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Short communication

# Activation of the kynurenine pathway is associated with striatal volume in major depressive disorder

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ABSTRACT

Inflammation, which may be present in a subgroup of individuals with major depressive disorder (MDD), activates the kynurenine metabolic pathway to produce kynurenine metabolites kynurenic acid (KynA) and quinolinic acid (QA). We have previously reported an association between the ratio of KynA to QA and hippocampal volume in MDD. In animals, inflammation leads to deficits in incentive motivation. Given the central role of the nucleus accumbens (NAcc) and other regions of the striatum in motivated behavior, reward processing, and anhedonia, we hypothesized that abnormalities in the concentrations of kynurenine pathway metabolites would be associated with striatal volumes. As previously reported, after controlling for relevant confounds, the KynA/QA ratio was reduced in the serum of unmedicated patients with MDD ($n = 53$) versus healthy controls (HC, $n = 47$) and there was a non-significant trend in the correlation between KynA/QA and severity of anhedonia ($r = -0.27$, $p < 0.1$). There was no significant difference between the MDD and HC groups in any of the individual kynurenine metabolites or volume of the striatum defined as the sum of the volumes of the NAcc, caudate, and putamen. After regressing out the effects of sex, analysis batch, and supratentorial volume, the kynurenine concentration and the ratio of kynurenine to tryptophan were inversely associated with striatal volumes in the MDD sample ($p < 0.05$, uncorrected). Further, striatal volume was correlated with the items, "concentration difficulties", "lassitude", and "pessimism" from the Montgomery-Asberg Depression Rating Scale. Our results raise the possibility that activation of the kynurenine pathway is a marker of an inflammatory process that leads to reductions in striatal volume. However, unlike the hippocampus, the association does not appear to be mediated by the relative balance between KynA and QA.



## 1. Introduction

Reductions in hippocampal volume are widely reported in major depressive disorder (MDD) and are thought to reflect dendritic atrophy (Savitz and Drevets, 2009; Stockmeier et al., 2004). We previously reported that the ratio of kynurenic acid (KynA, an NMDA receptor antagonist) to quinolinic acid (QA, an NMDA receptor agonist) in serum was positively correlated with hippocampal volume, raising the possibility of an inflammatory, glutamate-mediated contribution to certain structural brain abnormalities observed in MDD. The current paper builds on this work by addressing the regional specificity of these findings. We focused on the striatum given the relationship between inflammation-induced deficits in incentive motivation and anhedonia (Dantzer et al., 2011; Vichaya et al., 2014; Yirmiya et al., 2000), evidence for reductions

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**Table 1**
Means and standard deviations of demographic data, clinical ratings, basal ganglia volumes, and kynurenine metabolite concentrations in the MDD and HC groups.

| | MDD | Healthy | Statistic |
|---|---|---|---|
| *N* | 53 | 47 | – |
| Age | 34.6 ± 9.80 | 34.3 ± 11.4 | $t_{99} = 0.885$ |
| Sex (% F) | 79 | 62 | $X^2 = 3.7$, $p = 0.054$ |
| BMI | 27.5 ± 5.20 | 26.8 ± 6.31 | $t_{99} = 0.567$ |
| HAM-D (24) | 23.7 ± 8.8 | 0.9 ± 1.6 | $t_{99} < 0.001$ |
| MADRS | 27.5 ± 10.0 | 0.7 ± 1.7 | $t_{97} < 0.001$ |
| SHAPS | 30.4 ± 6.3 | 18.8 ± 5.3 | $t_{94} < 0.001$ |
| Striatum | 18400 ± 2147 | 18699 ± 2004 | $F_{3,100} = 1.4$, $p = 0.240$ Ψ |
| NAcc | 1096 ± 176 | 1106 ± 214 | $F_{3,100} = 3.0$, $p = 0.084$ Ψ |
| Caudate | 7057 ± 1033 | 7223 ± 1004 | $F_{3,100} = 0.9$, $p = 0.350$ Ψ |
| Putamen | 10053 ± 1163 | 10370 ± 1009 | $F_{3,100} = 0.1$, $p = 0.743$ Ψ |
| Supratentorial | 986931 ± 87387 | 1039414 ± 11072 | $F_{3,100} = 3.6$, p = 0.061 Φ |
| hs-CRP | 2.65 ± 2.96 | 2.61 ± 3.60 | $F_{2,75} = 1.3$, $p = 0.263$ Φ |
| TRP | 52.4 ± 9.8 | 56.6 ± 11.9 | $F_{3,100} = 0.1$, $p = 0.706$ Ω |
| Kyn | 1.90 ± 0.48 | 1.95 ± 0.49 | $F_{3,100} = 0.2$, $p = 0.667$ Ω |
| KynA | 38.0 ± 11.4 | 40.6 ± 14.0 | $F_{3,91} = 0.8$, $p = 0.361$ Ω |
| 3HK | 37.2 ± 12.6 | 35.9 ± 17.4 | $F_{3,100} = 0.01$, $p = 0.950$ Ω |
| QA | 382.8 ± 172.8 | 340.1 ± 102.8 | $F_{3,100} = 1.3$, $p = 0.252$ Ω |
| Kyn/TRP | 0.037 ± 0.013 | 0.034 ± 0.009 | $F_{3,100} = 0.1$, $p = 0.862$ Ω |
| KynA/3HK | 1.059 ± 0.35 | 1.236 ± 0.40 | $F_{3,91} = 2.9$, $p = 0.091$ Ω |
| KynA/QA | 0.107 ± 0.04 | 0.125 ± 0.04 | $F_{3,91} = 5.2$, $p = 0.024$ Ω |

*Note*: CRP data were available for 76 individuals and KYNA data were available for 91 individuals. One healthy control with a BMI of 35 was an outlier with a CRP score of 26.8. After including this individual the mean CRP score of the HC was 3.27 ± 4.69.
Ψ = after controlling for sex and supratentorial volume.
Φ = after controlling for sex.
Ω = after controlling for sex and batch.
Abbreviations: MDD = major depressive disorder; BMI = body mass index; HAM-D 24 = Hamilton depression rating scale (24 item version); MADRS = montgomery-asberg depression rating scale; SHAPS = snaith hamilton pleasure scale; NAcc = nucleus accumbens; hs-CRP = high-sensitivity c-reactive protein; TRP = tryptophan; Kyn = kynurenine; KynA = kynurenic acid; 3HK = 3-hydroxykynurenine; QA = quinolinic acid; Kyn/TRP = ratio of kynurenine to tryptophan; KynA/3HK = ratio of kynurenic acid to 3-hydroxykynurenine; KynA/QA = ratio of kynurenic acid to quinolinic acid.

in striatal volume in MDD (Kempton et al., 2011), and reports of interferon α-induced changes in glutamatergic neurotransmission in the striatum that correlated with motivation and fatigue (Capuron et al., 2007; Haroon et al., 2014), as well as interferon α and endotoxin-induced decreases in the hemodynamic response to rewarding stimuli in the ventral striatum (Capuron et al., 2012; Eisenberger et al., 2010).

## 2. Methods

*Subjects provided written informed consent as approved by the IRB*

The clinical characteristics of the sample, neuroimaging procedures, and kynurenine metabolite measurements have been described in detail elsewhere (Savitz et al., 2015a). Briefly, MDD and HC participants were interviewed with the Structured Clinical Interview for the DSM-IV-TR and in addition, unstructured interviews with psychiatrists were obtained on all MDD subjects. The severity of depressive symptoms was assessed with the Hamilton Depression Rating Scale (HAM-D, 24-item) and the Montgomery Asberg Depression Rating Scale (MADRS); the majority of the MDD participants were moderately-to-severely depressed (Table 1). Anhedonic symptoms were assessed with the Snaith–Hamilton Pleasure Scale (SHAPS).

The unmedicated MDD participants had not received any psychotropic medication for at least 3 weeks (8 for fluoxetine) prior to the blood-draw and MRI scan. Exclusion criteria were as follows: serious suicidal behavior; medical conditions or concomitant medications likely to influence CNS or immunological function including cardiovascular, respiratory, endocrine and neurological diseases, and a history of drug or alcohol abuse within 6 months or a history of drug or alcohol dependence within 1 year. Healthy controls met the same entrance criteria and in addition had no first-degree relative with a psychiatric disorder.

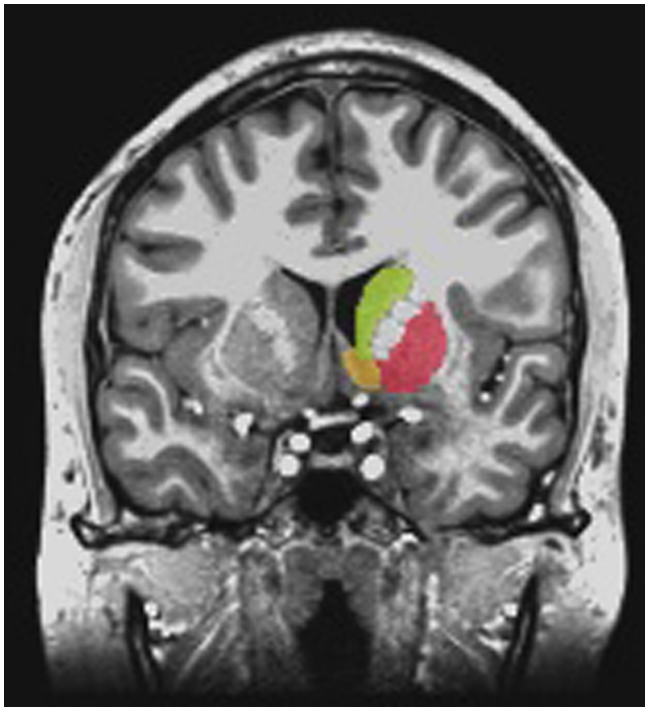

**Fig. 1.** Representative example of the segmentation of the caudate (yellow), nucleus accumbens (orange), and putamen (red) by FreeSurfer shown in the coronal plane. The FreeSurfer mask is shown for the right hemisphere with the corresponding unsegmented structures in the left hemisphere (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

Participants fasted overnight and blood was sampled between 8 am–11 am. Serum samples were collected within 3 days of the MRI scan with BD Vacutainer serum tubes, processed according to the standard BD Vacutainer protocol, and stored at −80 °C. Concentrations of tryptophan (TRP), kynurenine (KYN), kynurenic acid (KynA), 3-hydroxykynurenine (3HK), and quinolinic acid (QA) were measured blind to diagnosis by Brains Online, LLC in 3 separate batches. The metabolite concentrations were determined by high performance liquid chromatography with tandem mass spectrometry detection using their standard protocols. High-sensitivity C-reactive protein (CRP) was measured using the Kamiya Biomedical K-Assay.

Images were acquired on a 3T GE MRI scanner with a 32 channel coil using a magnetization-prepared, rapid gradient echo (MP-RAGE) pulse sequence with sensitivity encoding optimized for tissue contrast resolution. The automated segmentation program, FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) was used to obtain unbiased GM volumes of the NAcc, caudate, putamen, and supratentorial volume using the default analysis settings (Fig. 1). Total striatal volume was defined as the sum of the NAcc, caudate, and putamen.

Non-normally distributed variables (the Kolmogorov–Smirnov test) were log normalized. Diagnostic group differences in kynurenine metabolites and striatal volumes were evaluated with ANOVA (two-tailed, $p < 0.05$). Sex, which trended towards differing among the subject groups (Table 1), and analysis batch were used as covariates for the kynurenine metabolite analysis. Supratentorial volume and sex were added as covariates for the volumetric analysis. Lin-