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Gray matter regions statistically mediating the cross-sectional association of eotaxin and set-shifting among older adults with major depressive disorder

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Abstract

Objective—Eotaxin is a chemokine that exerts negative effects on neurogenesis. We recently showed that peripheral eotaxin levels correlate with both lower gray matter volume and poorer executive performance in older adults with major depressive disorder. These findings suggest the relationship between eotaxin and set-shifting may be accounted for by lower gray matter volume in specific regions. Prior studies have identified specific gray matter regions that correlate with set-shifting performance, but have not examined whether these specific gray matter regions mediate the cross-sectional association between eotaxin and set-shifting.

Method—In 27 older adults (mean age: 68 ± 5.2 years) with major depressive disorder, we performed a whole brain (voxel-wise) analysis testing whether/where gray matter density statistically mediates the cross-sectional association of eotaxin and set-shifting performance.

Results—We found the association between eotaxin and set-shifting performance was fully statistically mediated by lower gray matter density in left middle cingulate, right pre-/post-central, lingual, inferior/superior frontal, cuneus, and middle temporal regions.

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Conclusion—These regions may therefore be both susceptible to a potential neurodegenerative effect of eotaxin, and critical to preserving set-shifting function. Longitudinal and intervention studies are needed to further evaluate whether targeting eotaxin levels will prevent neurodegeneration and executive impairment in older adults with depression.

Keywords

Magnetic resonance imaging (MRI); gray matter; depression; executive function; set-shifting; eotaxin; immunology; geriatric

In mice, experimentally increasing levels of the chemokine eotaxin (CCL11) decreases neurogenesis and impairs cognitive function (Villeda et al., 2011). We recently explored relationships among 13 immunological markers (including eotaxin) and multiple aspects of brain health in older adults with major depressive disorder (Smagula et al., in press). Eotaxin correlated negatively with both total gray matter volume and set-shifting performance (a core aspect of executive function). These findings raise the possibility that, in aging and depression, the association of eotaxin with set-shifting performance is accounted for by atrophy affecting key gray matter regions.

Set-shifting capability is an aspect of executive function, referring to the ability to quickly alternate attention while inhibiting automatic responses. Low set-shifting performance not only predicts disability in older adults (Cahn-Weiner et al., 2002), it also predicts poorer treatment response to second-line pharmacotherapy for major depression (Kaneriya SH, 2016). Therefore, understanding the biological mechanisms associated with set-shifting performance can lead to novel targets for interventions aimed at combating depression and maintaining cognitive function in older adults with depression.

Previous research demonstrates lower gray matter volumes in insular (Hatton et al.), medial temporal (Oosterman et al., 2008), parietal (Pa et al., 2010), and frontal (Tsuchida and Fellows, 2013, Pa et al., 2010, Kramer et al., 2007) regions correlate with poorer set-shifting performance. Despite growing recognition of inter-relations between immunology, brain structure, and cognition, to our knowledge, only one prior study has investigated whether immunological markers are associated with cognitive function due to their relationship with brain structure (Marsland et al., 2015). This study found evidence consistent with a mediational model: pro-inflammatory cytokine levels were associated with cognitive function, partially due to intermediate associations with gray matter structure.

Given that late-life depression is associated with increased dementia risk (Diniz et al., 2013, Gatz et al., 2005, Cherbuin et al., 2015), understanding the potential neuro-immunological basis of variability in cognitive function among older adults with depression is particularly important. Furthermore, depression is thought to be characterized by altered levels of several immunological markers, for example, higher levels of the chemokine eotaxin (e.g., see Simon et al. (2008), Grassi-Oliveira et al. (2012), Magalhaes et al. (2014) and for a review see Stuart et al. (2015)). Since the chemokine eotaxin demonstrably affects neurogenesis in animals (Villeda et al., 2011), it is plausible that eotaxin is associated with cognitive function in older adults with depression due to intermediate associations with specific gray matter structures. We evaluated evidence for this hypothesized model by performing a whole

brain (voxel-wise) analysis testing whether lower gray matter density in particular regions statistically mediates the cross-sectional association of eotaxin and set-shifting performance. A voxel-wise mediation approach was chosen to explore the neuroanatomical localization of the hypothesized statistical mediation.

Methods

Participants

Participants had current nonpsychotic major depressive disorder as diagnosed by the Structured Clinical Interview for DSM-IV (First, 2002) plus a Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979) (MADRS) score ≥ 15 . The current report pertains to data collected prior to the initiation of a 12-week open-label venlafaxine trial. Exclusion criteria included current psychotic symptoms, any lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective, or other psychotic disorders; cognitive impairment as indicated by a score of ≤ 20 on the Mini Mental Status Exam (Folstein et al., 1975) or a clinical history of dementia (the lowest Mini Mental Status Exam score in the sample was 27); alcohol or substance abuse in the past 3 months; high suicide risk; or unstable medical illness. To be included in the analysis, participants were required to contribute valid MRI, eotaxin, and set-shifting data ($n=27$). All participants provided written informed consent.

Measures

Plasma levels of eotaxin were assessed using a Meso Scale Discovery V-PLEX Human Cytokine 30-Plex Kit on a Quickplex-120 machine (Rockville, MD, USA). We applied a log transformation to normalize the distribution of eotaxin levels. Acute health events (e.g., infection) may lead to elevated eotaxin levels (Scheerens et al., 1999), therefore we excluded outliers defined as those exceeding the biomarker's 75th percentile value added to 3 times its interquartile range; only 1 sample was excluded due to this criteria.

The Delis-Kaplan Executive Function System's Trail Making Test condition 4 (also known as the Number-Letter Switching condition) requires that participants switch back and forth between connecting numbers and letters (i.e., 1, A, 2, B, etc., to 16, P). Condition 5 is a motor speed condition in which participants trace over a dotted line connecting circles on the page as quickly as possible to gauge their motor drawing speed. Comparing performance on Condition 4 with performance on Condition 5 removes the fine motor speed element from the test score so that cognitive flexibility can be ascertained independent of motor speed (Lezak et al., 2012). We used the D-KEFS normed scaled score (with a mean of 10 and standard deviation of 3) based on the difference in speeds on "time to complete" condition 4 and 5, representing set-shifting performance (Delis DC, 2001).

MRI data were collected using a 3T Siemens Trio TIM scanner located at the Magnetic Resonance Center at the University of Pittsburgh. MPRAGE images were acquired on the axial plane: repetition time=2,300 milliseconds (ms); echo time=3.43 ms; inversion time=900 ms; flip angle=9°; slice thickness=1 mm; field of view=256 $\times$ 224 mm²; voxel size=1 $\times$ 1 $\times$ 1 mm; number of slices=176.

Structural images were segmented into tissue classes using statistical parametric mapping (SPM12) software. Structural images were segmented and normalized (coregistered to a common space using the Montreal Neurological Institute (MNI) template. A set of probability maps was generated for use in the next step of processing.

The brains of older adults with depression are expected to differ when compared to the standard MNI template (which is based on a healthy sample). Therefore, we used Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Goto et al., 2013) to generate study-specific templates for normalization. Briefly, DARTEL takes all the normalized/segmented images (in this case, from SPM12) and generates a mean image. The participant's individual images are then coregistered to this mean template. A new mean is then generated and this process is repeated iteratively, which generates a study-specific template. Next, a smoothed (full-width at half-maximum (FWHM) of 8mm), modulated, and normalized gray matter map was generated. The modulation step multiplied the normalized gray matter probability maps with the Jacobian determinant from the deformation field (which is generated as part of the normalization procedure). Modulation aims to preserve the original local volumes in each subject that may have been expanded/shrunk through the non-linear process of normalization/co-registration to a standard space. The modulated image can be interpreted as gray matter density.

Statistical Analysis

Mediation analysis was performed using bootstrap regression analysis of voxel-wise observations (BRAVO; <https://sites.google.com/site/bravotoolbox>) software. BRAVO uses the Preacher and Hayes (Preacher and Hayes, 2008) approach for mediation analysis (indirect effect) where statistical significance is determined via bootstrapping. Our aim was to test whether specific regions of gray matter density statistically mediated the cross-sectional association between eotaxin and set-shifting. In this model (Figure 1), the association between eotaxin and set-shifting is known as path C. The mediation toolbox performs two important regressions at each voxel. The first regression uses gray matter density as the outcome with eotaxin as the independent variable (path A). The second regression uses the set-shifting outcome with gray matter density as one independent variable while covarying for eotaxin level (path B). The regression coefficients for eotaxin and gray matter density from path A and B, respectively, are then multiplied to obtain the parameter value for the indirect (mediated) path.

The association between eotaxin and set-shifting after accounting for the mediator (gray matter density) is known as path C' (C prime). When C' retains significance retains significance and the mediated (indirect) path is statistically significant, this is known as partial mediation (i.e., a significant indirect path that does not entirely the association of eotaxin and set-shifting). When a significant indirect effect is detected that attenuates the association of eotaxin and set-shifting to non-significance, this is known as full mediation. A p-value map determining the significance of mediated path (indirect effect) is generated via bootstrapping with 5000 iterations. Finally, AlphaSim (Ward, 2002) was used to determine (given an uncorrected p-value threshold of $p=0.005$ and a FWHM=8mm) the minimum cluster size required to pass multiple comparisons correction ($p<0.05$, corrected). AlphaSim

computes the probability that a random field of noise (with a particular smoothing kernel) will produce a cluster of a given size (minimum $k=156$ voxels in this particular analysis) after thresholding at a particular level. We present a map of the indirect parameter estimates and list the significant clusters by region named with the automatic anatomic labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) illustrating the clusters which achieved AlphaSim correlated statistical significance.

Results

Participants had a mean ($\pm$ SD) age of 68 ± 5.2 years and were 74% female (see Table 1 for additional descriptive information). We found seven regions that statistically mediated the relationship between eotaxin and set-shifting ($p<0.05$, corrected). Table 2 provides detailed descriptions of each region, and Figure 2 overlays the indirect parameter estimates on a single structural image in MNI space. The seven regions statistically mediating the association between eotaxin and set-shifting were: the right middle temporal gyrus, lingual gyrus, inferior frontal gyrus/insula, superior frontal gyrus, cuneus, post-/pre-central gyri, and left middle cingulate (see Figure 2).

Both path A (eotaxin and gray matter density) and path B (gray matter density and set-shifting covaried for eotaxin) were statistically significant in all regions where a significant indirect path was detected. Specifically, for all regions where the indirect path was significant, the correlation between eotaxin and gray matter density (path A) was significantly negative ($p<0.05$, corrected). The correlation between gray matter density and set-shifting (covaried for eotaxin, path B) was significantly positive ($p<0.05$, corrected). In every region where the indirect path was significant, the association between eotaxin and set-shifting was not significant after accounting for the mediator; thus, gray matter density fully statistically mediates the cross-sectional association between eotaxin and set-shifting.

Discussion

The current report provides a novel test of whether gray matter density in specific regions statistically mediates the cross-sectional association between eotaxin and set-shifting. Our results demonstrate that gray matter density in seven regions (left middle cingulate, right pre-/post-central, lingual, inferior frontal, insula, superior frontal, cuneus, and middle temporal regions) fully statistically mediate the association between eotaxin levels and set-shifting performance. These particular regions may therefore be both crucial to preserving set-shifting function and susceptible to potential neurodegenerative effects of eotaxin. These findings are consistent with the results of prior investigations of the gray matter substrates of set-shifting (Hatton et al., 2012, Oosterman et al., 2008, Tsuchida and Fellows, 2013, Pa et al., 2010, Kramer et al., 2007), and extend them by suggesting that atrophy in these regions is associated with circulating levels of eotaxin.

The observed indirect effects were mostly lateralized to the right hemisphere, but also included the left middle cingulate. Future research is needed to investigate whether these observed localizations represent nodes in a functional circuit underlying set-shifting function. In general, it remains unclear how aging-related immunological changes, brain

atrophy, and depression act to influence changes in functional brain networks over time. This pertains not only to the role of eotaxin, atrophy, and the functional networks responsible for set-shifting, but also to other immunological biomarkers, such as those related to demyelination (e.g., tumor necrosis factor (Selmaj and Raine, 1988)), as well as other functional networks, such as those responsible for emotion regulation and reward.

Some limitations should be noted: our findings cannot necessarily generalize to other populations such as younger adults or individuals without depression. While our set-shifting measure was designed to control for motor speed, it is possible that some of the associations detected are driven by differences in other cognitive processes involved in completing condition five of the Trail Making Test, such as information processing speed. In addition, the cross-sectional design prohibits temporal inferences in these associations, e.g., inferring that elevation of eotaxin levels preceded and caused gray matter atrophy and decrease in set-shifting performance. However, the biological plausibility of this temporal cascade is supported by a previous animal study that demonstrated that manipulating eotaxin levels negatively regulate neurogenesis (Villeda et al., 2011), and by the fact that neurodegeneration is a well-recognized antecedent of executive impairment. Future research is needed to confirm whether eotaxin has a generalizable role in neurodegeneration and executive impairment, and whether this effect is amplified or driven by depression (e.g., using case-controlled designs examining the relationship between eotaxin and brain health in patients with and without depression).

In conclusion, we found that the association of eotaxin and set-shifting performance could be accounted for by an indirect effect through gray matter density in specific regions. In addition to assessing whether these findings generalize to older adults who are without depression, longitudinal and intervention studies in older adults with depression are needed to examine the potential impact of eotaxin on neurodegeneration and cognitive function. Longitudinal studies are needed to confirm whether increasing levels of eotaxin leads to neurodegeneration and executive function impairment, and intervention studies are needed to test whether reducing eotaxin levels preserves gray matter and prevents executive function impairment in aging.

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References

- Cahn-Weiner DA, Boyle PA, Malloy PF. Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Appl Neuropsychol*. 2002; 9:187–91. [PubMed: 12584085]
- Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. *BMJ Open*. 2015; 5

- Delis DC, Kramer, JH. *Dellis Kaplan Executive Function System Examiner's Manual*. The Psychological Corporation; 2001.
- Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. 2013; 202:329–35. [PubMed: 23637108]
- First, MB., Spitzer, Robert, L., Gibbon, Miriam, Williams, Janet, BW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–98. [PubMed: 1202204]
- Gatz JL, Tyas SL, St John P, Montgomery P. Do depressive symptoms predict Alzheimer's disease and dementia? *J Gerontol A Biol Sci Med Sci*. 2005; 60:744–7. [PubMed: 15983177]
- Goto M, Abe O, Aoki S, Hayashi N, Miyati T, Takao H, Iwatsubo T, Yamashita F, Matsuda H, Mori H, Kunimatsu A, Ino K, Yano K, Ohtomo K. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra provides reduced effect of scanner for cortex volumetry with atlas-based method in healthy subjects. *Neuroradiology*. 2013; 55:869–75. [PubMed: 23619702]
- Grassi-Oliveira R, Brieztke E, Teixeira A, Pezzi JC, Zanini M, Lopes RP, Bauer ME. Peripheral chemokine levels in women with recurrent major depression with suicidal ideation. *Rev Bras Psiquiatr*. 2012; 34:71–5. [PubMed: 22392392]
- Hatton SN, Lagopoulos J, Hermens DF, Naismith SL, Bennett MR, Hickie IB. Correlating anterior insula gray matter volume changes in young people with clinical and neurocognitive outcomes: an MRI study. *BMC Psychiatry*. 2012; 12:45. [PubMed: 22607202]
- Kaneriya SHR-WG, Smagula SF, Karp JF, Butters MA, Lenze EJ, Mulsant BH, Blumberger D, Anderson SJ, Dew MA, Lotrich FL, Aizenstein HJ, Diniz BS, Reynolds CF. Predictors and moderators of remission with aripiprazole augmentation in treatment-resistant late-life depression. *JAMA Psychiatry*. 2016; 73:329–336. [PubMed: 26963689]
- Kramer JH, Quitania L, Dean D, Neuhaus J, Rosen HJ, Halabi C, Weiner MW, Magnotta VA, Delis DC, Miller BL. Magnetic resonance imaging correlates of set shifting. *J Int Neuropsychol Soc*. 2007; 13:386–92. [PubMed: 17445286]
- Lezak, MD., Howieson, DB., Bigler, ED., Tranel, D. *Neuropsychological assessment* (5th ed.). 5. Neuropsychological assessment; 2012.
- Magalhaes PV, Jansen K, Stertz L, Ferrari P, Pinheiro RT, Da Silva RA, Kapczinski F. Peripheral eotaxin-1 (CCL11) levels and mood disorder diagnosis in a population-based sample of young adults. *J Psychiatr Res*. 2014; 48:13–5. [PubMed: 24182965]
- Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun*. 2015; 48:195–204. [PubMed: 25882911]
- Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382–9. [PubMed: 444788]
- Oosterman JM, Vogels RL, Van Harten B, Gouw AA, Scheltens P, Poggesi A, Weinstein HC, Scherder EJ. The role of white matter hyperintensities and medial temporal lobe atrophy in age-related executive dysfunctioning. *Brain Cogn*. 2008; 68:128–33. [PubMed: 18450353]
- Pa J, Possin KL, Wilson SM, Quitania LC, Kramer JH, Boxer AL, Weiner MW, Johnson JK. Gray matter correlates of set-shifting among neurodegenerative disease, mild cognitive impairment, and healthy older adults. *Journal of the International Neuropsychological Society : JINS*. 2010; 16:640–650. [PubMed: 20374676]
- Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008; 40:879–91. [PubMed: 18697684]
- Scheerens J, Folkerts G, Van Der Linde H, Sterk PJ, Conroy DM, Williams TJ, Nijkamp FP. Eotaxin levels and eosinophils in guinea pig broncho-alveolar lavage fluid are increased at the onset of a viral respiratory infection. *Clin Exp Allergy*. 1999; 29(Suppl 2):74–7. [PubMed: 10421826]
- Selmaj KW, Raine CS. Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. *Ann Neurol*. 1988; 23:339–46. [PubMed: 3132891]

- Simon NM, Mcnamara K, Chow CW, Maser RS, Papakostas GI, Pollack MH, Nierenberg AA, Fava M, Wong KK. A Detailed Examination of Cytokine Abnormalities in Major Depressive Disorder. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. 2008; 18:230–233. [PubMed: 17681762]
- Smagula S, Lotrich F, Aizenstein H, Diniz B, Krystek J, Wu G, Mulsant B, Butters M, Reynolds C, Lenze E. Immunological biomarkers associated with brain structure and executive function in late-life depression: exploratory pilot study. *International Journal of Geriatric Psychiatry*. in press.
- Stuart MJ, Singhal G, Baune BT. Systematic Review of the Neurobiological Relevance of Chemokines to Psychiatric Disorders. *Front Cell Neurosci*. 2015; 9:357. [PubMed: 26441528]
- Tsuchida A, Fellows LK. Are core component processes of executive function dissociable within the frontal lobes? Evidence from humans with focal prefrontal damage. *Cortex*. 2013; 49:1790–800. [PubMed: 23206529]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15:273–89. [PubMed: 11771995]
- Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Despres S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*. 2011; 477:90–4. [PubMed: 21886162]
- Ward, BD. AlphaSim. Bethesda, MD: National Institute of Mental Health; 2002.

Key points

- Past animal research shows eotaxin negatively affects neurogenesis and cognition.
- Eotaxin correlates with set-shifting performance in older adults with depression.
- Lower gray matter density in seven regions statistically mediated this association.
- Eotaxin-related neurodegeneration may underlie set-shifting impairment in late-life depression; longitudinal and intervention studies testing this model are warranted.

Figure 1.
Illustration of the model and paths examined

Figure 2.

Regions where gray matter density statistically mediated the association between eotaxin and set-shifting. Colors show the effect size of the indirect effect parameter estimate (path A times path B), which are all negative. Top row, left to right: left middle cingulate, right cuneus, right postcentral/precentral gyrus, and right middle temporal gyrus. Bottom row, left to right: right lingual gyrus, right inferior frontal gyrus/insula, and right superior frontal gyrus.

Table 1

Participants' (n=27) clinical and demographic information

	Mean (SD) *
Age	68 (5.2)
Gender, number (percent)	20 (74)
Educational attainment (years)	15 (2.3)
MADRS Severity	26.2 (6.5)
MMSE, median (IQR)	29 (28–30)
Trail Making Test (condition 4 vs. 5, scaled score)	9.1 (3.5)
Eotaxin (pg/mL), median (IQR)	43.5 (38.3–60.5)

* unless otherwise noted;

Abbreviations: MADRS, Montgomery Asberg Depression Rating Scale; MMSE, Mini Mental Status Exam; pg/mL, Picogram per milliliter;

Table 2

Regions where gray matter density statistically mediates the cross-sectional association between eotaxin and set-shifting

Region	Cluster Size	Max Parameter Estimates				
		Path A	Path B	Indirect Path	X	Y Z
Right Middle Temporal Gyrus	509	-2.26	3.18	-1.61	39	12 -47
Right Superior Temporal Gyrus						
BA 38						
Fusiform Gyrus						
Right Lingual Gyrus	311	-2.47	3.72	-1.98	17	-57 -2
Right Posterior Cingulate						
Right Inferior Frontal Gyrus	214	-3.22	3.34	-2.16	33	27 14
Right Insula						
Right BA 13						
Right Superior Frontal Gyrus	318	-3.12	3.21	-2.03	30	51 9
Right Middle Frontal Gyrus						
Right Cuneus	268	-3.12	3.57	-2.07	20	-90 30
Right Superior Occipital Gyrus						
Right BA 19						
Left Middle Cingulate	161	-2.3	2.97	-1.62	-9	-26 35
Right Postcentral Gyrus	373	-2.88	4.15	-2.5	47	-27 63
Right Precentral Gyrus						
BA 3						

Some clusters span multiple regions thus multiple descriptions are given under the region tab. A cluster size, coordinates (in Montreal Neurological Institute space), and a max parameter estimate (for path A, B, and the indirect path) are also given for each region.