ABSTRACT

Background: The amygdala is an integral part of the extrahypothalamic stress-response system, and its volume related to childhood trauma has been studied, but less is known of associations with recent stressful life events. We hypothesized that stressful experiences may be associated with amygdala volumetric differences in the context of depression. ***Methods:*** Right-handed participants (n=61) experiencing a major depressive episode during major depressive disorder (n=40) or bipolar depression (n=21) and healthy volunteers (n=60) underwent 1.5 T magnetic resonance imaging (MRI). Amygdala volumes were determined blind to diagnosis. A detailed psychiatric history included self-reported history of physical or sexual abuse. Stressful life events within the past six months were recorded using the St. Paul-Ramsey Scale. ***Results:*** We found no association between physical and/or sexual abuse history and amygdala volume. Life stress within the last six months, however, was associated with smaller left amygdala volume (F=7.580, df=1,117, p=0.007). The association between stress and amygdala volume did not differ by diagnostic group. ***Limitations:*** Most depressed patients were off medications for at least 2 weeks; however, this may not have been long enough to reverse effects of medications on amygdala structure. ***Conclusions:*** That life stress of relatively short duration was associated with amygdala size in the entire sample, while temporally distant life stress was not, suggests that amygdala volume changes may occur rapidly and reversibly, and independent of depression status.

Title: **Relationship of recent stress to amygdala volume in depressed and healthy adults**

Running title: **Stress and amygdala volume**

Authors: ***M. Elizabeth Sublette[1,2], M.D., Ph.D.**

Hanga C. Galfalvy[1,2], Ph.D.

Maria A. Oquendo[1,2], M.D.

Corinne P. Bart[1], B.A.

Noam Schneck[1,2], Ph.D.

Victoria Arango[1,2], Ph.D

J. John Mann[1,2,4], M.D.

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Addresses: Departments of [1]Molecular Imaging and Neuropathology,
New York State Psychiatric Institute, and
[2]Psychiatry and [3]Radiology,
Columbia University.

*Corresponding author
Dr. M. E. Sublette
Department of Molecular Imaging and Neuropathology
New York State Psychiatric Institute
Columbia University, Unit 42
1051 Riverside Drive
NY, NY 10032
Tel 646-774-7514
FAX 646-774-7589
e-mail sublett@nsypi.columbia.edu

INTRODUCTION

The amygdala is part of the extrahypothalamic stress-response system. In rats the medial amygdala activates the hypothalamic-pituitary-adrenal (HPA) axis in response to acute immobilization stress (Ma and Morilak, 2005). Elevated glucocorticoids associated with recent stress mediate hippocampal atrophy via glutamate excitotoxicity (Sapolsky, 2000), and it was previously hypothesized that the amygdala may be similarly vulnerable (Sheline et al., 1998, Sheline et al., 1999) since, like the hippocampus, it contains a high concentration of glucocorticoid receptors. Recombinant mice with the strongest fear conditioning and greatest glucocorticoid responses to stress also exhibit smaller basolateral amygdala complex volumes (Yang et al., 2008). However, others report that glucocorticoids induce dendritic hypertrophy in the basolateral nucleus of the amygdala in conjunction with heightened anxiety (Mitra and Sapolsky, 2008), and that neurons of specific subnuclei of the amygdala manifest growth in response to stress (Kerchner et al., 1995, Salm et al., 2004, Henckens et al., 2015, Vyas et al., 2002, Mitra et al., 2005).

Clinical evidence concerning the effects of stress on amygdala volume in humans is sparse. Congenital adrenal hyperplasia, a condition that results from gene mutations of enzymes crucial for cortisol production, results in increased cortisol secretion and is accompanied by smaller amygdala volume in children (Merke et al., 2003). One study of early life trauma on brain structure found that childhood adversity is associated with smaller amygdala volumes in adolescents but not adults (Korgaonkar et al., 2013). This is consistent with most studies in adults that find no significant amygdala volumetric differences associated with post-traumatic stress disorder (PTSD) (Gurvits et al., 1996, Bremner et al., 1997, Fennema-Notestine et al., 2002, Lindauer et al., 2004, Wignall et

al., 2004, Levy-Gigi et al., 2013, Gilbertson et al., 2002, Bonne et al., 2001) with few exceptions that include combat-related PTSD (Morey et al., 2012, Depue et al., 2014) and cancer-related intrusive thoughts (Matsuoka et al., 2003).

Reasoning that the timing of stress might have effects on the amygdala, and that differential effects might be seen in mood disorders compared with healthy volunteers, we examined the effects of 1) childhood abuse and 2) recent self-reported life events on amygdala volume, in currently depressed patients with mood disorders and healthy volunteers.

METHODS AND MATERIALS

Participants and assessments

Right-handed depressed participants (n=61) and healthy volunteers (n=60) were recruited from community referrals and advertisements to participate in neuroimaging protocols that comprised magnetic resonance imaging (MRI) and positron emission tomography (not discussed here). Participants were not on medications at time of study enrollment or underwent a medication washout so they were off medications for $\geq$ 2 weeks (6 weeks for fluoxetine), with the exception of 10 participants who were on medication at the time of MRI scanning. Participants met DSM-IV criteria for MDD or BD based on the Structured Clinical Interview I (SCID-I) for Axis I disorders (First et al., 1997). Depression severity was assessed with the Hamilton Depression Rating Scale (17-item) (Hamilton, 1967, Hamilton, 1960). Healthy volunteers did not have an Axis I diagnosis, based on the non-patient (NP) version of the SCID, or first-degree relatives with a mood disorder or schizophrenia, based on a DSM-IV checklist of diagnostic criteria for family history. All participants underwent physical examination and routine

laboratory screening to exclude pregnancy, neurologic illness, active major medical disease, and evidence of current illicit drug use. A detailed psychiatric history was obtained including self-reported history of physical or sexual abuse. Stressful life experiences within the prior six months were assessed using the St. Paul-Ramsey Scale (Paykel, 1983), which rates the impact of specific stressful life experiences on a 7-point severity scale, from "none" to "catastrophic." This scale is reliable in our hands with an intra-class correlation of 0.96 (Zalsman et al., 2006). The outcome variable used was the highest rating score in any of six categories of life events, called the "global rating." Participants gave written informed consent for participation in the study, which was approved by the New York State Psychiatric Institute IRB.

MRI acquisition and analysis

MRI scans were acquired as described previously (Parsey et al., 2006). Briefly, a sagittal scout localizer scan was performed on a GE 1.5 T Signa Advantage system, followed by a transaxial T1 weighted sequence (1.5 mm slice thickness) in a coronal plane orthogonal to the AC-PC plane, over the whole brain. Scan parameters of the 3-dimensional Spoiled Gradient Recalled Acquisition in the Steady State (SPGR) sequence were as follows: TR 34 msec, TE 5 msec, flip angle 45^{o}, no gap, 124 slices, field of view 22 x 16 cm, 256 x 192 matrix, reformatted to 256 x 256 (yielding a voxel size 1.5 mm x 0.9 mm x 0.9 mm), time of acquisition 11 min.

Coronal MRI images were cropped to remove non-brain material, utilizing the Exbrain v.2 utility (Lemieux et al., 2003). In some cases, the Brain Extraction Tool (BET) v1.2 of the Oxford Centre for Functional Magnetic Resonance Imaging of the

Brain (FMRIB) (Smith, 2002) was used, followed by manual removal of any imaged non-brain matter.

Amygdala volume measurements

Criteria for delineation of the amygdala region of interest (ROI) were developed by author V.A., based on anatomical landmarks, as follows. On consecutive 1.5-mm-thick coronal slices, the amygdala perimeter was manually traced with an electronic mouse using 3D image analysis software (MEDX, Sensor); corresponding sagittal and axial views aided in the accuracy of border definition (see Figure 1). For each participant, the entire rostrocaudal extent of the amygdala was measured and the summed areas were multiplied by the slice thickness to obtain the volume. Anteriorly, the amygdala appeared as an oval mass of gray matter that increased in size in subsequent slices (Bogerts et al., 1990, Niu et al., 2004). Temporal lobe white matter comprised the lateral border; the medial border was separated from the entorhinal cortex by the thin white matter strip, the angular bundle, in the parahippocampal gyrus (Hammers et al., 2003, Niu et al., 2004). The entorhinal sulcus served as the superior border (Hammers et al., 2003, Pruessner et al., 2000). In anterior slices, the inferior border was defined by white matter, whereas in more posterior slices the hippocampus and ventricle served as the inferior border. In the most caudal slices, the amygdala thinned out to a strip of gray matter just dorsal to the alveus and inferior horn of the lateral ventricle (Convit et al., 1999, Pruessner et al., 2000). The optic tract and fundus of the inferior portion of the circular sulcus of the insula defined the dorsal border (Pruessner et al., 2000). Repeated measurements (two raters each traced left and right amygdalae in the same 9 participants)

yielded an intraclass coefficient (ICC) of 0.87 for left amygdala and 0.92 for right amygdala. Raters were blind to diagnosis.

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics (version 23, Armonk, NY). The effects of stress on amygdala volume corrected for mean total cerebral volume (TCV) were examined in separate linear regression models using the following two independent variables: presence or absence of self-reported physical/sexual abuse, and highest category score on the St. Paul-Ramsey scale of stressful life events within the past 6 months. Age, sex, race, and depression status (depressed vs healthy volunteers) were also entered separately into the models as covariates/cofactors. Multivariate repeated measures analyses of stress effects on amygdala volume examined laterality by including side as a covariate and testing for within-subject side by stress interactions. In sensitivity analyses, to control for possible confounds of illness phase or current medication treatment, we removed from the models participants whose depression was in remission (n=8) and (in a separate analysis) those who were on medications (n=10) at time of scan.

RESULTS

Participant characteristics

At the time of scan, all participants with BD (n=21) and 32/40 participants with MDD were acutely depressed, having a Hamilton Depression Rating Scale (HDRS) 17-item score $\geq$ 16. The remaining 8 participants with MDD were in remission (having had at least two lifetime episodes of major depression but not meeting criteria for a major depressive episode during the last 12 months, with an HDRS score of less than 8 on

presentation). Eighty-four percent of depressed participants (n=51) were off psychotropic medications for at least 14 days (6 weeks for fluoxetine and 4 weeks for oral antipsychotics) prior to scanning except for short-acting benzodiazepines or chloral hydrate, which were stopped 3 days prior to scan. Mean duration of time since first lifetime episode of major depression or mania was 16.1 $\pm$ 10.3 years (median 15 years, range 49 years). The depressed group contained a higher proportion of white participants, but depressed and healthy volunteer groups did not differ on the basis of sex, mean age, or years of education (see Table 1).

A history of physical and/or sexual abuse was reported by 28 participants; in 22/28 this occurred prior to age 15. Of depressed participants, 38% reported abuse, compared with 8% of healthy volunteers (χ^2 = 14.7, df=1, p<0.001). The St. Paul-Ramsey Life Events Scale mean score was higher in depressed participants (3.9 $\pm$ 1.0) compared with healthy volunteers (2.8 $\pm$ 1.2; t = 5.09, df =117, p<0.001).

Effects of environmental stress on amygdala volume

Analyses in all participants (depressed and healthy volunteers) found no association between self-reported physical and/or sexual abuse history and amygdala volume (left amygdala, F=0.902, df=1,119, p=0.344; right amygdala, F=0.077, df=1,119, p=0.781). However, life stress within the last six months, as represented by the highest category scores on the St. Paul-Ramsey Scale, was associated with smaller amygdala volume (F=4.59; df=1,116; p=0.034), and the association did not differ by side (within-subject side by stress interaction, F=1.024; df=1,116; p=0.314). When right and left sides were analyzed separately, however, only the left side was significant (left: F=7.580, df=1,117; p=0.007; right: F=1.83, df=1,117, p=0.179). The association between stress

and amygdala volume did not differ significantly between depressed and healthy groups (interaction, F=1.402; df=1,115; p=0.239; see Figure 2.) Thus, the negative correlation between left amygdala volume and life stress was still observed when only the healthy volunteer group (n=60) was considered for recent life stressors (right amygdala, Pearson's r = -0.222, p=0.091; left amygdala, Pearson's r = -0.287, p=0.028). These results remained essentially the same when sex, race, or age were included in the models; no interactions or main effects were observed (data not shown), so they were removed from the models. Sensitivity analyses excluding remitted depressed patients and those on medications did not change the results.

DISCUSSION

Temporal aspects of amygdala volume changes

Our finding that recent life stresses correlate with amygdala volume opens up the possibility that volumetric change may occur rapidly and, if so, future work needs to determine whether it is also rapidly reversible. Consistent with this premise, a large-scale MRI study (n=352) of the effects of early life trauma on brain structure across the life span provides evidence that childhood adversity is associated with smaller amygdala volumes but only in adolescents (Korgaonkar et al., 2013), indicating that volumetric effects were reversed by the time of attaining adulthood. From this we may hypothesize that effects of adversity on amygdala volume are related to the temporal proximity of the stressor, although in the Korgaonker study (Korgaonkar et al., 2013), specific maturation processes could be responsible for brain repair during the transition to adulthood.

Supporting the premise of recent stress as a volumetric influence and opposing the notion of a maturation-specific process, we note that the majority of adult studies in PTSD find no volumetric associations, but several studies that did find smaller amygdala size were investigating trauma that had occurred within 5-10 years previously (Morey et al., 2012, Depue et al., 2014, Matsuoka et al., 2003). Our findings of no volumetric differences associated with childhood abuse history, and smaller left amygdala volumes associated with recent stressful life events comport with this hypothesis and extend it by demonstrating that quite recent events, i.e. within 6 months, may impact amygdala volume, although we cannot be certain whether high stress levels in the past 6 months may reflect characteristically high levels of stress extending back for longer periods of time.

Laterality of amygdala findings

The right amygdala tends to be larger than the left amygdala across diagnostic categories (Woon and Hedges, 2009), and there is a growing body of evidence for different functional roles of right and left amygdala. Meta-analyses and systematic reviews of functional MRI studies of emotion tasks in healthy adults tend to support left lateralized as opposed to bilateral findings (Wager et al., 2003, Baas et al., 2004, Murphy et al., 2003, Sergerie et al., 2008). There is also some evidence for sex-related differences in functional amygdala lateralization, with males showing greater right amygdala activity in emotional contexts (Schneider et al., 2011). These patterns suggest that lateralized amygdala findings are not simply a product of measurement error or acquisition artifact (Mathiak et al., 2012). Multiple theories have been proposed for functional amygdala differences across hemispheres. Some have proposed that amygdala laterality

corresponds to emotional valence (Davidson, 1992) however, this has not borne out in meta-analyses (Sergerie et al., 2008, Wager et al., 2003). An alternative suggestion, based on meta-analytic neuroimaging data of amygdala responses to perception of emotional visual stimuli (Sergerie et al., 2008), is that the right amygdala appears to be involved in rapid detection while the left amygdala subserves longer, more sustained signal processing. If true, then in the context of our study, stress-induced changes to left amygdala may influence the interpretation of emotional stimuli rather than the immediate attentional response to them.

Amygdala volume and depression

Depression status was not a determinant of amygdala size in this study, even controlling for sex and other relevant variables. Other studies, including one from our group (Hastings et al., 2004), disagree as to volumetric deficits in MDD, variously reporting no difference in MDD (Axelson et al., 1993, Coffey et al., 1993, Pantel et al., 1997, Sheline et al., 1999, Ashtari et al., 1999, Bremner et al., 2000, Mervaala et al., 2000, Frodl et al., 2003, Caetano et al., 2004, Frodl et al., 2004, Munn et al., 2007, Lorenzetti et al., 2009) or BD (Swayze et al., 1992, Noga et al., 2001); smaller volumes in MDD (Sheline et al., 1999, von Gunten et al., 2000, Siegle et al., 2003, Hastings et al., 2004, Xia et al., 2004, Tang et al., 2007) and BD (Pearlson et al., 1997, Rosso et al., 2006, Blumberg et al., 2003); or larger volumes in MDD (Frodl et al., 2003, Lange and Irle, 2004, Weniger et al., 2006) and BD (Strakowski et al., 1999, Altshuler et al., 2000, Brambilla et al., 2003, Frangou, 2005). These discrepant findings may be due in part to the effects of psychotropic medications on atrophy through increasing neurotrophic factors (reviewed in (Gray et al., 2003)). This is supported by a meta-regression analysis

of thirteen studies in depression which found that the proportion of patients taking antidepressant medication was associated with greater amygdala volume in depressed compared to healthy participants, and also found larger amygdala volumes in studies of only-medicated depressed patients and smaller volumes in studies of only-unmedicated patients compared with healthy volunteers (Hamilton et al., 2008). Our current findings also suggest that recent levels of life stress are a robust influence on amygdala volume that could be an important confounder of the depression studies.

We did not find the reverse to be true, i.e. depression status did not influence the association of amygdala volumes with stressful life events. However, others (Klimes-Dougan et al., 2014) report that larger amygdala volumes predict HPA functioning differently in MDD and healthy volunteer participants. Using structural MRI and the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), designed to measure stress responses in a laboratory setting, larger amygdala volumes in healthy volunteers predicted more effective stress responses, i.e. lower cortisol levels, as opposed to depressed individuals, in whom larger amygdala volumes predicted higher cortisol levels (Klimes-Dougan et al., 2014). Thus it may be that larger amygdala volumes indicate maladaptive stress responses in depressed individuals, but not in healthy participants.

Limitations of the study

Most of the depressed patients in our study were off medications for at least 2 weeks, and this may not have been long enough to reverse any beneficial medication effects on brain structure.

Conclusions

We find smaller left amygdala volume in association with more life stresses in the preceding 6 months, independent of the presence of depression. Therefore, association of life stress and amygdala size could be a source of sample bias contributing to heterogeneity of previous results among studies of amygdala volume and depression. What remains to be demonstrated by future, longitudinal studies is whether a causal relationship exists between stressful life events and amygdala volume, and the time course of potential reversibility of volume changes.

Titles and Legends to Figures and Tables:

Figure 1. Amygdala region of interest measurement from magnetic resonance images. Representative amygdala tracings from coronal images of a single subject are shown. The series is pictured here from caudal to rostral, with 6 intervening slices omitted for clarity of visualization.

Figure 2. Associations between St. Paul Ramsey Life Events Scale and left amygdala volume, stratified by diagnosis. Correlations between left amygdala volume, normalized for total cerebral volume, and highest score (range 0-6) on the St. Paul-Ramsey Life Events Scale (F=7.58, r=0.24, df=117, p = 0.007). Gray markers = depressed participants; black markers = healthy volunteers. Data are jittered for easier visibility.

Table 1. Demographic characteristics of sample population.

Demographic characteristics are compared between depressed subjects and healthy volunteers. Data are mean ± SD unless otherwise indicated.

References

Altshuler, L.L., Bartzokis, G., Grieder, T., Curran, J., Jimenez, T., Leight, K., Wilkins, J., Gerner, R.Mintz, J., 2000. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry. 48**,** 147-62.

Ashtari, M., Greenwald, B.S., Kramer-Ginsberg, E., Hu, J., Wu, H., Patel, M., Aupperle, P.Pollack, S., 1999. Hippocampal/amygdala volumes in geriatric depression. Psychol Med. 29**,** 629-38.

Axelson, D.A., Doraiswamy, P.M., Mcdonald, W.M., Boyko, O.B., Tupler, L.A., Patterson, L.J., Nemeroff, C.B., Ellinwood, E.H., Jr.Krishnan, K.R., 1993. Hypercortisolemia and hippocampal changes in depression. Psychiatry Res. 47**,** 163-73.

Baas, D., Aleman, A.Kahn, R.S., 2004. Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. Brain Res Brain Res Rev. 45**,** 96-103.

Blumberg, H.P., Kaufman, J., Martin, A., Whiteman, R., Zhang, J.H., Gore, J.C., Charney, D.S., Krystal, J.H.Peterson, B.S., 2003. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry. 60**,** 1201-8.

Bogerts, B., Ashtari, M., Degreef, G., Alvir, J.M., Bilder, R.M.Lieberman, J.A., 1990. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res. 35**,** 1-13.

Bonne, O., Brandes, D., Gilboa, A., Gomori, J.M., Shenton, M.E., Pitman, R.K.Shalev, A.Y., 2001. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am J Psychiatry. 158**,** 1248-51.

Brambilla, P., Harenski, K., Nicoletti, M., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S.Soares, J.C., 2003. MRI investigation of temporal lobe structures in bipolar patients. J Psychiatr Res. 37**,** 287-95.

Bremner, J.D., Narayan, M., Anderson, E.R., Staib, L.H., Miller, H.L.Charney, D.S., 2000. Hippocampal volume reduction in major depression. Am J Psychiatry. 157**,** 115-8.

Bremner, J.D., Randall, P., Vermetten, E., Staib, L., Bronen, R.A., Mazure, C., Capelli, S., Mccarthy, G., Innis, R.B.Charney, D.S., 1997. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. Biol Psychiatry. 41**,** 23-32.

Caetano, S.C., Hatch, J.P., Brambilla, P., Sassi, R.B., Nicoletti, M., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S.Soares, J.C., 2004. Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. Psychiatry Res. 132**,** 141-7.

Coffey, C.E., Wilkinson, W.E., Weiner, R.D., Parashos, I.A., Djang, W.T., Webb, M.C., Figiel, G.S.Spritzer, C.E., 1993. Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. Arch Gen Psychiatry. 50**,** 7-16.

Convit, A., Mchugh, P., Wolf, O.T., De Leon, M.J., Bobinski, M., De Santi, S., Roche, A.Tsui, W., 1999. MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. Psychiatry Res. 90**,** 113-23.

Davidson, R.J., 1992. Anterior cerebral asymmetry and the nature of emotion. Brain Cogn. 20**,** 125-51.

Depue, B.E., Olson-Madden, J.H., Smolker, H.R., Rajamani, M., Brenner, L.A.Banich, M.T., 2014. Reduced amygdala volume is associated with deficits in inhibitory control: a voxel- and surface-based morphometric analysis of comorbid PTSD/mild TBI. Biomed Res Int. 2014**,** 691505.

Fennema-Notestine, C., Stein, M.B., Kennedy, C.M., Archibald, S.L.Jernigan, T.L., 2002. Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. Biol Psychiatry. 52**,** 1089-101.

First, M., Williams, J., Spitzer, R.Gibbon, M. 1997. *Structured Clinical Interview for DSM-IV Axis I Disorders,* Washington D.C., American Psychiatric Publishing, Inc.

Frangou, S., 2005. The Maudsley bipolar disorder project. Epilepsia. 46 Suppl 4**,** 19-25.

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Born, C., Jager, M., Groll, C., Bottlender, R., Leinsinger, G.Moller, H.J., 2003. Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. Biol Psychiatry. 53**,** 338-44.

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Hohne, T., Banac, S., Schorr, C., Jager, M., Leinsinger, G., Bottlender, R., Reiser, M.Moller, H.J., 2004. Hippocampal and

amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. J Clin Psychiatry. 65**,** 492-9.

Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P.Pitman, R.K., 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci. 5**,** 1242-7.

Gray, N., Zhou, R., Du, J., Moore, G.Manji, H., 2003. The use of mood stabilizers as plasticity enhancers in the treatment of neuropsychiatric disorders. J Clin Psychiatry. 64 Suppl 5**,** 3-17.

Gurvits, T.V., Shenton, M.E., Hokama, H., Ohta, H., Lasko, N.B., Gilbertson, M.W., Orr, S.P., Kikinis, R., Jolesz, F.A., Mccarley, R.W.Pitman, R.K., 1996. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry. 40**,** 1091-9.

Hamilton, J.P., Siemer, M.Gotlib, I.H., 2008. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Mol Psychiatry. 13**,** 993-1000.

Hamilton, M., 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry. 23**,** 56-62.

Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 6**,** 278-96.

Hammers, A., Allom, R., Koepp, M.J., Free, S.L., Myers, R., Lemieux, L., Mitchell, T.N., Brooks, D.J.Duncan, J.S., 2003. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum Brain Mapp. 19**,** 224-47.

Hastings, R.S., Parsey, R.V., Oquendo, M.A., Arango, V.Mann, J.J., 2004. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. Neuropsychopharmacology. 29**,** 952-9.

Henckens, M.J., Van Der Marel, K., Van Der Toorn, A., Pillai, A.G., Fernandez, G., Dijkhuizen, R.M.Joels, M., 2015. Stress-induced alterations in large-scale functional networks of the rodent brain. Neuroimage. 105**,** 312-22.

Kerchner, M., Malsbury, C.W., Ward, O.B.Ward, I.L., 1995. Sexually dimorphic areas in the rat medial amygdala: resistance to the demasculinizing effect of prenatal stress. Brain Res. 672**,** 251-60.

Kirschbaum, C., Pirke, K.M.Hellhammer, D.H., 1993. The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 28**,** 76-81.

Klimes-Dougan, B., Eberly, L.E., Westlund Schreiner, M., Kurkiewicz, P., Houri, A., Schlesinger, A., Thomas, K.M., Mueller, B.A., Lim, K.O.Cullen, K.R., 2014. Multilevel assessment of the neurobiological threat system in depressed adolescents: interplay between the limbic system and hypothalamic-pituitary-adrenal axis. Dev Psychopathol. 26**,** 1321-35.

Korgaonkar, M.S., Antees, C., Williams, L.M., Gatt, J.M., Bryant, R.A., Cohen, R., Paul, R., O'hara, R.Grieve, S.M., 2013. Early exposure to traumatic stressors impairs emotional brain circuitry. PLoS One. 8**,** e75524.

Lange, C.Irle, E., 2004. Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. Psychol Med. 34**,** 1059-64.

Lemieux, L., Hammers, A., Mackinnon, T.Liu, R.S., 2003. Automatic segmentation of the brain and intracranial cerebrospinal fluid in T1-weighted volume MRI scans of the head, and its application to serial cerebral and intracranial volumetry. Magn Reson Med. 49**,** 872-84.

Levy-Gigi, E., Szabo, C., Kelemen, O.Keri, S., 2013. Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. Biol Psychiatry. 74**,** 793-800.

Lindauer, R.J., Vlieger, E.J., Jalink, M., Olff, M., Carlier, I.V., Majoie, C.B., Den Heeten, G.J.Gersons, B.P., 2004. Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. Biol Psychiatry. 56**,** 356-63.

Lorenzetti, V., Allen, N.B., Whittle, S.Yücel, M., 2009. Amygdala volumes in a sample of current depressed and remitted depressed patients and healthy controls. Journal of Affective Disorders.

Ma, S.Morilak, D.A., 2005. Norepinephrine release in medial amygdala facilitates activation of the hypothalamic-pituitary-adrenal axis in response to acute immobilisation stress. J Neuroendocrinol. 17**,** 22-8.

Mathiak, K.A., Zvyagintsev, M., Ackermann, H.Mathiak, K., 2012. Lateralization of amygdala activation in fMRI may depend on phase-encoding polarity. MAGMA. 25**,** 177-82.

Matsuoka, Y., Yamawaki, S., Inagaki, M., Akechi, T.Uchitomi, Y., 2003. A volumetric study of amygdala in cancer survivors with intrusive recollections. Biol Psychiatry. 54**,** 736-43.

Merke, D.P., Fields, J.D., Keil, M.F., Vaituzis, A.C., Chrousos, G.P.Giedd, J.N., 2003. Children with classic congenital adrenal hyperplasia have decreased amygdala volume: potential prenatal and postnatal hormonal effects. J Clin Endocrinol Metab. 88**,** 1760-5.

Mervaala, E., Fohr, J., Kononen, M., Valkonen-Korhonen, M., Vainio, P., Partanen, K., Partanen, J., Tiihonen, J., Viinamaki, H., Karjalainen, A.K.Lehtonen, J., 2000. Quantitative MRI of the hippocampus and amygdala in severe depression. Psychol Med. 30**,** 117-25.

Mitra, R., Jadhav, S., Mcewen, B.S., Vyas, A.Chattarji, S., 2005. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci U S A. 102**,** 9371-6.

Mitra, R.Sapolsky, R.M., 2008. Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. Proc Natl Acad Sci U S A. 105**,** 5573-8.

Morey, R.A., Gold, A.L., Labar, K.S., Beall, S.K., Brown, V.M., Haswell, C.C., Nasser, J.D., Wagner, H.R., Mccarthy, G.Mid-Atlantic, M.W., 2012. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry. 69**,** 1169-78.

Munn, M.A., Alexopoulos, J., Nishino, T., Babb, C.M., Flake, L.A., Singer, T., Ratnanather, J.T., Huang, H., Todd, R.D., Miller, M.I.Botteron, K.N., 2007. Amygdala volume analysis in female twins with major depression. Biol Psychiatry. 62**,** 415-22.

Murphy, F.C., Nimmo-Smith, I.Lawrence, A.D., 2003. Functional neuroanatomy of emotions: a meta-analysis. Cogn Affect Behav Neurosci. 3**,** 207-33.

Niu, L., Matsui, M., Zhou, S.Y., Hagino, H., Takahashi, T., Yoneyama, E., Kawasaki, Y., Suzuki, M., Seto, H., Ono, T.Kurachi, M., 2004. Volume reduction of the amygdala in patients with schizophrenia: a magnetic resonance imaging study. Psychiatry Res. 132**,** 41-51.

Noga, J.T., Vladar, K.Torrey, E.F., 2001. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res. 106**,** 25-34.

Pantel, J., Schroder, J., Essig, M., Popp, D., Dech, H., Knopp, M.V., Schad, L.R., Eysenbach, K., Backenstrass, M.Friedlinger, M., 1997. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. J Affect Disord. 42**,** 69-83.

Parsey, R.V., Kent, J.M., Oquendo, M.A., Richards, M.C., Pratap, M., Cooper, T.B., Arango, V.Mann, J.J., 2006. Acute Occupancy of Brain Serotonin Transporter by Sertraline as Measured by [(11)C]DASB and Positron Emission Tomography. Biol Psychiatry. 59**,** 821-8.

Paykel, E.S., 1983. Methodological aspects of life events research. J Psychosom Res. 27**,** 341-52.

Pearlson, G.D., Barta, P.E., Powers, R.E., Menon, R.R., Richards, S.S., Aylward, E.H., Federman, E.B., Chase, G.A., Petty, R.G.Tien, A.Y., 1997. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol Psychiatry. 41**,** 1-14.

Pruessner, J.C., Li, L.M., Serles, W., Pruessner, M., Collins, D.L., Kabani, N., Lupien, S.Evans, A.C., 2000. Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. Cereb Cortex. 10**,** 433-42.

Rosso, I.M., Killgore, W.D., Cintron, C.M., Gruber, S.A., Tohen, M.Yurgelun-Todd, D.A., 2006. Reduced Amygdala Volumes in First-Episode Bipolar Disorder and Correlation with Cerebral White Matter. Biol Psychiatry.

Salm, A.K., Pavelko, M., Krouse, E.M., Webster, W., Kraszpulski, M.Birkle, D.L., 2004. Lateral amygdaloid nucleus expansion in adult rats is associated with exposure to prenatal stress. Brain Res Dev Brain Res. 148**,** 159-67.

Sapolsky, R.M., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 57**,** 925-35.

Schneider, S., Peters, J., Bromberg, U., Brassen, S., Menz, M.M., Miedl, S.F., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Conrod, P.J., Dalley, J.W., Flor, H., Gallinat, J., Garavan, H., Heinz, A., Itterman, B., Mallik, C., Mann, K., Artiges, E., Paus, T., Poline, J.B., Rietschel, M., Reed, L., Smolka, M.N., Spanagel, R., Speiser, C., Strohle, A., Struve, M., Schumann, G., Buchel, C.Consortium, I., 2011. Boys do it the right way: sex-dependent amygdala lateralization during face processing in adolescents. Neuroimage. 56**,** 1847-53.

Sergerie, K., Chochol, C.Armony, J.L., 2008. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 32**,** 811-30.

Sheline, Y.I., Gado, M.H.Price, J.L., 1998. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport. 9**,** 2023-8.

Sheline, Y.I., Sanghavi, M., Mintun, M.A.Gado, M.H., 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 19**,** 5034-43.

Siegle, G.J., Konecky, R.O., Thase, M.E.Carter, C.S., 2003. Relationships between amygdala volume and activity during emotional information processing tasks in depressed and never-depressed individuals: an fMRI investigation. Ann N Y Acad Sci. 985**,** 481-4.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum Brain Mapp. 17**,** 143-55.

Strakowski, S.M., Delbello, M.P., Sax, K.W., Zimmerman, M.E., Shear, P.K., Hawkins, J.M.Larson, E.R., 1999. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry. 56**,** 254-60.

Swayze, V.W., 2nd, Andreasen, N.C., Alliger, R.J., Yuh, W.T.Ehrhardt, J.C., 1992. Subcortical and temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. Biol Psychiatry. 31**,** 221-40.

Tang, Y., Wang, F., Xie, G., Liu, J., Li, L., Su, L., Liu, Y., Hu, X., He, Z.Blumberg, H.P., 2007. Reduced ventral anterior cingulate and amygdala volumes in medication-naive females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. Psychiatry Res. 156**,** 83-6.

Von Gunten, A., Fox, N.C., Cipolotti, L.Ron, M.A., 2000. A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. J Neuropsychiatry Clin Neurosci. 12**,** 493-8.

Vyas, A., Mitra, R., Shankaranarayana Rao, B.S.Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci. 22**,** 6810-8.

Wager, T.D., Phan, K.L., Liberzon, I.Taylor, S.F., 2003. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage. 19**,** 513-31.

Weniger, G., Lange, C.Irle, E., 2006. Abnormal size of the amygdala predicts impaired emotional memory in major depressive disorder. J Affect Disord. 94**,** 219-29.

Wignall, E.L., Dickson, J.M., Vaughan, P., Farrow, T.F., Wilkinson, I.D., Hunter, M.D.Woodruff, P.W., 2004. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. Biol Psychiatry. 56**,** 832-6.

Woon, F.L.Hedges, D.W., 2009. Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. J Neuropsychiatry Clin Neurosci. 21**,** 5-12.

Xia, J., Chen, J., Zhou, Y., Zhang, J., Yang, B., Xia, L.Wang, C., 2004. Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression. J Huazhong Univ Sci Technolog Med Sci. 24**,** 500-2, 506.

Yang, R.J., Mozhui, K., Karlsson, R.M., Cameron, H.A., Williams, R.W.Holmes, A., 2008. Variation in mouse basolateral amygdala volume is associated with differences in stress reactivity and fear learning. Neuropsychopharmacology. 33**,** 2595-604.

Zalsman, G., Huang, Y.Y., Oquendo, M.A., Burke, A.K., Hu, X.Z., Brent, D.A., Ellis, S.P., Goldman, D.Mann, J.J., 2006. Association of a triallelic serotonin

transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. Am J Psychiatry. 163**,** 1588-93.

Figure 1. Amygdala region of interest measurement from magnetic resonance images.

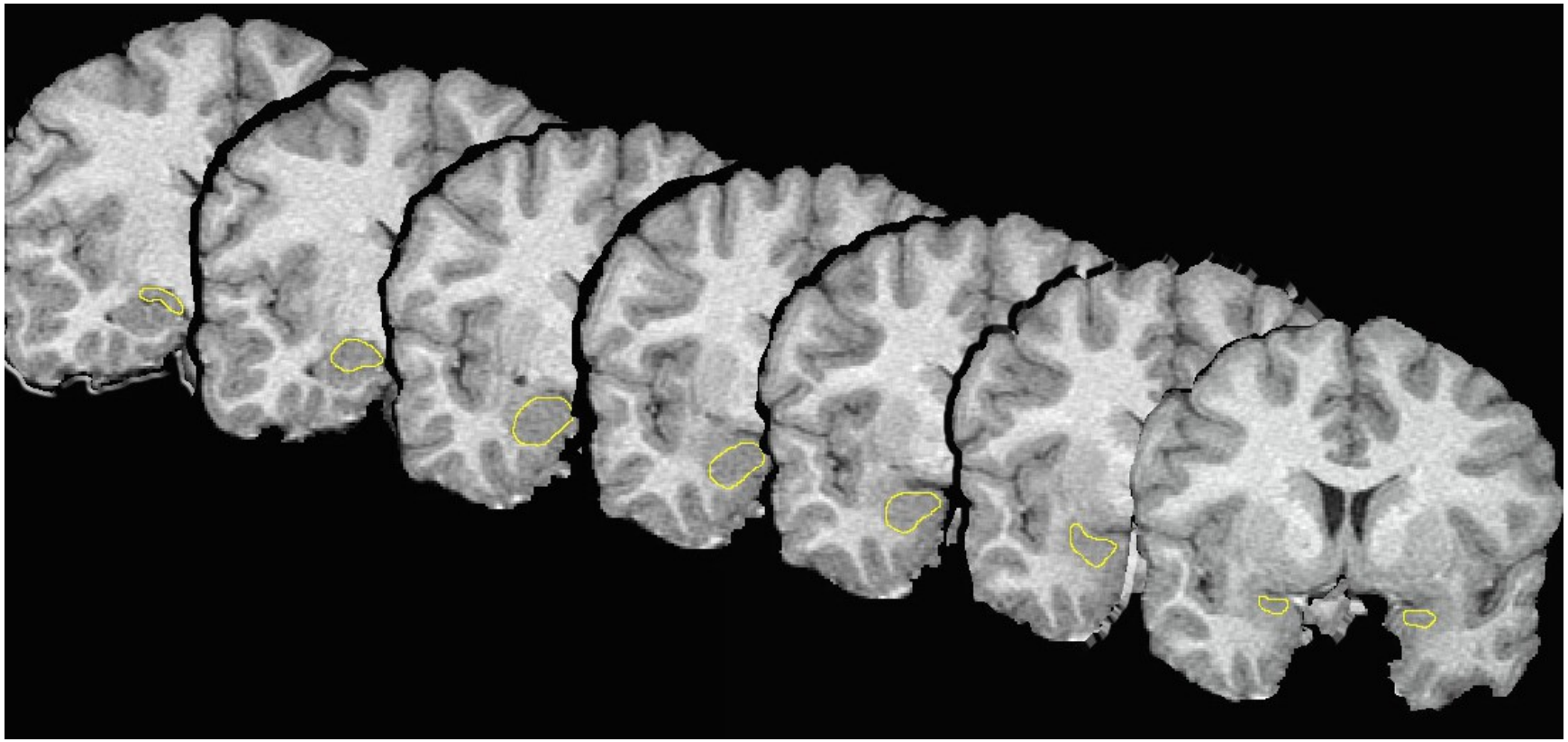

Figure 2. Association between St. Paul Ramsey Life Events Scale and left amygdala volume, stratified by diagnosis.

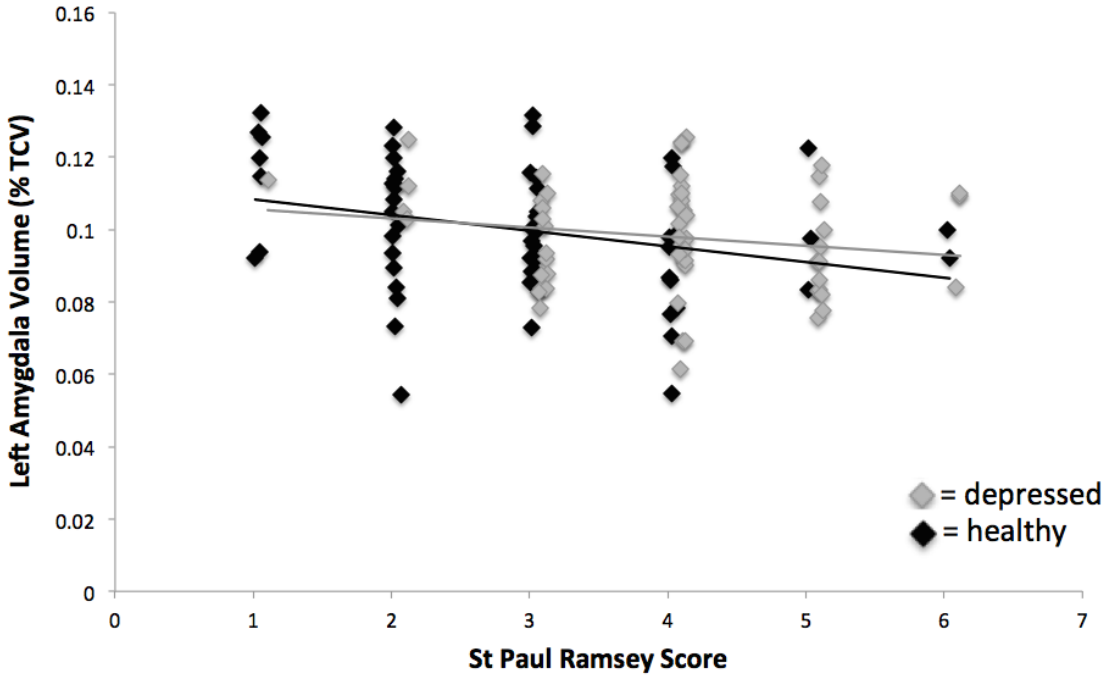

Table 1. Demographic characteristics of sample population.

	n	**Depressed** (*n* =61)	***n***	**Healthy** (*n* =60)	***t***	***df***	***p*-value**
Age, mean ± SD, years	60	37.8 ± 11.8	60	34.9 ± 13.8	-1.247	118	0.215
Sex, *n* (%) male	61	24 (39.3)	60	30 (50.0)	-1.176	119	0.240
Race, *n* (%) white	52	43 (70.5)	50	27 (45.0)	-3.250	100	0.002
Total Education, mean ± SD, yrs	61	15.5 ± 2.8	60	16.4 ± 2.9	1.624	119	0.107
Annual Income, mean ± SD, $K	59	23.1 ± 23.4	59	31.3 ± 28.5	1.704	116	0.091

Highlights

(1) Smaller left amygdala volumes were associated with stressful life events within six months - suggesting that relatively short-term stress can have measurable structural effects.

(2) No association was seen between amygdala volume and childhood physical/sexual abuse history - suggesting that over time volume may renormalize.

(3) Stress effects on amygdala volume did not differ between depressed and healthy participants; thus history of stress may be a confounder in studies of amygdala volume and depression.