Published in final edited form as:

J Trauma Stress. 2017 October ; 30(5): 537–544. doi:10.1002/jts.22222.

A Pilot Study of Reduced Olfactory Bulb Volume as a Marker of PTSD in Childhood Trauma-Exposed Adult HIV-Infected Patients

Evaristus A. Nwulia¹, Narayan Rai¹, Kamyar Sartip², MariaMananita S. Hipolito¹, Charlee K. McLean¹, Kyla Flanagan³, Flora Hamilton³, Sharon Lambert⁴, Huynh-Nhu Le⁴, John VanMeter⁵, and Suad Kapetanovic⁶

¹Department of Psychiatry and Behavioral Sciences, Howard University, Washington, DC, USA

²Department of Radiology, Howard University, Washington, DC, USA

³Family and Medical Counseling Service, Inc., Washington, DC, USA

⁴Department of Psychology, George Washington University, Washington, DC, USA

⁵Department of Neurology, Center for Functional and Molecular Imaging, Georgetown University Medical Center, Washington, DC, USA

⁶Department of Psychiatry, University of Southern California, Los Angeles, California, USA

Abstract

Evidence suggests that olfactory bulb (OB), a key structure in odor processing, may also be involved in mechanisms of traumatic stress. In animals, chronic stress reduces OB plasticity, and olfactory bulbectomy results in stress-enhanced startle reflex and autonomic dysregulation. However, OB morphometry has not been adequately studied in the development of stress disorders following childhood trauma in humans. We conducted a pilot study evaluating the relationships between OB volume, childhood trauma, and lifetime posttraumatic stress disorder (PTSD) in a sample of 16 HIV-positive individuals, 13 of whom were exposed to childhood trauma, of which 9 developed PTSD. Participants were recruited from a larger cohort of inner city-dwelling HIV-positive populations in Washington DC. Mean OB volumes were significantly reduced when PTSD and non-PTSD groups ($p = .019$) were compared, as well as when trauma-exposed PTSD-positive and trauma-exposed PTSD-negative groups ($p = .008$) were compared. No significant difference was observed when trauma-exposed and nonexposed participants were compared. The association between PTSD and right OB volume remained strong ($p < .010$) after adjusting for group differences in sex, age, depression, hippocampal volume, and total intracranial volume. Because this study is limited by small sample size, further elucidation of relationships between OB, trauma, and PTSD should be investigated in larger cross-sectional and prospective studies and in diverse cohorts.

Elucidating the biological factors that moderate the development of chronic stress disorders such as posttraumatic stress disorder (PTSD) and identifying the social and cultural

mechanisms at the interface of stress vulnerability and stress resilience promises to improve efforts to identify people at risk, implementing interventions promptly, and develop novel interventions engaging individual-level biomarkers (Auxemery, 2012). For instance, if the structure or integrity of the olfactory bulb (OB) is associated with the development of, or resilience from, PTSD following trauma exposure, then these structures could potentially be used as biomarkers for proof-of-concept of olfactory training (Altundag et al., 2015; Negoias, Pietsch, & Hummel, 2016). Our current understanding of the neurobiological effects of trauma is largely informed by preclinical studies that have demonstrated that biologically relevant adversity exerts lasting effects on vulnerable areas of the brain, notably the hippocampus, amygdala, and medial prefrontal cortex (Bremner, 2006). Additionally, preclinical evidence indicates that OB ablation results in enhanced auditory startle reflex, activated hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysregulation, impaired hippocampal neurogenesis, and structural reorganization of other limbic regions involved in the neurobiology of stress (Jaako-Movits, Zharkovsky, Pedersen, & Zharkovsky, 2006; Lumia, Teicher, Salchli, Ayers, & Possidente, 1992; McNish & Davis, 1997; Morales-Medina et al., 2013; Song & Leonard, 2005; Yang et al., 2014). Moreover, OB is highly enriched in corticotropin-releasing factor (CRF) receptor 1 (Imaki, Nahon, Sawchenko, & Vale, 1989; Van Pett et al., 2000) and glucocorticoid receptors (Morimoto, Morita, Ozawa, Yokoyama, & Kawata, 1996), chronic activation of which leads to neuronal cell death and atrophy. Therefore, investigation of OB may help identify a clinical biomarker of susceptibility and/or resilience to development of PTSD.

More than 50% of HIV-positive (HIV+) individuals are survivors of psychological trauma (Brief et al., 2004). In HIV+ populations, trauma and childhood adversity have been associated not only with the development of PTSD and other psychiatric disorders, but also with higher rates of sexual and substance use behaviors that may result in transmission of HIV to others and nonadherence to antiretroviral therapy (Pence et al., 2012; Whetten et al., 2012). Therefore, improved understanding of the mechanisms underlying PTSD and other consequences of psychological trauma in HIV+ populations might have significant clinical, research, and public health implications.

We conducted a pilot study on a sample of HIV+ participants with or without severe childhood trauma, to obtain preliminary data on the independent associations between OB volume, trauma exposure, and lifetime PTSD, after adjusting for group differences in sex, age, depression severity, hippocampal volume, and total intracranial volume. We hypothesized that right and left OB volumes would be significantly, independently associated with PTSD.

Method

Participants and Procedure

Participants in this pilot study were recruited from a larger cohort of participants who were participating in an ongoing study aimed at developing cultural adaptations of evidence-based interventions for depression in medically-underserved communities in Southeast Washington, DC. Participants were asked to respond to questionnaires targeting their background, demographic, social, and medical history. Study procedures were approved by

the Howard University Institutional Review Board for the ethical conduct of research involving human participants in accordance with the Declaration of Helsinki; participants provided written informed consent to participate.

This substudy was initiated by a small institutional pilot fund aimed at developing novel research ideas from the parent study. To identify childhood trauma, we screened all patients for criterion A1 exposures of PTSD, in accordance with the *DSM-IV* diagnostic criteria (American Psychiatric Association, 2000). For participants who responded affirmative to the A1 questions, we subsequently inquired about Criterion A2 experience. Then, we asked if any of these A1 events happened when the participant was between the ages of 3 and 12 years, or after that time period. Finally, we surveyed for non-A1 Criterion events using the Childhood Life Exposures Screening questionnaire (Anand et al., 2015). To be included in the childhood trauma-exposed group, a participant must have met criterion A1, only as a child (i.e. before the age of 13 years). Inclusion as a control participant for childhood trauma exposure required absence of both A1 and non-A1 events, as non-A1 events can be significant as well (Alessi, Meyer, & Martin, 2013). We defined PTSD based on A1 criteria, along with meeting *DSM-IV* requirements for Criterion B through F. The coefficient of inter-rater agreement (i.e. Cohen's kappa) between the two raters (EN and MH) for PTSD is .97. We also determined whether those participants with a lifetime PTSD diagnosis met the criteria within the past month. Because our sample size was limited by funding, we decided to exclude people with head trauma, stroke, severe neurological diseases (e.g. multiple sclerosis), noncompliance on antiretroviral therapy, CD4 counts less than 350, detectable viral load, AIDS defining illness, and current substance use disorder in order to minimize confounding effects. A total of 17 participants were eligible for this substudy.

Measures

Diagnostic interview—All participants received a comprehensive psychiatric diagnostic interview, with the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) performed by the study psychiatrist (EN) and a psychiatry research associate with 10 years of experience (MH). The coefficient of agreement (i.e., kappa coefficient) between EN and MH for major depression and PTSD are .94 and .97, respectively.

Client Diagnostic Questionnaire (CDQ)(Aidala et al., 2004)—All participants also completed self-report surveys in the CDQ, which is a collection of screening tools for depression, anxiety, PTSD, and substance use in clinical populations (Aidala et al., 2004). It has a sensitivity of 91%, specificity of 78%, and an overall accuracy of 85% (Aidala et al., 2004). The depression severity screening component of the CDQ is the well-validated patient health questionnaire, PHQ-9 (Aidala et al., 2004). In a study examining the criterion validity of PHQ-9 using the Mental Health Professional interview as the criterion standard, a PHQ-9 score ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression (Kroenke., Spitzer, & Williams, 2001).

Cambridge Neuropsychological Test Automated Battery (CANTAB; (Fray & Robbins, 1996)—Verbal recognition memory (VRM) was assessed in all participants using the CANTAB. Verbal recognition memory measures verbal memory and new learning,

including the ability to encode and subsequently retrieve verbal information, with recall tapping into fronto-temporal networks and recognition assessing hippocampal areas (Peters, Thoma, Koch, Schwarz, & Daum, 2009). In our previous pilot repeat testing of 10 patients, 4 weeks apart the point estimates of test-retest Pearson's correlations for VRM recall and recognition were .89 and .92, respectively.

Magnetic resonance imaging (MRI) acquisition, anatomical localization, and image processing—We implemented a well-documented approach for measurement of OB volume (Rombaux, Potier, Bertrand, Duprez, & Hummel, 2008; Rombaux et al., 2006). Participants were examined following a standard protocol on a 3.0 Tesla Signa HDx scanner (General Electric Medical Systems, Milwaukee, WI). A T2-weighted fast spin-echo sequence of the OB was then performed with the following parameters: repetition time (TR) = 2066 ms, echo time (TE) = 80 ms, echo train length = 13, slice thickness = 2 mm without gap, FOV (field of view) = 160 x 130, acquisition matrix = 3403 273 (in-plane resolution = 0.47 x 0.48 mm²) and reconstruction matrix = 512 x 512 (in-plane resolution = 0.31 x 0.31 mm²), and number of signal average = 4. Acquisition time was 5 min, 51 s.

Afterwards, 23 slices were placed in coronal planes perpendicular to the cribriform plane and covering the middle segment of the basifrontal area. The OB volumes were calculated by planimetric manual contouring on each slice, where it was present in the coronal plane, and surfaces were then multiplied by the 2-mm thickness of slices to obtain a volume in mm³. These measurements were performed twice by 2 observers (JVM and PW). A third observer was used when the volumes between these two observers showed a difference of > 10%. Images acquired from two participants were very noisy (i.e. full of artifacts), leading to unreliable measures, and a third observer advised against using those poorly acquired images; although these two participants were contacted and asked to come in for repeat imaging, only one returned. In the end, we had reliable images from 16 participants. Intraclass correlations between observers for left and right OB volumes from these 16 participants were .90 (95% CI [.72, .97]) and .92 (95% CI [.76, .97]), respectively. Hippocampal volumes were calculated by manually tracing the structure using the MIPAV software (<https://mipav.cit.nih.gov>). The boundaries of the hippocampus were identified first in the sagittal plane, followed by correction as necessary by verifying the boundaries in coronal plane (Konrad et al., 2009). Total intracranial volume (TIV) was calculated by using the Segment and Tissue Volumes functions in SPM12 (Malone et al., 2015).

Psychophysical tasks of olfaction—This was performed using the OLFACCT-Combo (Osmic Enterprises, Inc. OH), a flow-dilution olfactometer (Johnson & Sobel, 2007). This olfactometer delivers different odorants intranasally for clinical assessment of odor identification (OI), odor memory (OM), odor threshold (OT), and odor discrimination (OD; Doty, 2001). In our previous studies of 15 individuals that received repeated assessments 6 weeks apart, estimated intraclass correlations for OI, OM, OT and OD through olfactometry were, .86, .84, .77 and .79 respectively. The general consensus in the field is that adequate performance on odor threshold requires just the integrity of the peripheral olfactory system (Breer, Fleischer, & Strotmann, 2006; Doty, 2001; Patel & Pinto, 2014). However, we also included scores on higher-order olfactory tasks as well (Table 1).

Data Analysis

All statistical analyses were conducted in Stata 13 (StataCorp. 2013). We used the Student *t* test to compute mean estimates of continuous variables between groups; *p* values for group differences in nonnormal continuous variables were derived from Mann-Whitney rank test. Chi-square and exact tests were used to compare categorical variables (e.g. gender). Huber and White sandwich estimators were used to derive robust standard errors for *p* values in all regression analyses (Huber, 1976; White, 1980). All correlations, including kappa, Pearson's and intraclass correlations, were estimated using the 'Correlations and Covariances' suite in Stata 13. Results of linear regression analysis were presented as beta coefficients, robust standard errors of these coefficients, *t* statistics, *p* values, and R^2 (i.e. the proportion of variance explained by each statistical model).

Results

Participants' Characteristics

Distributions of demographic and clinical characteristics of the 16 participants, by lifetime PTSD status, are shown in Table 1. The two groups were comparable in: demographic features including age, gender, self-reported ethnicity, education, religious affiliation, and employment status; behavioral features including lifetime diagnosis of substance dependence, depression, anxiety, and prescribed psychotropics; and cognitive features including VRM and olfactory tasks. Similarly, no significant group differences in CD4 counts or viral loads were observed. There were no missing values for any of these variables in all 16 participants.

Relationship between Olfactory Bulb Volumes, Trauma Exposure, and PTSD

Differences in the mean left and right OB volumes comparing the group with PTSD ($n = 9$) with the group without PTSD ($n = 7$) are highlighted in Figure 1A. The mean left OB volumes in the PTSD and non-PTSD groups were 25.10 mm³ ($SD = 8.22$) and 46.23 mm³ ($SD = 18.50$), respectively ($p = .013$). The mean right OB volume in the PTSD group was 25.93 mm³ ($SD = 12.84$) compared with 47.99 mm³ ($SD = 19.12$) in the non-PTSD group, $p = .019$. Figure 1 also depicts OB comparisons between trauma-exposed group ($n = 13$) versus nonexposed group ($n = 3$), and between the trauma-exposed group in which participants developed PTSD ($n = 9$) versus the trauma-exposed group in which participant did not develop PTSD ($n = 4$). As shown in Figure 1B, the mean left and right OB volumes in trauma-exposed versus unexposed groups were not significantly different, $p = .979$ and $p = .793$, respectively. Among trauma-exposed individuals, the left OB volumes comparing those who developed PTSD with those who did not were 25.10 mm³ ($SD = 8.22$) versus 55.26 mm³ ($SD = 19.11$), respectively, $p = .008$; and corresponding measures for right OB were 25.93 mm³ ($SD = 12.84$) versus 55.09 mm³ ($SD = 19.12$), respectively, $p = .003$ (Figure 1C).

Results of multivariate regression analyses estimating the independent mean 'effect' (i.e. beta coefficient) of having a PTSD diagnosis on the mean OB volumes, adjusting for sex and age differences (Model 1) and including depression severity (i.e. Model 2) are shown in Table 2. In Model 1, PTSD was independently associated with 21.31 mm³ mean reduction of

left OB, $SE = 6.36$, $t(3) = -3.35$, $p = .006$, $R^2 = .45$, and with 25.74 mm^3 mean reduction of right OB volume, $SE = 4.90$, $t(3) = -5.25$, $p < .001$, $R^2 = .75$. These statistical relationships remained significant with inclusion of depression severity in the Model 2. We also included adjustment for the ipsilateral hippocampal volume to the latter model (i.e. Model 3) and finally, for all covariates in Model 3 with the inclusion of total intracranial volume, TIV (i.e. Model 4). The level of significance and strength of association between PTSD and reduced right OB volume remained very strong (Table 2). Posthoc power analysis revealed that, given a 5% error rate, we had power of .99 and .80, to detect the effects of PTSD on right OB and left OB, respectively. Table 2 also shows the results of unadjusted associations between PHQ-9 scores and left and right OB, as well as multivariate models adjusting for sex, age and hippocampi (Model 1) and sex, age, hippocampi and TIV (Model 2). None of these models revealed a significant relationship between PHQ-9 and OB volumes.

Discussion

In this sample, lifetime diagnosis of PTSD was associated with lower OB volumes bilaterally. Moreover, both OB volumes were substantially higher among trauma-exposed participants who did not develop PTSD, compared with trauma-exposed individuals who developed PTSD. These preliminary findings suggest a direct involvement of OB in the mechanism of PTSD. However, like most pilot studies, the present study is aimed at developing testable hypotheses for future adequately powered studies, and given the small sample size of this pilot, we recommend cautionary interpretations. In this context, we discuss several thought-provoking findings from the present study, along with the relevant limitations of study design.

It was surprising that severity of current depression was not associated with olfactory OB volumes. However, it should be noted that studies comparing OB volumes between depressed and nondepressed human populations are also remarkably few. At the time of writing our work, only two studies from the same group of authors have actually shown good or modest relationship between OB volume and depression (Negoias et al., 2010; Negoias, Hummel, et al., 2016). While these latter studies are quite informative, replication of their findings by other authors and in other populations are needed to demonstrate consistency of the independent relationship between OB and depression. The only other report outside this group was in a population of multiple sclerosis (MS) patients, in which depression severity was indirectly associated with OB only in those with progressive MS (Yaldizli et al., 2016). An alternative interpretation of our finding is that our selection approach, by childhood trauma exposure, might have introduced a selection bias that systematically reduced the 'true' association between depression and OB volume in the target population.

Although some preclinical studies highlight important correlations between hippocampi and OB plasticity (Yuan & Slotnick, 2014), we did not observe such relationship. The lack of association observed between OB and hippocampi in this study is unsurprising when viewed in the context of the corresponding lack of association between OB and depression, and was likely reflective of our selection approach for childhood trauma exclusively. On the other hand, we found that some of the association between OB and PTSD might have been

confounded by differences in TIV. Although we recommend cautionary interpretation, it is, however, interesting to find that the relationship between right OB is very robust to differences in TIV.

Furthermore, there are other unmeasured factors that could have confounded our results. For instance, we did not determine the degree of smoking. Also, although all patients were on psychotropics, these medications were too varied to include as separate covariates in multivariate analysis. Finally, we did not directly include duration of years since onset of first childhood trauma in our model. Rather, we used current age as a surrogate of the latter in order to minimize the errors in recollection in consistency we noticed when participants with validated childhood trauma were asked to repeatedly state the exact age at which the childhood trauma event first occurred. Ideally, a prospective study design with a childhood cohort would provide a more accurate measure of this variable.

In conclusion, there is a need to follow-up on these findings in larger cohorts. Importantly, it would be useful to also examine the impact of non-A1 adversities and traumatic exposures that occurred after the age of 13 years, as these could be important as well. There is emerging evidence that olfactory training can reverse secondary OB hypotrophy in different populations (Gudziol et al., 2009; Negoias, Pietsch, et al., 2016). Therefore, if our findings are validated in future studies, it would be interesting to examine if prompt institution of olfactory-training in trauma-exposed p can prevent subsequent development of PTSD.

Acknowledgments

This study is not possible without the foresight and support from Drs. Henry Masur and Maryland Pao of the National Institutes of Health. We are also grateful to the staff at the medical records division of the Family Medical Counseling Service, Inc., notably Ms. Deborah Parris, for making the data extraction possible. Finally, we are thankful to Dr. Thomas Mellman, Director of Stress and Sleep Center, Howard University for his useful insight into mechanisms of PTSD.

This project has been funded in whole with federal funds from the National Cancer Institute, National Institutes of Health (HHSN261200800001E).

References

- Aidala A, ... Ko P. Development and validation of the Client Diagnostic Questionnaire (CDQ): a mental health screening tool for use in HIV/AIDS service settings. *Psychology, Health & Medicine*. 2004; 9:362–380. DOI: 10.1080/13548500410001721927
- Alessi EJ, ... Martin JI. PTSD and Sexual Orientation: An Examination of Criterion A1 and Non-Criterion A1 Events. *Psychological Trauma: theory, research, practice and policy*. 2013; 5:149–157. DOI: 10.1037/a0026642
- Altundag A, Cayonu M, ... Hummel T. Modified olfactory training in patients with postinfectious olfactory loss. *The Laryngoscope*. 2015; 125:1763–1766. DOI: 10.1002/lary.25245 [PubMed: 26031472]
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4. Washington, DC: 2000.
- Anand A, Koller DL, Lawson WB, Gershon ES, ... Bi GSC. Genetic and childhood trauma interaction effect on age of onset in bipolar disorder: An exploratory analysis. *Journal of Affective Disorders*. 2015; 179:1–5. DOI: 10.1016/j.jad.2015.02.029 [PubMed: 25837715]
- Auxemery Y. Posttraumatic stress disorder (PTSD) as a consequence of the interaction between an individual genetic susceptibility, a traumatogenic event and a social context. *L'Encephale*. 2012; 38:373–380. DOI: 10.1016/j.encep.2011.12.003

- Breer H, Fleischer J, Strotmann J. The sense of smell: multiple olfactory subsystems. *Cellular and Molecular Life Sciences*. 2006; 63:1465–1475. DOI: 10.1007/s00018-006-6108-5 [PubMed: 16732429]
- Bremner JD. Stress and brain atrophy. *CNS & Neurological Disorders Drug Targets*. 2006; 5:503–512. DOI: 10.2174/187152706778559309 [PubMed: 17073653]
- Brief DJ, Brady SM. ... Cost Study, G. Understanding the interface of HIV, trauma, post-traumatic stress disorder, and substance use and its implications for health outcomes. *AIDS Care*. 2004; 16(Suppl 1):S97–120. DOI: 10.1080/09540120412301315259 [PubMed: 15736824]
- Doty RL. Olfaction. *Annual Review of Psychology*. 2001; 52:423–452. DOI: 10.1146/annurev.psych.52.1.423
- Fray PJ, Robbins TW. CANTAB battery: proposed utility in neurotoxicology. *Neurotoxicology and Teratology*. 1996; 18:499–504. DOI: 10.1016/0892-0362(96)00027-X [PubMed: 8866544]
- Gudziol V, Buschhuter D, Abolmaali N, Gerber J, Rombaux P, Hummel T. Increasing olfactory bulb volume due to treatment of chronic rhinosinusitis--a longitudinal study. *Brain*. 2009; 132:3096–3101. DOI: 10.1093/brain/awp243 [PubMed: 19773353]
- Huber, PJ. The behavior of maximum likelihood estimates. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*; Berkeley, CA: University of California Press; 1967. p. 221-233.
- Imaki T, Nahon JL, Sawchenko PE, Vale W. Widespread expression of corticotropin-releasing factor messenger RNA and immunoreactivity in the rat olfactory bulb. *Brain Research*. 1989; 496:35–44. DOI: 10.1016/0006-8993(89)91050-0 [PubMed: 2804647]
- Johnson BN, Sobel N. Methods for building an olfactometer with known concentration outcomes. *Journal of Neuroscience Methods*. 2007; 160:231–245. DOI: 10.1016/j.jneumeth.2006.09.008 [PubMed: 17081618]
- Konrad C, Ukas T, Nebel C, ... Narr KL. Defining the human hippocampus in cerebral magnetic resonance images--an overview of current segmentation protocols. *NeuroImage*. 2009; 47:1185–1195. DOI: 10.1016/j.neuroimage.2009.05.019 [PubMed: 19447182]
- Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine*. 2001; 16:606–613. doiorg/10.1046/j.1525-1497.2001.016009606.x. [PubMed: 11556941]
- Lumia AR, Teicher MH, Salchli F, Ayers E, Possidente B. Olfactory bulbectomy as a model for agitated hyposerotonergic depression. *Brain Research*. 1992; 587:181–185. DOI: 10.1016/0006-8993(92)90995-L [PubMed: 1525654]
- Malone IB, Leung KK, ... Ridgway GR. Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. *NeuroImage*. 2015; 104:366–372. DOI: 10.1016/j.neuroimage.2014.09.034 [PubMed: 25255942]
- McNish KA, Davis M. Olfactory bulbectomy enhances sensitization of the acoustic startle reflex produced by acute or repeated stress. *Behavioral Neuroscience*. 1997; 111:80–91. DOI: 10.1037/0735-7044.111.1.80 [PubMed: 9109626]
- Morales-Medina JC, Juarez I, ... Quirion R. Impaired structural hippocampal plasticity is associated with emotional and memory deficits in the olfactory bulbectomized rat. *Neuroscience*. 2013; 236:233–243. DOI: 10.1016/j.neuroscience.2013.01.037 [PubMed: 23357118]
- Morimoto M, Morita N, ... Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neuroscience Research*. 1996; 26:235–269. DOI: 10.1016/S0168-0102(96)01105-4 [PubMed: 9121734]
- Negoias S, Croy I, Gerber J, Puschmann S, ... Hummel T. Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. *Neuroscience*. 2010; 169:415–421. DOI: 10.1016/j.neuroscience.2010.05.012 [PubMed: 20472036]
- Negoias S. Olfactory bulb volume predicts therapeutic outcome in major depression disorder. *Brain Imaging and Behavior*. 2016; 10:367–372. DOI: 10.1007/s11682-015-9400-x [PubMed: 25977168]
- Negoias S, Pietsch K, Hummel T. Changes in olfactory bulb volume following lateralized olfactory training. *Brain Imaging and Behavior*. 2016; doi: 10.1007/s11682-016-9567-9

- Nurnberger JI Jr, Blehar M, ... Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Archives of General Psychiatry. 1994; 51:849–859. discussion 863–844. DOI: 10.1001/archpsyc.1994.03950110009002 [PubMed: 7944874]
- Pence BW, Mugavero MJ, Carter, ... Whetten K. Childhood trauma and health outcomes in HIV-infected patients: an exploration of causal pathways. Journal of Acquired Immune Deficiency Syndromes. 2012; 59:409–416. DOI: 10.1097/QAI.0b013e31824150bb [PubMed: 22107822]
- Peters J, Th, Daum I. Impairment of verbal recollection following ischemic damage to the right anterior hippocampus. Cortex. 2009; 45:592–601. DOI: 10.1016/j.cortex.2008.09.001 [PubMed: 19019352]
- Rombaux P, Hummel T. Olfactory function assessed with orthonasal and retronasal testing, olfactory bulb volume, and chemosensory event-related potentials. Archives of Otolaryngology – Head & Neck Surgery. 2006; 132:1346–1351. DOI: 10.1001/archotol.132.12.1346 [PubMed: 17178947]
- Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neuroscience and Biobehavioral Reviews. 2005; 29:627–647. DOI: 10.1016/j.neubiorev.2005.03.010 [PubMed: 15925697]
- Whetten K, Reif S, Toth M, Jain E, Leserman J, Pence BW. Relationship between trauma and high-risk behavior among HIV-positive men who do not have sex with men (MDSM). AIDS Care. 2012; 24:1453–1460. DOI: 10.1080/09540121.2012.712665 [PubMed: 22909318]
- White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica. 1980; 48:817–838. DOI: 10.2307/1912934
- Yaldizli O, Penner IK, Yonekawa T, Naegelin Y, ... Sprenger T. The association between olfactory bulb volume, cognitive dysfunction, physical disability and depression in multiple sclerosis. European Journal of Neurology. 2016; 23:510–519. DOI: 10.1111/ene.12891 [PubMed: 26699999]
- Yang SJ, Yu HY, Ma SP. Antidepressant-like effects of salidroside on olfactory bulbectomy-induced pro-inflammatory cytokine production and hyperactivity of HPA axis in rats. Pharmacology, Biochemistry and Behavior. 2014; 124:451–457. DOI: 10.1016/j.pbb.2014.07.015
- Yuan TF, Slotnick BM. Roles of olfactory system dysfunction in depression. Progress in Neuro-psychopharmacology and Biological Psychiatry. 2014; 54:26–30. DOI: 10.1016/j.pnpbp.2014.05.013 [PubMed: 24879990]

Figure 1.

Figure 1A shows the left and right mean olfactory bulb (OB) volumes comparing HIV-infected men and women with lifetime posttraumatic stress disorder (PTSD) diagnosis ($n = 9$) with HIV-infected men and women who had no lifetime PTSD diagnosis ($n = 7$). Figure 1B shows left and right mean olfactory bulb volumes comparing HIV-infected participants who were exposed to severe childhood trauma ($n = 13$) with HIV-infected participants who were not exposed to severe childhood trauma ($n = 3$). Figure 1C shows left and right mean olfactory bulb volumes comparing HIV-infected men and women who developed PTSD following severe childhood trauma exposure ($n = 9$) with HIV-infected men and women who did not develop PTSD following exposure to severe childhood trauma ($n = 4$). The error bars represent standard deviations.

Table 1
Demographic and Clinical Characteristics by Posttraumatic Stress Disorder (PTSD) Status among the Study Participants

Characteristics	Lifetime PTSD (<i>n</i> = 9)				No Lifetime PTSD (<i>n</i> = 7)			
	Mean	SD	<i>n</i>	%	Mean	SD	<i>n</i>	%
Age (years)	49.55	6.65			49.14	8.11		
VRM	22.11	3.89			21.43	2.76		
Odor threshold	6.17	2.15			4.83	1.83		
Odor discrimination	7.89	1.90			7.17	1.17		
Odor memory	15.78	2.90			14.33	5.54		
Odor identification	7.78	2.11			7.17	1.33		
Monthly income (dollars)	972.11	652.80			1197.50	545.96		
PHQ-9	13.78	9.85			12.43	7.50		
CD4	678	438.79			724	201.52		
Log Viral load	2.19	0.71			2.71	1.04		
L. Hippocampus (mm3)	2958.84	461.87			3086.6	501.48		
R. Hippocampus (mm3)	2949.52	506.83			3171.76	407.22		
TIV (ml)	1254.26	167.53			1412.72	259.18		
Female			3	33.3			4	57.1
Childhood trauma ^a			9	100.0			4	57.1
Non-A1 trauma events ^b			7	77.8			0	0
Current PTSD ^{**}			8	88.9			0	0
African Americans			8	88.9			6	85.7
> 12 grade education			2	22.2			1	14.3
Religion (Protestant)			4	44.4			3	42.9
Employed			1	11.1			1	14.3
Tobacco use, current			9	100.0			7	100.0
Substance use, lifetime			9	100.0			7	100.0
Substance use, current			3	33.3			1	14.3

Characteristics	Lifetime PTSD (n = 9)				No Lifetime PTSD (n = 7)			
	Mean	SD	n	%	Mean	SD	n	%
Major Depression			8	88.9			5	85.7
Anxiety, General			7	77.8			5	71.4
Psychotropics ^c			9	100.0			7	100.0

Note. VRM = Verbal recognition memory-recognition scores; CD4 current CD4 T-lymphocyte count (cells/ μ l).

Log viral load, log base 10 transformation of their current viral count (copies/ml)

^aTrauma refers to criterion A1 events in *DSM-IV* PTSD criteria (American Psychiatric Association, 2000).

^bNon-A1 events include death of parent, death of sibling, beginning of chronic illness, permanent injury or disability, loss of home, and similar events, and were derived from the Childhood Life Exposure Screening; absence in non-PTSD group is due to exclusion of controls with non-A1 events during screening.

^cPsychotropics mentioned by participants included sedatives and antidepressants; additionally, two participants reported use of second-generation antipsychotics for depression.

* $p < .05$.

** $p < .01$.

Table 2

Simple and Multiple Regression Analyses of Olfactory Bulb Volumes on Posttraumatic Stress Disorder (PTSD) and Depression.

	Left Olfactory Bulb				Right Olfactory Bulb			
	B ^c	SE	<i>t</i> ^d	R ²	B ^c	SE	<i>t</i> ^d	R ²
PTSD ^a								
Model 1	-21.31	6.36	-3.35**	.45	-25.74	4.9	-5.25***	.75
Model 2	-19.51	7.25	-2.69*	.52	-25.51	5.24	-4.87***	.75
Model 3	-17.68	6.85	-2.58*	.57	-26.21	5.75	-4.56**	.75
Model 4	-9.49	4.13	-2.30*	.82	-29.34	6.37	-4.61**	.79
PHQ-9 ^b								
Unadjusted	-0.58	0.42	-1.36	.09	-0.46	0.53	-0.88	.04
Model 1	-0.76	0.7	-1.09	.33	-0.37	0.51	-0.74	.34
Model 2	-0.19	0.25	-0.74	.73	-0.12	0.61	-0.2	.41

Note. PHQ = patient health questionnaire.

^aFor PTSD: Model 1 included age and sex as covariates; Model 2 included age, sex, and depression severity as covariates; Model 3 included age, sex, depression severity, and left hippocampal volume as covariates; and Model 4 all variables included in Model 3, as well as total intracranial volume (TIV).

^bFor PHQ-9: Unadjusted model did not include any covariates; Model 1 adjusted for sex, age, and ipsilateral hippocampus; and Model 2 adjusted for age, sex, ipsilateral hippocampus, and TIV.

^cB is the coefficient or mean effect comparing HIV-positive patients with PTSD, to HIV-positive patients without PTSD, adjusting for other covariates in the respective model.

^dDegrees of freedom (*df*) for the *t* statistics were derived from the regression models correspond to the number covariates in each model.

* $p < .05$.

** $p < .01$.

*** $p < .001$.