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Short Communication

Kynurenine pathway metabolites selectively associate with impaired associative memory function in depression

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ABSTRACT

Activation of the kynurenine pathway (KP), an important downstream effect of inflammation, is a driver of depression and neurodegeneration. Damage from the end product of KP activation, quinolinic acid, may be responsible specifically for impairment in hippocampally mediated memory function, among its effects. We hypothesized that associative memory – the ability to recall relationships between items – would be sensitive to KP activation because it is heavily dependent on the hippocampus. We tested a sample of N = 80 adults with unmedicated depression using a face-name task which assesses the ability to recognize, as well as to recall correct pairings, of faces and names. Plasma samples were analyzed for KP metabolites – tryptophan (TRP), kynurenine (KYN), quinolinic acid (QUIN) and kynurenic acid (KYNA). Using linear models we examined whether the KYN/TRP and QUIN/KYNA ratios predicted performance of recognition memory and associative memory, accounting for item type and the number of learning exposures to items (1 vs. 3). We found that for rearranged items viewed three times, associative memory performance was inversely related to the QUIN/KYNA ratio ($p = 0.01$, $p = 0.001$ adjusted for age, gender and race/ethnicity). Recognition memory was not associated with KP activation. The results support our hypothesis that KP activation most sensitively impacts hippocampally mediated memory function.

1. Introduction

Depression is a heterogeneous disorder with great impact on quality of life and function (Depression and Other Common Mental Disorders, 2017). Some symptoms of depression appear to contribute more to disability than others, especially fatigue, somatic symptoms, and cognitive impairment (Greer et al., 2010). Of these, cognitive symptoms may be persistent even after the resolution of a depressive episode itself, increasing their impact (Conradi et al., 2011). Cognition impairment, whether due to uni- or bipolar depression, is present across domains, including attention, executive function, and memory (Salagre et al., 2017; Trivedi and Greer, 2014). However, consistent with overall heterogeneity of presentation, depression-associated cognitive deficits are not found consistently, and vary in severity across domains (McClintock et al., 2010). Unfortunately, we have little understanding of factors that may account for this variance, and which could be harnessed to develop personalized treatment.

To study this further we considered the theory that inflammation, a pathophysiologic contributor to depression, may drive some of the impairments in cognition. Chronic low-grade inflammation is associated with cognitive decline in aging populations, as well as with age-related neurodegenerative disorders, such as Parkinson's disease and Alzheimer's dementia (Fakhoury, 2016; Stone and Darlington, 2013). Many chronic medical illnesses (e.g. cardiovascular disease) are associated with increases in systemic inflammatory cytokines, which are thought to activate microglia, causing neuroinflammation. This alters neurotransmitter activity and functional connectivity, and eventually may lead to neural degeneration and inhibition of neurogenesis all of which may impair cognition (Cunningham, 2013).

One of the specific neuroinflammatory mechanisms linking systemic

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inflammation and decreased cognition may be activation of the kynurenine (KYN) pathway (KP). The rate limiting initial enzyme, indoleamine 2,3 dioxygenase (IDO), is activated by inflammatory cytokines and converts tryptophan (TRP) to KYN, which is further catabolized differentially depending on the cell type and local environment (for a detailed description of the pathway, see Dantzer, 2017 (Dantzer, 2017)). Inflammation directs the metabolism of KYN toward the production of quinolinic acid (QUIN) instead of Kynurenic Acid (KYNA), increasing the ratios of KYN to TRP and QUIN to KYNA. QUIN is a glutamate receptor agonist, whereas KYNA an antagonist; elevated QUIN levels cause excitotoxic cell damage or death of neurons and oligodendrocytes (Sas et al., 2018). Activation of KP is predictive of the development of depression in patients undergoing inflammatory cytokine therapies (Capuron et al., 2002; Dantzer et al., 2008) and increased ratios of KYN/TRP and QUIN/KYNA are associated with depression (Reus et al., 2015; Ogyu et al., 2018). Although there is at best an inconsistent relationship between increasing activation of KP and overall depression severity (Reus et al., 2015; Ogyu et al., 2018), there is some support for a correlation between metabolite ratios and specific symptoms, including anhedonia (Savitz et al., 2015a) and cognition. In healthy older adults, KP activation predicts poorer memory, but not executive function, performance (Solvang et al., 2019). KP activation is associated with lower hippocampal volume in MDD; volume of the hippocampus (HPC) in turn is associated with memory deficit (Travis et al., 2015; Doolin et al., 2018; Savitz et al., 2015b). However, there is limited evidence connecting KP directly memory performance in depressed, non-elderly, human subjects (Wu et al., 2018; Young et al., 2016; Zhou et al., 2019).

We hypothesized that because it has more dependence on hippocampal function than other memory types, associative memory (Bird, 2017) would be relatively impaired by KP activation (assessed by KYN/TRP and QUIN/KYNA). To test this hypothesis, we assessed a sample of non-elderly, unmedicated, depressed adults using a face-name pairing task which compares associative memory to recognition memory.

2. Materials and method

2.1. Study design

The sample consisted of 101 unmedicated adults in a current Major Depressive Episode (MDE), of whom 80 were included in this analysis after excluding subjects who failed screening and those with missing metabolite or task data. The sample was recruited at the Center for Depression Research and Clinical Care at The University of Texas Southwestern Medical Center in Dallas, Texas. The primary goal of the study was to determine the relationship between immune activity and specific symptom domains in depression, according to the RDOC framework (Morris and Cuthbert, 2012).

2.2. Subjects

Adults, age 18 to 60, were recruited from the community via advertising. Inclusion criteria were a diagnosis of an MDE (uni- or bipolar depression) and a score of $\geq$10 on the Quick Inventory of Depression Symptomatology-Clinician Rated (QIDS-C), indicating at least mild severity. They were free of psychotropic and immunomodulating medications, including daily non-steroidal anti-inflammatory drugs for two weeks or five half-lives, and were in general good health without any clinically significant infection for at least two weeks. Chronic medical conditions such as hypertension or diabetes were allowed if subjects were on stable treatment and passed laboratory screening. Active substance use or eating disorders in the last 6 months, psychosis, or primary anxiety disorders were exclusionary.

2.3. Clinical assessments

Trained raters administered the Structured Clinical Interview for DSM-IV (SCID) and the Inventory of Depression Symptomatology – Clinician Rated (IDS-C) (from which the QIDS-C score was extracted) (Rush et al., 1996, 2003). Subjects completed the interview, task, and blood draw during the same visit.

2.4. Blood

Subjects fasted the night before the study visit and provided blood samples between 8:30 and 10:30am. Plasma was isolated from EDTA anticoagulated blood via centrifugation at 1200×*g* for 15 min, within 2 h of sample acquisition, and frozen at −80 °C until analysis. Metabolite analysis was performed by Brains Online (San Francisco, CA), quantifying TRP, KYN, KYNA and QUIN by High Performance Liquid Chromatography/Mass Spectroscopy. Samples were assayed in two batches; lower limit of quantification was 3 mM for TRP, 0.5 mM for KYN, 7.5 nM for KYNA and 100 nM for QUIN. No samples were below detectable limits. A coefficients of variation were <5%. Blood samples were also analyzed for High-Sensitivity C-Reactive Protein (HS-CRP), a commonly assessed marker of systemic inflammation, and complete blood count and basic metabolic panel, to rule out active infection and illness.

2.5. Task

Subjects completed a face-name pairing task, using ePrime Studio software, version 2.0.10.252 (Psychological Software Tools Inc, Pittsburg, PA), consisting of a study phase followed by a test phase. In the study phase subjects viewed black and white photographs of faces with names underneath (Minear and Park, 2004), each displayed for 2 s separated by a variable duration fixation cross. Each study phase included 30 pairs, 15 shown once, 15 shown three times. During the test phase, subjects viewed three types of test items 1) **Intact items:** faces paired with the same name seen in the study phase, 2) **rearranged items**: familiar faces paired with familiar names, but not in the same pairings shown in the study phase, and 3) **new items**: new faces and new names not included in the study phase. Subjects had unlimited time to respond. Two sets of study-test phases were run, for a total of 60 trials.

Data was processed into a composite metric, D′, commonly used in tasks requiring discrimination of a target category from other categories of items (Stanislaw and Todorov, 1999). True and false positive ("false alarm") response rates are computed, then converted into Z scores. D′ is calculated by taking the difference between the Z-scores for the true and false positive rates. For item memory, "intact" and "rearranged" responses are true positives for either item type (i.e. the subject recalled these items regardless of pairing) and false positives are "intact" or "rearranged" responses to new items. For associative memory, true positives were correct identification of "intact" and "rearranged" items and responses to new items were not considered. Eight D' scores were calculated, one for each combination of 1) memory type (associative or item), 2) test item type (rearranged or intact) and 3) number of exposures (1x or 3x).

2.6. Statistical analysis

In order to investigate the relationship between the 8 D′ memory scores and the 2 metabolite ratios, for each of the 16 combinations, an unadjusted linear regression model was fit to the data with the D' as the response and metabolite ratio as the explanatory variable. Each unadjusted model was investigated for influential observations using DFFITS with a threshold $2\sqrt{(p+1)(n-p-1)}$ (where n is the number of observations and p is the number of predictors). If influential observations were identified, we performed a sensitivity analysis by removing these observations and refitting the model on the reduced data set. Adjusted linear regression analyses were conducted using the same 8 response and 2 explanatory variables with age, gender, and race as adjusters. A exploratory model using Body Mass Index (BMI) as a quadratic term

Table 1
Sample characteristics, N = 80.

	Mean (std) or %
Age (years)	39.71 (11.9)
Race	
White	0.40
Black	0.35
Hispanic	0.15
Multi-Racial/Other	0.10
Gender	
Female	0.64
Male	0.36
Diagnosis	
MDD	0.88
Bipolar I	0.09
Bipolar II	0.04
IDS-C Score	37.5 (8.0)
C-Reactive Protein (mg/L)	2.58 (4.8)
Body Mass Index (kg/m^2)	30.91 (7.1)
KYN/TRP	0.04 (0.01)
QUIN/KYNA	7.1 (3.6)

adjustment (accounting for potential negative effects of very low and very high BMI) was also calculated. Confidence intervals were computed using 2000 bootstrap samples and the bias-corrected and accelerated bootstrap interval. To account for multiple comparisons, a Bonferroni adjusted significance level of $\alpha = 0.05/16 = 0.003$ was used.

To validate that KYN/TRP and QUIN/KYNA were related to inflammation in our sample we fitted a linear regression model of HS-CRP and KP metabolites adjusting for age, gender, and race/ethnicity. We also assessed whether overall depression severity measured on the IDS-C was related to KP metabolite ratios in a similar manner. All analysis was performed in R 3.6.1.

3. Results

Descriptive statistics for the sample are reported in Table 1. In the adjusted models of the exploratory analyses, both KYN/TRP and QUIN/KYNA correlated with HS-CRP ($p = 0.02$ and 0.04, respectively). IDS-C score did not significantly correlate with either ratio with adjustment. The sensitivity analyses showed only one model, D' for rearranged-1x predicted by QUIN/KYNA, had a coefficient which changed directions, but because this model was not significant, we present results for the full sample in the text and in Table 2.

We did not find significant relationships between item memory and KP metabolites (Table 2). One unadjusted model of associative memory showed a significant result, D′ rearranged-3x and QUIN/KYNA ($\beta = -2.50$; $p = 0.01$). This model maintained its direction and significance in the sensitivity analysis, but did not remain significant after Bonferroni correction. In the adjusted model containing age, gender and race/ethnicity, the results were similar. Two associative memory models had inverse partial correlations with $p < 0.05$, D′ intact -3x with QUIN/KYNA (-0.31 $p = 0.007$), and D′ rearranged-3x with QUIN/KYNA (-0.38 $p = 0.001$). After Bonferroni adjustment for 16 comparisons only the partial correlation between D' rearranged-3x and QUIN/KYNA remained significant using the adjusted threshold of $\alpha = 0.003$. In the exploratory model including BMI, the same two regression models remained significant with Bonferroni correction, and no other results gained significance.

4. Conclusions

We examined the relationship between memory performance in item recognition and associative memory on a face-name pairing task and KP metabolites in depression. We found that QUIN/KYNA was inversely associated with associative memory performance when subjects had multiple exposures during the study phase. The strength of the association was stronger for rearranged items than for intact items, possibly because correct identification of rearranged items is more difficult, or because correct identification of intact items is more similar to recognition. Overall our results agree with our hypothesis that HPC dependent associative memory is more sensitive to KP activation. More broadly, this result supports the theory that KP activation is important in cognitive, especially memory, deficits in depression. Interestingly, we found that when adjusted for demographic variables the strength of the associations increased. This was likely mostly driven by ethnicity; face recognition is affected by whether faces are of the same or a different race than the subject (Herzmann et al., 2017); in our sample approximately 60% of subjects were non-Caucasian while all the faces included in the task were Caucasian.

A limitation of plasma KP markers is that it is unclear whether circulating KYN metabolites reflect pathway activity in the brain. However, KYN crosses the blood brain barrier, and there is good correlation between cerebrospinal fluid and peripheral metabolite levels (Haroon et al., 2020; Jacobs et al., 2019). An alternate potential confounder is that conversion of TRP to KYN is activated in the liver by cortisol as well as

Table 2
Linear model results for the relationship between memory performance for different item types (e.g. intact items viewed one time in the study phase) and kynurenine pathway metabolites, unadjusted and adjusted for age, gender, and race/ethnicity.

D′ Item Type	Ratio	N	Unadjusted			Adjusted		
			Corr.	95% CI	p	Partial Corr.	95% CI	p
Associative Memory								
Intact x1	KYN/TRP	79	−0.02	(-0.207, 0.178)	0.85	0.00	(-0.2, 0.19)	0.98
	QUIN/KYNA	78	0.04	(-0.25, 0.326)	0.71	0.04	(-0.25, 0.35)	0.72
Intact x3	KYN/TRP	79	−0.01	(-0.202, 0.232)	0.92	−0.05	(-0.27, 0.18)	0.65
	QUIN/KYNA	78	−0.20	(-0.381, 0.017)	0.07	−0.31	(-0.54, −0.08)	0.007*
Rearranged x1	KYN/TRP	79	−0.04	(-0.32, 0.226)	0.75	−0.06	(-0.34, 0.2)	0.64
	QUIN/KYNA	78	−0.06	(-0.302, 0.204)	0.62	−0.11	(-0.36, 0.19)	0.35
Rearranged x3	KYN/TRP	79	−0.04	(-0.246, 0.22)	0.73	−0.08	(-0.35, 0.17)	0.5
	QUIN/KYNA	78	−0.27	(-0.475, −0.033)	0.02*	−0.38	(-0.61, −0.13)	0.001**
Item Memory								
Intact x1	KYN/TRP	79	0.01	(-0.101, 0.175)	0.93	0.03	(-0.15, 0.19)	0.78
	QUIN/KYNA	78	−0.04	(-0.294, 0.164)	0.75	−0.03	(-0.32, 0.19)	0.79
Intact x3	KYN/TRP	79	0.04	(-0.136, 0.188)	0.72	0.07	(-0.12, 0.28)	0.54
	QUIN/KYNA	78	−0.04	(-0.382, 0.198)	0.75	−0.03	(-0.37, 0.24)	0.82
Rearranged x1	KYN/TRP	79	0.03	(-0.152, 0.217)	0.79	0.03	(-0.14, 0.19)	0.83
	QUIN/KYNA	78	−0.06	(-0.289, 0.157)	0.61	−0.11	(-0.39, 0.1)	0.38
Rearranged x3	KYN/TRP	79	0.03	(-0.12, 0.185)	0.81	0.06	(-0.11, 0.25)	0.59
	QUIN/KYNA	78	−0.09	(-0.457, 0.147)	0.45	−0.07	(-0.4, 0.19)	0.56

* Significant at unadjusted $p < 0.05$.
** Significant at the multiple comparison Bonferroni adjusted significance level $p = 0.05/16 = 0.0031$.

inflammation. It is not possible to exclude the possibility that hypercortisolemia may mechanistically account for the association of kynurenine metabolism, measured peripherally, with depression and its symptoms. In order to truly support our hypothesis that these findings relate to hippocampal function, further studies examining cognition, KP activation, and neural structure and function directly (e.g. with functional imaging) are necessary. Finally, although we did see a relationship between KP activation and systemic inflammation as determined by HS-CRP, our study was not designed to assess the likely contributions of factors such as specific medical comorbidities or obesity and determine the nature of their interaction with inflammation and brain health. In particular because we lacked a health control group, it is not possible to fully attribute our results to a depression specific process and exclude contributions from other disorders.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bbih.2020.100126.

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