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Elevated peripheral kynurenine/tryptophan ratio predicts poor short-term auditory memory in panic disorder patients

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ABSTRACT

Abnormalities in the kynurenine pathway (KP) have been implicated in the cognitive deficits of psychiatry disorders, possibly through cytokines that increase the activity of indoleamine-2,3 dioxygenase (IDO), a key enzyme for tryptophan-to-kynurenine conversion. Some studies on panic disorder (PD) have detected elevated cytokines in blood. We aimed to determine the extent to which elevated peripheral cytokine levels and kynurenine/tryptophan (kyn/tryp) ratio (1) are biological markers for PD patients and (2) are related to cognition in PD. Seventy-eight PD patients and matched healthy controls were assessed for peripheral serum levels of interleukin (IL)-2R, IL-1β, IL-10, kynurenine and tryptophan. The subjects were evaluated for episodic and short-term memory, selective attention and cognitive flexibility. In patients, IL-2R levels, which are involved in the regulation of IDO, were significantly associated with levels of kynurenine ($p = .029$), but this association was not observed in controls. Importantly, an elevated kyn/tryp ratio significantly predicted poor digit span forward ($p = .004$) and total ($p = .004$) scores in individuals with PD. This study is the first to link blood biomarkers of infiammation and the KP with cognitive deficits in PD subjects, suggesting that those with an elevated kyn/tryp ratio might have short-term auditory memory impairment. These findings indicate that treatments targeting the KP may ameliorate cognitive abnormalities in PD patients.

1. Introduction

Biological abnormalities reported in panic disorder (PD) suggest multiple causative pathways, with no single biological etiology likely to be responsible for all cases (Roberson-Nay and Kendler, 2011). Therefore, improving interventions for PD may depend on identifying particular biological abnormalities that can be targeted with specific treatments.

Group comparisons have indicated abnormalities in specific brain regions in PD patients compared to those in controls, including differences in metabolic activity in the hippocampal and parahippocampal areas (Bisaga et al., 1998) and abnormalities in temporal lobe structures (Vythilingam et al., 2000). Brain abnormalities such as these may contribute to learning and memory deficits (Zhou and Ni, 2017). Furthermore, studies have found associations between PD and impairment in a number of cognitive areas, including executive function and working memory (Airaksinen et al., 2005; Alves et al., 2013; Palomares Castillo et al., 2010; Zhou and Ni, 2017).

Recent evidence suggests that cognitive deficits in psychiatric disorders might be related to the kynurenine pathway (KP) (Schwarcz et al., 2012). The initial and rate-limiting step of the KP is the conversion of tryptophan (tryp) to kynurenine (kyn), catalyzed by indoleamine 2,3-dioxygenase (IDO) or tryp 2,3-dioxygenase (TDO2) enzymes, which, in the brain, are preferentially expressed in immune cells, such as microglia (Guillemin et al., 2003; Schwarcz et al., 2012) (Fig. 1). Kyn can subsequently be metabolized into quinolinic acid (QUIN) or kynurenic acid (KYNA). These neuroactive metabolites may contribute to the cognitive deficits observed in mental disorders, as the kyn/tryp ratio is frequently elevated in these disorders (Birner et al., 2017; Okusaga et al., 2016; Platzer et al., 2017). Thus, the KP is an attractive target for the development of novel treatment strategies (Akagbosu et al., 2012; Chess et al., 2007; Chiappelli et al., 2018; Misztal et al., 1996; Rahman et al., 2018; Schwarcz et al., 2012). In addition, brain kyn is linked to and influenced by the peripheral KP (Schwarcz et al., 2012). As tryp and kyn readily cross the blood-brain barrier, fluctuations in the blood levels of these metabolites directly affect metabolism in the KP (Schwarcz et al., 2012).

One plausible hypothesis for abnormal KP metabolism is that elevated inflammatory activity drives elevations in kyn levels through the activation of IDO (Schwarcz et al., 2012). This enzyme is strongly stimulated by immune activation, including the inflammatory cytokines interleukin (IL)-1β (Zunszain et al., 2012), IL-10 (Yanagawa et al.,

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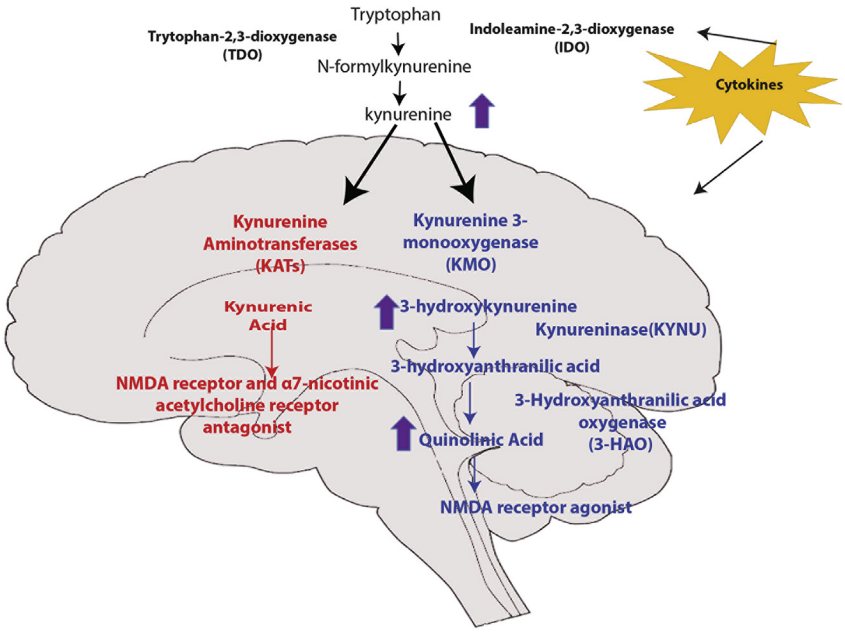

Fig. 1. The kynurenine pathway (KP) of tryptophan (tryp) metabolism. In the brain, kynurenine (kyn) metabolism can begin with the catabolism of tryp to kyn via either tryp 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). Kyn is metabolized either via kyn aminotransferases (KATs) to kynurenic acid (KYNA) in astrocytes or via kyn monooxygenase (KMO), kynureninase, and 3-hydroxyanthranilic acid oxygenase (3-HAO) to quinolinic acid (QUIN) in microglia. KYNA is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, and QUIN act as an agonist of this same receptor.

2009) and the IL 2 soluble receptor (IL-2R) (Szymona et al., 2017).

Comparisons of peripheral circulating cytokines between individuals with PD and controls have demonstrated that PD patients have higher mean serum levels of IL-6, IL-1β, IL-2 and other cytokines and even greater elevations in these substances during panic attacks (Quagliato and Nardi, 2018). Therefore, the relationship between peripheral cytokines and KP metabolites and especially their possible relevance for cognitive deficits in PD should be critically examined. Thus, we hypothesized that patients with PD display cognitive deficits in episodic, short-term memory, cognitive flexibility and selective attention, and that these deficits are associated with an elevated kyn/tryp ratio and elevated peripheral cytokine levels compared to those in healthy controls.

2. Materials and methods

2.1. Participants

Seventy-eight people with a diagnosis of PD and 78 age and sex-matched controls were recruited for this study (Supplementary Material). Patient recruitment was via either clinician or self/family referral. All patients were living in the community and had been receiving antidepressant medication, combined or not with a benzodiazepine, for at least 3 months prior to entry into the study (Supplementary Table 1). The diagnosis was determined by a structured clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) administered by a trained psychiatrist or psychologist and independently confirmed by a research psychiatrist. Antidepressant or benzodiazepine medication doses were obtained from the treating physician or from medical records and were converted to the mean daily fluoxetine or diazepam equivalent dose. The height and weight of all participants were recorded for body mass index (BMI) calculation. Healthy controls were recruited through self/family referral at the local community. The procedures were explained, and written informed consent was obtained from participants prior to participation in the study, which was approved by the research ethics committee of the Federal University of Rio de Janeiro. This study was performed according to the ethical standards of the Declaration of Helsinki.

2.2. Cognitive and symptom assessment

Cognitive function was assessed using the Rey Auditory Verbal Learning Test (RAVLT) for assessing episodic memory and learning (Moradi et al., 2017). Short-term and working memory were evaluated by the digit span task (Richardson, 2007; Sun et al., 2005). Selective attention was analyzed using the Stroop Neuropsychological Screening Test (Streeter et al., 2008). Cognitive flexibility was assessed as the time to complete the Trail Making Test, Part B minus the time to complete the Trail Making Test, Part A (TMT BA) (Hagenaars et al., 2018). The Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Panic and Agoraphobia Scale (PAS) were administered to all patients to obtain measures of general psychopathology and Clinical Global Impression (CGI) Scale were applied to evaluate total symptom severity. All assessments were made by psychiatrists trained in the administration and scoring of the assessments. For further details pertaining to cognitive test scoring, refer to the Supplementary Methods.

2.3. Inflammatory biomarkers

Blood was obtained in the morning (10 a.m. ± 1 h) in EDTA tubes through a catheter after participants had at least 30 min of rest. Blood was immediately centrifuged (1000 g for 10 min), and serum was removed and stored at −80 °C until the batched assay. The method used to measure tryp and kyn was the competitive inhibition immunoassay technique (cloud-Clone, Texas, USA). Concentrations of IL-1β, IL-10 and IL-2R were assessed using the Immulite System (Diagnostic Products Corporation), which is based on a solid phase two-site chemiluminescent enzyme immunometric assay (Berthier et al., 1999). See Supplementary Information for details of the biomarkers assays.

2.4. Statistical analyses

Statistical tests were performed using SPSS (version 17, OSX, IBM, Armonk, NY, USA) (IBM). The normal distribution of variables was tested using the Kolmogorov–Smirnov test. The quantitative cytokine IL-2R, IL-10, and IL-1β levels and kyn/tryp ratio were not normally distributed. We aimed to perform parametric tests, therefore we used log transformation in an intention to transform the data into normally distributed. However, no transformation resulted in satisfactory

normally distributed data of ILs, while log transformation resulted in normal distribution of the kyn/tryp ratio data. Thus, the Mann-Whitney *U* test and independent Student's t tests were performed to identify differences between diagnostic groups on cytokines and kyn/tryp, respectively. Multiple linear regression using stepwise methods were used to assess the relationship of the cytokine levels and kyn/tryp ratio with several potentially confounding variables related to sociodemographic, clinical, and physical characteristics (sex, age, years of education, years of illness, drug equivalents, ethnicity, physical activity, BMI, PAS, HAM-A, HAM-D and CGI) as independent variables. We used Bonferroni correction to control for multiple comparisons (a total of 13 variables were introduced; thus, the p-value threshold was set at 0.05/13 = 0.003). Multiple linear regression using stepwise methods was used to assess the relationship between cognitive scores and several potentially confounding factors related to sociodemographic and clinical characteristics (sex, age, years of education, years of illness, drug equivalents, PAS, HAM-A, HAM-D and CGI) as independent variables. We used Bonferroni correction to control for multiple comparisons (a total of 10 variables were introduced; thus, the p-value threshold was set at 0.05/10 = 0.005). Demographic differences between the groups were tested using t tests or $\chi 2$ tests for continuous and categorical variables, respectively. Student's t or Mann-Whitney U tests were performed on each cognitive measure to identify differences between diagnostic groups. Bonferroni corrections for multiple patient-control group comparisons were applied to analyses of cognitive measures, such that only group comparisons with $p < 0.008$ (0.05/6) for Student's t and $p < 0.01$ (0.05/5) for Mann-Whitney were considered significant. Linear regression using cognitive scores as the independent variable was performed to assess the strength of the relationships among cognition, levels of ILs, the kyn/tryp ratio, and possible cofounders, such as age, educational level and medications (a total of 8 variables were introduced; thus, the p-value threshold was set at 0.05/8 = 0.006). Furthermore, linear regression using kyn and tryp as the dependent variables was performed to assess the strength of the relationships among kyn and tryp expression and IL levels.

3. Results

3.1. Relationship of cytokines and the kyn/tryp ratio to demographic factors

The patient and control groups were not significantly different in educational level (Table 1). However, there was a significant difference between groups in the kyn/tryp ratio (t (2.75) = 95.9; p = 0.007). In addition, IL-1β levels also showed a significant difference between groups (U = 1798; p = 0.017), but this difference did not survive multiple testing corrections. There were no significant associations of cytokine levels and the kyn/tryp ratio with age, sex, years of education, BMI, physical activity, ethnicity, age of onset, fluoxetine or diazepam equivalent dose, PAS, HAM-A, HAM-D or CGI scores.

Table 1
Demographics of study participants.

Demographic	PD (n = 78)	Controls (n = 78)	Difference
Education in years (range)	13.24	12.57	ns
BMI (mean and s.d.)	22.92 (2.89)	23.04 (3.22)	ns
Physical exercise	44 N:34 Y	40 N:38 Y	ns
Age of onset (in years and range)	27.07 (17–46)		
PAS	26.30 (7.1)		
CGI	3.3 (0.69)		
HAM-A	24.25 (13.9)		
HAM-D	5.64 (4.07)		
Antidepressants and benzodiazepines (frequency in total cohort)	Antidepressants (100%) Benzodiazepines (11,5%)		

Abbreviations: ns, not significant; BMI, body mass index; PAS, Panic and Agoraphobia Scale; CGI, Clinical Global Impression Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale.

3.2. Relationship of cognitive scores to demographic and clinical factors

The multiple regression model showed that educational level and sex were associated with the RAVLT learning score (adjusted $R^2 = 0.83$, F = 16.66, β = 0.91, p = 0.001 and β = 0.69, p = 0.004, respectively) in PD patients. Although age was also associated with RAVLT learning scores (β = −0.36, p = 0.035), this model did not survive multiple test corrections. Years of illness predicted delta Trail Making Test scores (adjusted $R^2 = 0.43$, F = 7.93; β = −0.70, p = 0.023), and HAM-D scores were associated with the digit span backward score (adjusted $R^2 = 0.50$, F = 10.23; β = 0.74, p = 0.013). However, none of these models survived Bonferroni's correction.

3.3. Relationships among kyn, tryp and cytokines

Since cytokines, such as IL-10, IL-1β and IL-2R, increase the activity of IDO, a key enzyme for tryptophan-to-kynurenine conversion, we evaluated the relationships among kyn and tryp expression and cytokines levels. The multiple regression model showed that IL-2R levels explained 7.5% of the variance in kyn levels (adjusted $R^2 = 0.075$, F = 5.058; β = 0.306, p = 0.029) in PD patients; however, IL-2R levels did not predict kyn levels in controls. Tryp was not significantly correlated with any of the cytokines measured in either group examined independently.

3.4. Relationships between the kyn/tryp ratio and cognitive scores

Performance on the majority of cognitive tests was significantly lower in PD patients than in controls (for details see Table 2 and supplementary Table 2 on Supplementary materials). There was a significant difference between PD patients and the control group in digit span forward and total (t (134) = 2.63; p = 0.009; t (135) = 3.0; p = 0.003, respectively), RAVLT learning (t (128) = −5.3; $p < 0.0001$), RAVLT forgetting (t (128) = -7.4; $p < 0.0001$), RAVLT immediate (U = 17; $p < 0.0001$), TMT BA (U = 938, $p < 0.0001$), Stroop A (U = 829; $p < 0.0001$), and Stroop B (U = 1484.5; $p < 0.0001$) scores. The differences in digit span backwards and Stroop C scores were not significantly different between groups after multiple testing correction.

In individuals with PD, an elevated kyn/tryp ratio significantly predicted poor subdigit forward scores (adjusted $R^2 = 0.672$, F = 16.38; β = -0.82; p = 0.004) and subdigit total scores (adjusted $R^2 = 0.673$, F = 15.404; β = -0.811; p = 0.004), which remained statistically significant after Bonferroni's correction (Fig. 2). An elevated blood kyn/tryp ratio was also a biomarker of low Stroop B and C scores (adjusted $R^2 = 0.438$, F = 8.00; β = 0.70; p = 0.022; adjusted $R^2 = 0.389$, F = 6.72; β = 0.67; p = 0.032, respectively). However, this model did not remain statistically significant after multiple testing correction (Table 3). In addition, Stroop A scores were predicted by IL-2R levels (adjusted $R^2 = 0.400$, F = 6.99; β = -0.68; p = 0.030), and RAVLT learning was predicted by educational levels (adjusted $R^2 = 0.360$, F = 6.06; β = 0.657; p = 0.039). Nevertheless, none of these models remained statistically significant after Bonferroni's correction. No significant relationships were found through regression analysis between the kyn/tryp ratio and cognitive scores in healthy controls.

4. Discussion

Our study found evidence that patients with PD presented an elevated peripheral kyn/tryp ratio. An elevated peripheral kyn/tryp ratio

Table 2
PD patients performed worse than controls in short-term and episodic memory, selective attention and cognitive flexibility.

Cognitive domains	Cognitive tests	Patients (mean (sd))	Controls (mean (sd))	p-value
Short-term memory	Digit-span total	12.0 (4.2)	14.06 (3.58)	p = 0.003
Selective attention	Stroop B	21.49 (4.72)	18.42 (4.02)	p < 0.0001
	Stroop C	32.47 (9.47)	33.92 (9.60)	p = 0.45
Cognitive flexibility	TMT B-A	70.63 (12.62)	49.60 (42.78)	p < 0.0001
Episodic memory	RAVLT Learning	3.61 (2.51)	6.66 (3.62)	p < 0.0001

Abbreviation: TMT B-A, Trail making Test B minus A; RAVLT, Rey's Auditory Verbal Learning Test; sd, standard deviation.
Stroop C score did not remain statistically significant after multiple testing correction.

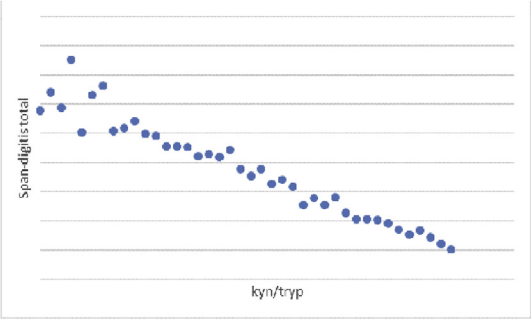

Fig. 2. Increases in kyn/tryp ratio predict decreases in span-digits total score in individuals with PD (β = −0.811, p = 0.004).

Table 3
Relationship between the kyn/tryp ratio and cognitive measurements in PD patients.

Cognitive test	β	Adjusted R Squared	p value
Subdigits total	- .811	.673	.004
Subdigits forward	- .82	.672	.004
Stroop B	.70	.438	.022
Stroop C	.67	.389	.032

kyn/tryp ratio, dependent variable. Associations between kyn/tryp and Stroop B and C tests did not remain statistically significant after multiple testing correction.

has been associated with cognitive deficits in a variety of mental disorders (Birner et al., 2017; Schwarcz et al., 2012). In PD, this increase in kyn metabolism was associated with poor short-term verbal memory. In addition, IL-2R levels predicted kyn levels in PD patients but not in controls. These observations may be indicative of abnormal peripheral IDO activation in PD patients, since cytokines, such as IL-2R, increase the activity of IDO, a key enzyme for kyn conversion.

In the current study, a high peripheral kyn/tryp ratio in PD patients but not healthy subjects was correlated with cognitive deficits, namely, low short-term verbal memory. Deficits in short-term memory, the ability to keep a small amount of information available for a short period of time, have been related to PD (Alves et al., 2013; Gordeev, 2008; Palomares Castillo et al., 2010) and might be associated with glia cells (Azevedo et al., 2013; Li et al., 2014). Activated microglia mediate synapse loss and short-term memory deficits in animal models (Azevedo et al., 2013). Furthermore, although the hippocampus has long been thought to be exclusively involved in long-term memory processes (Scoville and Milner, 1957; Squire et al., 1993), several studies have raised doubt on this traditional view by emphasizing its role within an integrated operational network that also covers short-term memory functions (Beyer et al., 2013; Finke et al., 2008; Henke, 2010; Nee and Jonides, 2008; von Allmen et al., 2014; von Allmen et al., 2013). In the hippocampal region of the central nervous system, the birth of new neurons occurs throughout life, and the amount of neurogenesis correlates closely with the hippocampal functions of learning and memory (Monje et al., 2003). Impaired adult neurogenesis is associated with short-term memory deficits (Denis-Donini et al., 2008). Proinflammatory cytokines have been shown to decrease adult hippocampal neurogenesis possibly through the KP (Zunszain et al., 2012). In the hippocampus, peripheral inflammation induces brain region-dependent changes in the balance of kyn metabolites, favoring neurotoxic metabolite production (Parrott et al., 2016). Specifically, microglia in the hippocampus are more responsive to proinflammatory stimuli, earning them the label 'immunovigilant' (Parrott et al., 2016). This hyperresponsive state of hippocampal microglia may underlie the region-specific elevation in neurotoxic kyn metabolism (Parrott et al., 2016). Therefore, metabolites of the KP and activation of glial cells could contribute to the observed deficits in short-term memory in PD (Fig. 3).

Cognitive deficits described in PD patients might also be related to hippocampal pattern separation (Hu and Dolcos, 2017). Hippocampal pattern separation is the process of encoding details of an environment in an intention to allow individuals to distinguish between similar memories (Lange et al., 2017), and is the resultant ability to resolve memory interference, or to discriminate previously encoded stimuli from highly similar stimuli (Bernstein and McNally, 2018; Lange et al., 2017). Pattern separation is related to the neuron suppression of the excitability of the dentate gyrus so that stimuli trigger unique patterns of activation in this region, decreasing the likelihood that two stimuli activate overlapping representations (Bernstein and McNally, 2018). Without this inhibitory action, two cues may be encoded as insufficiently distinct, and consequently interpreted as overly similar (Bernstein and McNally, 2018). Impaired pattern separation may be a risk factor for PD (Lange et al., 2017). Indeed, patterns of encoding ambiguous cues as more threatening could influence cognitive measurements and might be associate to a deficient pattern separation (Bernstein and McNally, 2018). Thus, it is possible that a non-functional behavioral pattern separation could be underlying the cognitive deficits demonstrated in PD patients.

Although PD patients performed worse than controls in almost all cognitive tests, not all cognitive measures were associated with an increase in kyn metabolism, which may be explained by the differential

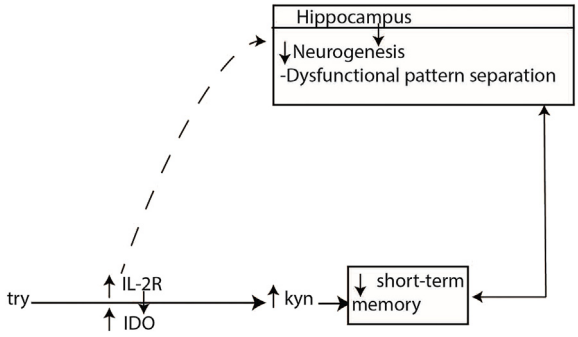

Fig. 3. IL-2R increases the activity of IDO, a key enzyme for kyn conversion, therefore contributing to an increase in kyn. This increase in kyn is associated with poor short-term verbal memory in PD patients. Poor short-term memory might be related to reduced hippocampal neurogenesis and dysfunctional hippocampal pattern separation.

expression of functional markers in microglia across brain regions (Chhor et al., 2013). Kyn metabolism may also differ across brain regions (Parrott et al., 2016). Microglial phenotypes are shaped by the local environment (Grabert et al., 2016), and the microenvironment is not uniform throughout the brain (Grabert et al., 2016). Variations in neuronal subtypes, neurotransmitter profiles, hemodynamics and metabolism could all influence and be influenced by the local microglial phenotype (Grabert et al., 2016; Quagliato et al., 2018).

There are several potential confounding factors common to case-control studies of PD that are relevant to the present study. The correlations between the kyn/tryp ratio and cognitive function may not be directly related in a causal manner, but, rather, both may change as a consequence of other factors. A worse performance on cognitive tests, for instance, could be related to the chronicity and severity of an illness, educational levels of a patient or even medication treatments. In the current study, medication treatments were not associated with cognitive deficits. However, this must be interpreted with caution since the small PD population may have contributed to this matter. Thus, since benzodiazepines are associated with cognitive deficits in specific populations (Nardi et al., 2018), the fact that some PD patients were on benzodiazepines medications, could have influenced memory scores tests of PD patients. The current data showed that only RAVLT learning scores in PD patients were associated with educational levels and sex, and other demographic and clinical factors were not related to any cognitive scores. One important potential confound is that all of the individuals with PD in our study were receiving antidepressants. Recent studies of cytokine measures have suggested that antidepressants may result in decreases in peripheral cytokine levels (Wiedlocha et al., 2018). Because all patients in the current study were on antidepressants, the antiinflammatory effects of these drugs cannot be ruled out. PD patients may display an infiammatory profile if not on antidepressants. Regarding the KP, different antidepressants exert a variety of effects on kyn and tryp levels (Reus et al., 2015). Treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants inhibits IDO, while treatment with tricyclic antidepressants, such as imipramine, decreases the kyn/tryp ratio (Reus et al., 2015). As exposure to antidepressants could suppress IDO and therefore decrease the kyn/tryp ratio, one would expect more subjects with an altered KP profile in an unmedicated sample; therefore, exposure to antidepressants is unlikely to explain our findings of many PD patients presenting an elevated kyn/tryp ratio. There are several other limitations to the current study; recent research has indicated that aerobic exercise can reduce kyn levels in humans (Schlittler et al., 2016). Although we did account for levels of physical exercise, which were not significantly different between patients and controls (Table 1), we did not control for exercise type, which could have interfered with the results. Another potentially relevant limitation is that up to 80% of kyn in the plasma appears to be bound to albumin or other circulating binding proteins (Fukui et al., 1991). As only total plasma levels of this metabolite were measured in the present study, we may have missed a higher group difference caused by the possible differential availability of free kyn, which can readily penetrate the blood-brain barrier and then function as a highly effective bioprecursor of KYNA and QUIN within the brain (Schwarcz et al., 2012).

The challenges of determining to what extent blood biomarkers vary across the course of the illness and in response to factors such as symptom status emphasize the importance of studying the relationship among brain structural changes, clinical features and blood biomarkers of the KP and inflammation using a longitudinal design that includes subjects after first-episode panic attacks and in acute relapses. Future studies should also systematically obtain data on lifestyle factors to aid in the interpretation of the potentially elevated kyn/tryp ratio. An interesting question raised by our study is the extent to which the elevated peripheral kyn/tryp ratio reported here is indicative of the elevated brain kyn, KYNA and QUIN levels found in postmortem samples of PD patients. The main boundary between peripheral circulation and the brain is the blood-brain barrier (Schwarcz et al., 2012). Increased kyn can cross the blood-brain barrier, be converted to QUIN and KYNA and lead to neurotoxicity, potentially resulting in alterations in brain morphology (Schwarcz et al., 2012). Therefore, further in vivo and postmortem research into a possible KP alteration-based mechanism could contribute to the pathophysiology of PD. Furthermore, because KP enzymes are mostly localized in glia cells (Schwarcz et al., 2012), the observed impaired short-term auditory memory related to the increase in the kyn/tryp ratio suggests that targeted treatment of individuals with PD displaying the elevated kyn biomarker with inhibitory KP agents may be beneficial for short-term memory deficits. Nevertheless, very few therapeutic agents specifically targeting glia cells and the KP have entered clinical studies (Biber et al., 2016), likely due to several unresolved issues, including challenges related to glia target specificity, central nervous system penetrance and the profound differences between mouse and human glia (Biber et al., 2016).

This study is the first to link blood biomarkers of infiammation and KP with cognitive deficits in people with PD. Independent replication of these findings would support further clinical trials of inhibitory KP drugs in PD patients presenting poor cognitive function, which could lead to effective novel treatments for people with PD. Importantly, future studies might focus on an estimation of the kyn/tryp ratio in parallel with a determination of other immune factors to confirm the involvement of IDO activity in deregulated tryp breakdown. These might be a valid tool to monitor the progression of cognitive deficits and has great potential to be applied to check treatments and estimate the necessity of psychiatric interventions before aggravation of symptoms, thus serving to personalize therapeutic strategies.

Conflicts of interest

The authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2019.03.027.

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