a CES-D score of 21 or higher for moderate to severe depression.

In addition to using the total score, we further divided the CES-D into its four subscales: depressive affect, positive affect, somatic, and interpersonal. This reflects the originally intended structure [Radloff, 1977], which was later replicated in a large sample [Knight et al., 1997].

Statistical Analysis

Clinical and demographic descriptors and hippocampal measures were compared between high depression and low depression patients with MS using independent samples t tests. If Levene's test indicated a violation of the equality of variance assumption ($P < 0.10$), degrees of freedom were adjusted accordingly. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were conducted using Predictive Analytics Software (PASW) Statistics 18.0 for Macintosh.

To localize hippocampal volume reductions, we defined a thickness measure at each vertex of the mapped surfaces [Shi et al., 2009]. At each vertex, a one-tailed t-test was applied to compare hippocampal shape between the depressed group and the group with low depressive symptoms. Correlations of CESD subscales with thickness measures were computed using Spearman's rank correlation. The resulting P-value maps were plotted onto the mean shape of the entire group. Permutation analysis was used to correct for multiple comparisons of the hippocampal surface mapping results.

TABLE I. Clinical characteristics of MS patients with low levels of depressive symptoms (CES-D 0–20) or high levels of depression (CES-D 21 or higher)

	Low depression ($n = 83$)	High depression ($n = 26$)	P (2-tailed)
Age	43.0 ± 1.08	42.4 ± 1.92	0.77
EDSS	3.08 ± 0.184	3.36 ± 0.258	0.42
Whole brain fraction	0.85 ± 0.003	0.85 ± 0.007	0.74
Number of Gd+ lesions	0.63 ± 0.32	0.38 ± 0.18	0.67
T2 lesion volume (cm^3)	9.7 ± 1.77	8.2 ± 1.76	0.67
Disease duration (years)	6.86 ± 0.90	8.58 ± 1.85	0.40
CES-D	9.6 ± 0.55	30.6 ± 1.56	<0.001
SSRI treatment (%)	36.1%	57.7%	0.05

EDSS: Expanded Disability Status Scale; Gd+ lesions: Gadolinium-enhancing lesions; SSRI selective serotonin reuptake inhibitor. Data are presented as mean ± standard error of mean (SEM).

RESULTS

This study is a secondary analysis of the baseline data from a randomized controlled trial examining the effects of a stress management intervention among patients with MS [Mohr et al., in press].

Sample Characteristics

A total of 138 subjects were eligible. Because there was only a small portion of male subjects ($n = 26$) and these had significantly bigger absolute hippocampal volumes ($P = 0.001$) but significantly smaller head-size corrected hippocampal volumes ($P = 0.04$), the analyses were conducted in the female group only. Of the 112 female patients, MRI scans and/or CES-D scores were not available from 3 women so that a total of 109 female patients were analyzed for this study.

Based on the cut-off defined above, 83 participants were classified as low depression (CES-D 0–20) vs. 26 participants classified with high depression (CES-D 21 or higher). High and low depression groups did not differ with regard to age, disease duration, the use of disease modifying treatment, or disability as measured by the EDSS (see Table I). Importantly, the groups also did not differ on normalized whole brain fraction, number of contrast-enhancing lesions (Gd+ lesions), or T_2 lesion volume (see Table I). As expected, a higher percentage of depressed subjects were receiving antidepressive medication.

Hippocampus Volume Differences

The high depression group showed a significantly smaller right hippocampal volume ($P < 0.04$). However, the two groups did not differ in left hippocampus ($P = 0.67$), or total hippocampal volumes ($P = 0.19$) (see Fig. 1). Importantly, the groups did not differ in global volume (SIENAX) as measured by brain percentage, indicating that brain volume differences were specific to the hippocampus.

Localization of Hippocampal Volume Differences

Surface rendering analysis revealed that the high depression group showed strongest inward hippocampal shape changes (i.e., smaller volumes) in several areas of the hippocampus including larger clusters suggestive of CA2-3 region (see Fig. 2) and the posterior subiculum. Corroborating the findings of the volumetric analysis, group differences were only seen in the right but not the left hippocampus.

Hippocampal Shape Differences are Linked to Affective Symptoms

Next, we aimed to dissect the contribution of subcomponents of depression (i.e., depressive affect, positive affect, somatic, and interpersonal symptoms) to hippocampal shape differences. Significant (albeit small) correlations were seen between depressive affect and right hippocampus ($r = -0.23$; $P = 0.02$) and total hippocampal volume ($r = -0.22$; $P = 0.02$) but not left hippocampus ($r = -0.15$; $P = 0.12$). No significant associations were seen with the positive affect, somatic, or interpersonal symptom subscales and hippocampal volumes (all coefficients $r < 0.10$).

Confirming the volumetric data, only the depressive affect subscale was significantly associated with

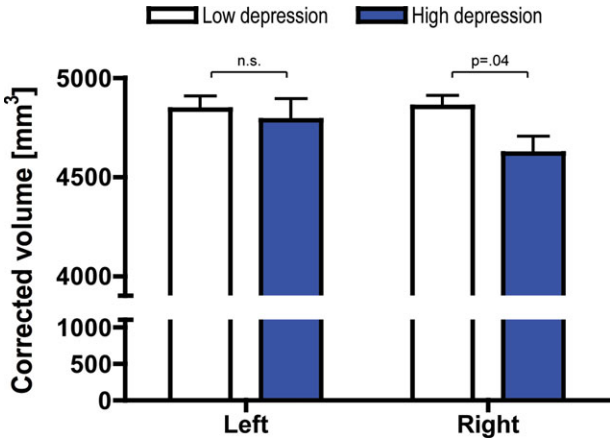

Figure 1.
Hippocampal volume in MS patients with low depression (CES-D 0–20) and high depression (CES-D 21 or higher). Depressed MS patients had significantly smaller right hippocampal volumes ($P = .04$) while no significant volume differences were seen in left hippocampus. Data are corrected for head size and given as mean ± standard error of mean (SEM). Group differences were tested using two-tailed independent samples t test.

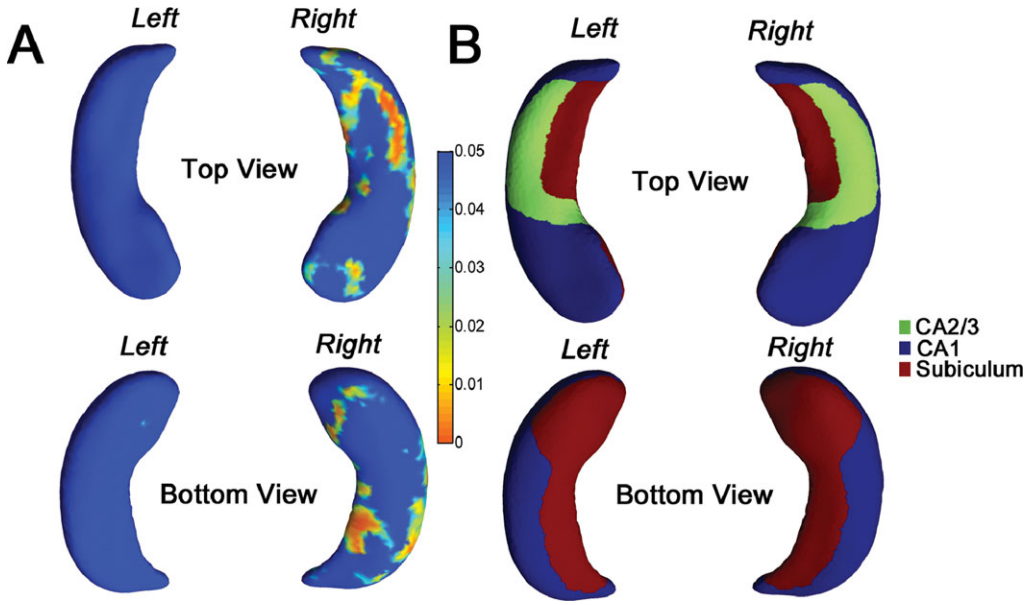

Figure 2.

Localization of hippocampal thickness differences between low depression (CES-D 0–20) and high depression (CES-D 21 or higher) MS patients. Statistical maps comparing hippocampal surface deformation/expansion indicate decreased thickness in depressed patients (**A**). The high depression group showed strongest inward hippocampal shape changes (i.e., smaller volumes) in several areas of the hippocampus including larger clusters suggestive of CA2-3 region and the posterior subiculum (**B**). For statistical maps, the color bar encodes the probability values for the observed effects. All statistical tests were performed one-tailed with adjustment for multiple comparisons.

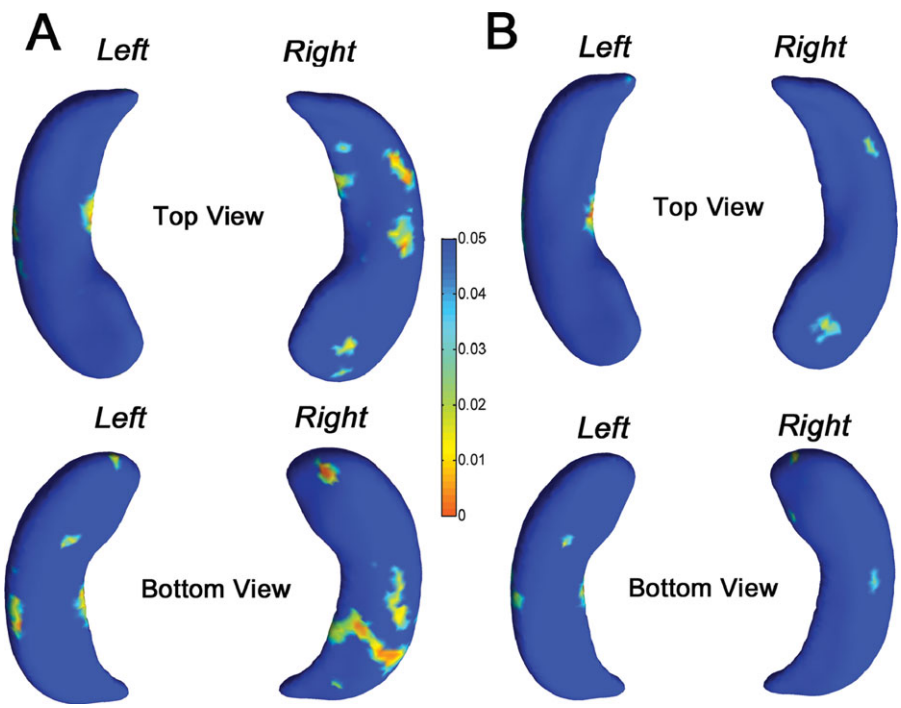

Figure 3.

Subregional hippocampal shape changes are selectively associated with depressed affect but not somatic symptoms. Statistical maps show significant correlations between regional hippocampal thickness and the affective mood subscale of the CES-D (**A**) or somatic symptoms on the CES-D (**B**). For all statistical maps, the color bar encodes the probability values for the observed effects. All statistical tests were performed one-tailed with adjustment for multiple comparisons.

deformations in the hippocampus (Fig. 3). The strongest associations were observed between hippocampal thickness and depressive affect (see Fig. 3A). In contrast, no associations were seen for somatic symptoms, (Fig. 3B), positive affect, or interpersonal symptoms. The addition of clinical and imaging variables including EDSS, gadolinium lesion numbers, T_2 lesion volume, age, and BPF into the regression model as potential confounding factors did not alter the results.

DISCUSSION

In this study, we provide evidence for an association between smaller hippocampal volumes and depressive symptoms in a large sample of female patients with MS. Importantly, using the subscales of the CES-D, we demonstrated that the affective component of depression is linked to hippocampal shape changes while vegetative or interpersonal symptoms are not. Thereby, we extend our previous findings in a study employing manual tracings of anatomically defined hippocampal subregions, which indicated that depression in MS is associated with smaller volumes specifically in the CA2-3 subregion of the hippocampus [Gold et al., 2010]. We obtained these results using automated volumetric and surface mapping techniques with easily obtainable 1 mm^3 T_1-weighted MRI scans, in contrast to the labor-intensive manual tracings requiring special high resolution T_2-weighted sequences. Thus, this methodology is suitable for large-scale studies where specialized imaging sequences might not be available, and could be used to better understand the differential associations of hippocampal subfields with affective disorders in the medically ill.

Patients with medical disorders and especially those with inflammatory diseases such as MS frequently suffer from fatigue that can resemble vegetative symptoms of depression. Thus, using the total scores of questionnaires such as the BDI or the CES-D in these populations may make it more difficult to identify biological substrates of mood disturbances. In our study, we found smaller hippocampal volume associated with depressed affect but not the somatic/vegetative or interpersonal components of depression. In line with a role for neuroendocrine-limbic pathways for mood dysregulation in MS (as opposed to vegetative symptoms), recent evidence suggests that elevated salivary cortisol levels are associated with depressed mood [Gold et al., 2010, 2011; Kern et al., 2011] but not fatigue [Gold et al., 2011] in MS. This suggests that while fatigue and depression often co-occur in MS, they may be mediated by different biological mechanisms.

One inherent limitation of surface mapping techniques is that only structures on the outside of the brain region in question can be examined. In addition, the thickness measure obtained uses distance from the midline as a reference point. Thus, a clustering of volume changes on a three-dimensional structure may be due to decreased volume of the surface area, in substructures underneath or changes in volume at the opposite side. Therefore, in the current analysis, inferences about a selective association of depression with anatomically defined hippocampal subfields are not possible. However, some of the clusters identified are consistent with shape changes in cornu ammonis 2-3. Given that these subfields were also implicated in our previous study [Gold et al., 2010] using anatomically defined manual tracings that circumvent the limitations of shape analyses, together, these studies provide evidence that there might be subregional clustering of hippocampal volume differences in MS-depression.

In the current study, we found significant differences in the right but not the left hippocampus. A possible hemispheric laterality has been proposed for idiopathic depression [Guinjoan et al., 2010]. However, data on a lateralization of structural brain changes are inconclusive. An early meta-analysis of studies on the hippocampus in MDD found significant associations between number of depressive episodes only on the right [Videbech and Ravnkilde, 2004] but a later meta-analysis did not find evidence for lateralization [McKinnon et al., 2009]. More recent studies using surface renderings found no lateralization [Ballmaier et al., 2008; Posener et al., 2003] or reported the right hippocampus to be more severely affected in MDD [Cole et al., 2010]. Thus, laterality findings might be simply due to chance or depend on the method used. However, one recent study in a sample including only female patients with familial depression showed reduced volumes of the right but not the left hippocampus [Nifosi et al., 2010]. The authors interpret this finding as an indication for sex-specific associations between lateralized hippocampal volumes and depression. In line with this hypothesis, our previous study including both male and female patients with MS with depression showed significant differences on both right and left hippocampus [Gold et al., 2010] while our current analysis including only female patients indicated hippocampal volume reductions only on the right. Whether or not there is indeed a sex-specific hippocampal lateralization in MS-depression remains to be elucidated in larger samples including both male and female subjects.

In addition, correlations between the hippocampus and depressive affect, while statistically significant, were comparatively low. Bivariate biopsychological associations are often low since functions such as mood regulation are highly complex and likely not determined by a single brain structure. Indeed, brain abnormalities in MDD have also been reported in frontal regions such as the anterior cingulate and the orbitofrontal cortex in several studies (see [Koolschijn et al., 2009] for review). However, smaller hippocampal volumes are among the most consistently documented neuroanatomical substrates of major depression. Hippocampal volume is also one of the few brain abnormalities that distinguish unipolar depression from bipolar disorder [Kempton et al., 2011]. In addition, a biological rationale for the importance of the hippocampus in depression is provided by a large body of evidence from

clinical and preclinical studies [Macqueen and Frodl, 2011]. Recent studies on MS depression have shown associations with the hippocampus [Gold et al., 2010; Kiy et al., 2011] and other temporal as well as frontal areas [Feinstein et al., 2010]. Future studies should therefore aim to dissect the individual contribution of these areas to MS-depression to better understand the complex neuroanatomical network underlying depressive symptomatology in this population.

It is interesting to note that the correlations between related biological functions in this context tend to be stronger. For example, in our previous report, the correlation between cortisol levels and smaller subregional hippocampal volumes was stronger than the associations of either of those two biological components with depression severity [Gold et al., 2010]. Thus, future studies on the pathogenesis of depression in MS should include additional mechanistic markers.

REFERENCES

Ballmaier M, Narr KL, Toga AW, Elderkin-Thompson V, Thompson PM, Hamilton L, Haroon E, Pham D, Heinz A, Kumar A (2008): Hippocampal morphology and distinguishing late-onset from early-onset elderly depression. Am J Psychiatry 165:229–237.

Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH (2002): Depressive symptoms and severity of illness in multiple sclerosis: Epidemiologic study of a large community sample. Am J Psychiatry 159:1862–1868.

Cole J, Toga AW, Hojatkashani C, Thompson P, Costafreda SG, Cleare AJ, Williams SC, Bullmore ET, Scott JL, Mitterschiffthaler MT, Walsh ND, Donaldson C, Mirza M, Marquand A, Nosarti C, McGuffin P, Fu CH (2010): Subregional hippocampal deformations in major depressive disorder. J Affect Disord 126:272–277.

Dutta R, Chang A, Doud MK, Kidd GJ, Ribaudo MV, Young EA, Fox RJ, Staugaitis SM, Trapp BD (2011): Demyelination causes synaptic alterations in hippocampi from multiple sclerosis patients. Ann Neurol 69:445–454.

Feinstein A (2011): Multiple sclerosis and depression. Mult Scler 17:1276–1281.

Feinstein A, Roy P, Lobaugh N, Feinstein K, O'Connor P, Black S (2004): Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology 62:586–590.

Feinstein A, O'Connor P, Akbar N, Moradzadeh L, Scott CJ, Lobaugh NJ (2010): Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. Mult Scler 16:189–196.

Geurts JJ, Reuling IE, Vrenken H, Uitdehaag BM, Polman CH, Castelijns JA, Barkhof F, Pouwels PJ (2006): MR spectroscopic evidence for thalamic and hippocampal, but not cortical, damage in multiple sclerosis. Magn Reson Med 55:478–483.

Geurts JJ, Bo L, Roosendaal SD, Hazes T, Daniels R, Barkhof F, Witter MP, Huitinga I, van der Valk P (2007): Extensive hippocampal demyelination in multiple sclerosis. J Neuropathol Exp Neurol 66:819–827.

Gold SM, Kern KC, O'Connor MF, Montag M, Kim A, Yoo YS, Giesser BS, Sicotte NL (2010): Smaller cornu ammonis (CA) 2–3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. Biol Psychiatry 68:553–559.

Gold SM, Kruger S, Ziegler KJ, Krieger T, Schulz KH, Otte C, Heesen C (2011): Endocrine and immune substrates of depressive symptoms and fatigue in multiple sclerosis patients with comorbid major depression. J Neurol Neurosurg Psychiatry 82:814–818.

Guinjoan SM, Mayberg HS, Costanzo EY, Fahrer RD, Tenca E, Antico J, Cerquetti D, Smyth E, Leiguarda RC, Nemeroff CB (2010): Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. J Neuropsychiatry Clin Neurosci 22:265–277.

Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, Williams SC (2011): Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 68:675–690.

Kern S, Schultheiss T, Schneider H, Schrempf W, Reichmann H, Ziemssen T (2011): Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis. Psychoneuroendocrinology 36:1505–1512.

Kiy G, Lehmann P, Hahn HK, Eling P, Kastrup A, Hildebrandt H (2011): Decreased hippocampal volume, indirectly measured, is associated with depressive symptoms and consolidation deficits in multiple sclerosis. Mult Scler 17:1088–1097.

Knight RG, Williams S, McGee R, Olaman S (1997): Psychometric properties of the Centre for Epidemiologic Studies Depression Scale (CES-D) in a sample of women in middle life. Behav Res Ther 35:373–380.

Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS (2009): Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 30:3719–3735.

Kurtzke JF (1983): Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444–1452.

Leocani L, Colombo B, Comi G (2008): Physiopathology of fatigue in multiple sclerosis. Neurol Sci 29 (Suppl 2):S241–S243.

Macqueen G, Frodl T (2011): The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 16:252–264.

McKinnon MC, Yucel K, Nazarov A, MacQueen GM (2009): A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J Psychiatry Neurosci 34:41–54.

Mohr DC, Lovera J, Brown T, Cohen B, Neylan T, Henry RG, Siddique J, Jin L, Daikh D, Pelletier D: A randomized trial of stress management for the prevention of new brain lesions in MS. Neurology (in press).

Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B (2007): Depression, chronic diseases, and decrements in health: Results from the World Health Surveys. Lancet 370:851–858.

Nifosi F, Toffanin T, Follador H, Zonta F, Padovan G, Pigato G, Carollo C, Ermani M, Amista P, Perini GI (2010): Reduced right posterior hippocampal volume in women with recurrent familial pure depressive disorder. Psychiatry Res 184:23–28.

Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011): A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56:907–922.

Patten SB, Beck CA, Williams JV, Barbui C, Metz LM (2003): Major depression in multiple sclerosis: A population-based perspective. Neurology 61:1524–1527.

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG,

Wolinsky JS (2005): Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 58:840–846.

Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI, Babb CM, Csernansky JG (2003): High-dimensional mapping of the hippocampus in depression. Am J Psychiatry 160:83–89.

Radloff LS (1977): The CES-D Scale: a self-report depression scale for research in the general population. J Appl Psychol Meas 1:385–401.

Roosendaal SD, Hulst HE, Vrenken H, Feenstra HE, Castelijns JA, Pouwels PJ, Barkhof F, Geurts JJ (2010): Structural and functional hippocampal changes in multiple sclerosis patients with intact memory function. Radiology 255:595–604.

Schulberg HC, Saul M, McClelland M, Ganguli M, Christy W, Frank R (1985): Assessing depression in primary medical and psychiatric practices. Arch Gen Psychiatry 42:1164–1170.

Shi Y, Thompson PM, de Zubicaray GI, Rose SE, Tu Z, Dinov I, Toga AW (2007): Direct mapping of hippocampal surfaces with intrinsic shape context. Neuroimage 37:792–807.

Shi Y, Morra JH, Thompson PM, Toga AW (2009): Inverse-consistent surface mapping with Laplace-Beltrami eigen-features. Inf Process Med Imaging 21:467–478.

Sicotte NL, Kern KC, Giesser BS, Arshanapalli A, Schultz A, Montag M, Wang H, Bookheimer SY (2008): Regional hippocampal atrophy in multiple sclerosis. Brain 131 (Part 4):1134–1141.

Stuke K, Flachenecker P, Zettl UK, Elias WG, Freidel M, Haas J, Pitschau-Michel D, Schimrigk S, Rieckmann P (2009): Symptomatology of MS: Results from the German MS registry. J Neurol 256:1932–1935.

Videbech P, Ravnkilde B (2004): Hippocampal volume and depression: A meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966.

Ziehn MO, Avedisian AA, Tiwari-Woodruff S, Voskuhl RR (2010): Hippocampal CA1 atrophy and synaptic loss during experimental autoimmune encephalomyelitis, EAE. Lab Invest 90:774–786.

Zorzon M, de Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G, Bratina A, Zivadinov R (2001): Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. J Neurol 248:416–421.

Zorzon M, Zivadinov R, Nasuelli D, Ukmar M, Bratina A, Tommasi MA, Mucelli RP, Brnabic-Razmilic O, Grop A, Bonfigli L, Cazzato G (2002): Depressive symptoms and MRI changes in multiple sclerosis. Eur J Neurol 9:491–496.