Stress-Induced Increase in Kynurenic Acid as a Potential Biomarker for Patients With Schizophrenia and Distress Intolerance

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IMPORTANCE Several lines of evidence have linked the endogenous neuromodulator kynurenic acid (KYNA) to schizophrenia. The pathophysiology of schizophrenia is commonly associated with stress, and stress plays a key regulatory role in the first, rate-limiting step of the kynurenine pathway, which produces KYNA.

OBJECTIVE To determine whether the level of KYNA changes following psychological stress and whether this change is associated with stress-related behavior.

DESIGN, SETTING, AND PARTICIPANTS The KYNA level was measured in saliva samples taken at baseline and at 2 times following a laboratory-based psychological stress challenge in 128 participants (64 patients with schizophrenia from outpatient clinics and 64 healthy controls from the community).

EXPOSURE Laboratory-based psychological stress challenge.

MAIN OUTCOMES AND MEASURES Quitting the stressful task early was used as a behavioral marker of distress intolerance.

RESULTS Patients with schizophrenia showed a significantly higher rate of distress intolerance compared with healthy controls ($P = .003$). Salivary KYNA levels increased significantly between baseline and 20 minutes following the stress task in both patients and controls (mean [SEM], 6.72nM [0.65nM] vs 8.43nM [1.05nM], respectively; $P = .007$). Patients who were unable to tolerate the stressful tasks and quit early showed significantly higher levels of KYNA than patients who tolerated the psychological stressor ($P = .02$) or healthy controls ($P = .02$). In patients with distress intolerance, KYNA elevation significantly correlated with the severity of clinical symptoms ($p = 0.64; P = .008$).

CONCLUSIONS AND RELEVANCE Distress intolerance is more common in patients with schizophrenia. Patients with this behavioral phenotype have elevated salivary KYNA levels. This stress response behavior-linked biomarker may aid heterogeneity reduction in schizophrenia and other stress-related psychiatric conditions.
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onverging lines of evidence implicate abnormalities in the kynurenine pathway (KP) of tryptophan degradation in schizophrenia. Increased concentrations of the KP metabolites kynurenine and kynurenic acid (KYNA) have been found in postmortem brain tissue and cerebrospinal fluid of individuals with schizophrenia. Moreover, genetic variants in KP enzymes have been linked to psychotic symptoms, cognitive dysfunctions, and abnormal levels of KYNA. At higher concentrations, KYNA can also be neuroprotective in conditions of excitotoxicity. However, the clinical significance of kynurenines, KYNA can also be neuroprotective in conditions of fluids of individuals with schizophrenia. Moreover, genetic dioxygenase (IDO-1 and IDO-2). Then, KYNA is produced from kynurenine through irreversible transamination by kynurenine aminotransferases (see the article by Schwarcz et al for review).

The rate-limiting step of the KP is the initial conversion of tryptophan to kynurenine, which is controlled by 2 enzymes, tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO-1 and IDO-2). Then, KYNA is produced from kynurenine through irreversible transamination by kynurenine aminotransferases (see the article by Schwarcz et al for review).

Stress, broadly defined as environmental factors that threaten well-being and demand a homeostatic response from an individual, has been implicated in all stages of schizophrenia. Specifically, stress is a risk factor in the neuropathological etiology of schizophrenia during pregnancy. Stress is also associated with the onset and progression of symptoms in adolescence and is often linked to exacerbation of psychotic symptoms in adulthood. In animal models, stressors robustly induce TDO activity and thereby stimulate the formation of KYNA and other KP metabolites, in part through activation of the hypothalamic-pituitary-adrenal axis. Stress also increases kynurenines through IDO, an enzyme typically regulated by cytokines. For example, acoustic stress and restraint stress in animals induce IDO gene expression and the subsequent increase in kynurenine and KYNA levels, and this effect is blocked by pretreatment with antibodies to inflammatory cytokines. In humans, the stress of anticipating surgery was found to be associated with an increased plasma kynurenine to tryptophan ratio, suggestive of increased IDO activity. These findings collectively suggest the existence of pathways by which stress can increase the formation of KYNA and other KP metabolites.

Thus, the KP, with TDO and IDO as critical points of regulation, is a potential nexus for mechanisms linking stress to clinical dysfunctions in schizophrenia. However, direct evidence of stress responsiveness of this pathway in schizophrenia is lacking. In this study, we aimed to investigate responsiveness of KYNA to psychological stress in people with and without schizophrenia and to test the hypothesis that a KYNA response to stress can serve as a biomarker for maladaptive stress-related behaviors in the disease. Using a noninvasive method to functionally interrogate this pathway, we examined KYNA reactivity in saliva collected before and after a laboratory-based psychological stress task.

Methods

Participants

Patients were recruited from the outpatient clinics at the Maryland Psychiatric Research Center and neighboring mental health clinics. Healthy controls were recruited through media advertisements and random digit dialing. Diagnoses were confirmed with the Structured Clinical Interview for DSM-IV in all participants. Major medical and neurological illnesses, history of head injury with cognitive sequelae, mental retardation, substance dependence within the past 6 months, or current substance abuse (except nicotine) were exclusionary. Controls had no current DSM-IV Axis I diagnoses and no family history of psychosis in the prior 2 generations. Participants gave written informed consent, and this study was approved by the University of Maryland institutional review board.

A total of 148 participants of an ongoing study were included, consisting of 69 persons with schizophrenia (including 15 individuals with schizoaffective disorder) and 79 community controls, all of whom completed the behavioral task for stress challenge. (Behavioral data on the initial 108 participants of the current study have been presented previously.) Salivary KYNA was assayed in 64 patients and 64 controls, frequency matched for age, sex, and smoking status. These 128 participants were selected based only on these demographic characteristics, i.e., without knowledge of behavioral results and prior to the salivary assay. Demographic characteristics of the samples are shown in the Table.

Of the patients with schizophrenia tested for salivary KYNA, 11 were not taking any medication for 1 month or longer, 6 were receiving first-generation antipsychotic medications, and the remaining 47 were receiving second-generation antipsychotic medications, including 11 receiving clozapine and 8 receiving or more antipsychotic medications.

Psychiatric symptoms were assessed with the 20-item Brief Psychiatric Rating Scale total score, and cognitive capacities were assessed by processing speed (digit symbol coding subtest of the Wechsler Adult Intelligence Scale, third edition) and working memory (digit sequencing task). Processing speed is considered the most robust cognitive domain deficit in schizophrenia.

Psychological Stress Challenge Task

The stressor used for this study was developed to examine distress intolerance, defined as an inability to persist in goal-directed behavior while distressed. This was operationalized using the experimental procedure illustrated in Figure 1. All participants completed a psychological stress challenge consisting of 2 computer tasks, the Paced Auditory Serial Addition Task and the Mirror-Tracing Persistence Task. The tasks were designed to be arbitrarily difficult and punitive to induce psychological stress to the extent that some participants would choose to forego the reward for success and quit. The Paced Auditory Serial Addition Task requires participants to sum consecutive numbers presented briefly on the computer screen and to respond by using the mouse to click on the correct answer. Incorrect answers cause the
Questions on negative affect

Abbreviations: BPRS, Brief Psychiatric Rating Scale; KYNA, kynurenic acid.

Completed a self-rating of emotions (see later) and then (Figure 1). After completion of the first task, the participants were debriefed; this consisted of disclosing that the task was meant to be stressful and giving the participant an opportunity to ask questions.

The stress challenge consisted of the Paced Auditory Serial Addition Task (PASAT) and the Mirror-Tracing Persistence Task (MTPT). The order of the tasks was randomized across participants. Subjective feeling of negative affect was measured using the Positive and Negative Affect Schedule at 3 points during the study session (arrowheads). Saliva was collected at baseline and then again at 20 and 40 minutes after the end of the stress challenge. The duration of the stress challenge varied between participants depending on whether a participant quit 2, 1, or 0 tasks.

The Mirror-Tracing Persistence Task asks participants to use the mouse to trace a dot along the outline of a star on the computer screen. Tracing is challenging because the cursor movement is opposite to the movement of the mouse, similar to tracing a mirror image. The width of the star outline is titrated depending on performance to make the challenge similarly difficult across participants. Any error (touching or tracing outside the outline) or delay in moving triggers the loud explosion noise and forces the participant to restart from the beginning. The Mirror-Tracing Persistence Task lasted up to 13 minutes, including a training session.

Combining the 2 tasks allows for a more rigorous definition of distress intolerance by reducing the potential skill-dependent bias that would result if some participants were particularly skilled at arithmetic or eye-hand coordination. The order of tasks was randomized across participants (Figure 1). After completion of the first task, the participants completed a self-rating of emotions (see later) and then immediately began reviewing instructions for the next task, all under a computerized automatic sequence. Participants were informed that they would receive a monetary reward based on completing the tasks but were not told the maximum amount of time allowed. Participants were given the operational definition of distress intolerant if they quit both tasks before completion. They were considered distress tolerant if they tolerated 1 or 2 tasks. A monetary bonus of $20 was given for not quitting, and $10 was given if the participant quit any or both tasks, although this was revealed only after completion of testing. After completion, participants were debriefed; this consisted of disclosing that the task was meant to be stressful and giving the participant an opportunity to ask questions.

Participants completed the Positive and Negative Affect Schedule at baseline and after each of the 2 tasks to measure subjective affect reactivity (Figure 1). This scale asks participants to rate how they feel along a 5-point Likert scale for 10 positive affect and 10 negative affect (NA) items. In this study, we used only NA scores. This score represents a general dimension of subjective distress. Negative affect reactivity was defined as the maximum change in NA after completing either task compared with baseline, and it was used to examine whether the KYNA response, if any, was associated with a subjective change in NA.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire Sample</th>
<th>KYNA Sample*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Controls (n = 79)</td>
<td>Patients With Schizophrenia (n = 69)</td>
</tr>
<tr>
<td>Age, mean (SEM), y</td>
<td>38.9 (12.8)</td>
<td>38.1 (12.4)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>42 (53.2)</td>
<td>47 (68.1)</td>
</tr>
<tr>
<td>Smoker, No. (%)</td>
<td>28 (35.4)</td>
<td>33 (47.8)</td>
</tr>
<tr>
<td>Working memory normalized z score, mean (SEM)</td>
<td>0.25 (0.89)</td>
<td>−0.35 (1.06)</td>
</tr>
<tr>
<td>Processing speed normalized z score, mean (SEM)</td>
<td>0.43 (1.35)</td>
<td>−0.40 (0.68)</td>
</tr>
<tr>
<td>BPRS total score, mean (SEM)</td>
<td>2.0 (0.52)</td>
<td>2.0 (0.52)</td>
</tr>
</tbody>
</table>

Values are χ².

The BPRS scores were the total scores divided by the number of items (I indicates no symptoms in any items).

Abbreviations: BPRS, Brief Psychiatric Rating Scale; KYNA, kynurenic acid.

* All participants in the KYNA assay sample were in the overall sample but were preselected to achieve better match in age, sex, and smoking status.

Values are F scores.

Figure 1. Schematic Illustration of the Experimental Procedure

The computer program tracks participant skill and titrates the speed of the presentation of the numbers to ensure that the task remains challenging despite variability in the participants’ cognitive abilities. The Paced Auditory Serial Addition Task could last up to 12 minutes, including a training session.

Computer to play a loud (90- to 95-dB sound pressure level) explosion noise. The computer program tracks participant skill and titrates the speed of the presentation of the numbers to ensure that the task remains challenging despite variability in the participants’ cognitive abilities. The Paced Auditory Serial Addition Task could last up to 12 minutes, including a training session.
Saliva samples were collected at 3 times: at baseline (before participants started either task) and at 20 minutes and then 40 minutes following the completion or quitting of the second task. To minimize variability in salivary KYNA levels, all participants were instructed to avoid eating, smoking, or brushing their teeth in the hour before the distress task, and all participants were asked to rinse their mouth with water 10 minutes prior to the first saliva collection.

Saliva was collected into cryovials through passive drool, and the cryovials were stored at −80°C. The volume of saliva and the time used to collect each saliva sample were recorded. On the day of the assays, saliva samples were thawed and centrifuged (10 000g for 10 minutes), and 50 μL of saliva was mixed with 50 μL of ultrapure water and then acidified with 25 μL of 6% perchloric acid. After centrifugation (10 000g for 10 minutes), 20 μL of the supernatant was subjected to high-performance liquid chromatography, and KYNA was isocratically eluted and fluorimetrically detected as previously described.26 Assays were performed by investigators blinded to group or behavior information. Intra-assay reliability was assessed using triplicates. Cortisol was assayed in the same saliva samples using a commercial kit (Salimetrics, LLC).

Statistical Analysis
Biochemical data are presented as mean (SEM). Repeated-measures analysis of variance (ANOVA) was used to examine effects of diagnosis (patients or controls), distress intolerance (yes or no), and time on salivary KYNA levels. Statistical significance used Greenhouse-Geisser corrections when there were more than 2 levels of repeated measure. Group categorical comparisons used 2-sided χ² tests. Nonparametric tests were used to examine group differences and correlations for dependent variables that did not exhibit normal distributions. All comparisons were 2-tailed.

Results

Behavioral Differences in Distress Intolerance
Patients were significantly more likely to be distress intolerant than controls (χ² = 8.55; P = .003) (Figure 2). Among patients, those identified as distress intolerant had lower processing speed than those who were not distress intolerant (F₁,₁₁₁ = 4.29; P < .001), but they did not differ in working memory performance (P = .10) or Brief Psychiatric Rating Scale total score (t = 0.25). Controls did not differ in processing speed (P = .69) or working memory (P = .41) based on distress intolerance classification.

Salivary KYNA Levels
In excellent agreement with findings by Kuc et al,26 the mean (SEM) basal salivary KYNA level in the control group was 6.02nM (0.74nM). In patients, the mean (SEM) level was 7.40nM (1.05nM) (Figure 3 and eTable in Supplement). The average intra-assay coefficient of variation was 5.1%.

Repeated-measures ANOVA of time (baseline, and 20 minutes and 40 minutes after test) and diagnosis (patients or controls) revealed a main effect of time (F₁,₁₁₁ = 6.01; P = .007) but no significant interaction between time and diagnosis (P = .56) or main effect of diagnosis (P = .84). Post hoc tests revealed that KYNA levels were significantly higher at 20 minutes after the test (mean [SEM], 8.43nM [1.05nM]) than at baseline (mean [SEM], 6.72nM [0.65nM]) (P = .007). At 40 minutes after test, levels had declined (mean [SEM], 7.22nM [0.74nM]) but were still elevated compared with baseline (P = .09). These results demonstrate a transient increase in salivary KYNA following a stressful task that was similar in patients with schizophrenia and healthy controls when not accounting for distress intolerance.

Because of the possibility that stress can cause “dry mouth” and thus concentrate salivary analytes, we calculated a proxy measure of salivary flow rate based on the volume and time of collection for each sample. Salivary flow rate actually increased between baseline and the poststress periods in the combined sample (F₁,₁₁₁ = 6.01; P = .007). Controls did not differ in processing speed (t = .25) or working memory (t = .31) but were between distress-intolerant and distress-tolerant participants (P = .24).

Distress Intolerance and KYNA Interaction
To account for behavioral differences between groups, a repeated-measure ANOVA tested the KYNA response where time (baseline and 20 minutes after test) was the repeated measure and diagnosis (patients or controls) and distress response (yes or no) were 2 factors. This analysis revealed a significant main effect of time (F₁,₁₁₁ = 5.84; P = .02) and a diagnosis × distress response interaction (F₁,₁₁₁ = 4.56; P = .04) (Figure 3). As shown in Figure 3, increased mean KYNA levels were seen at 20 minutes in all groups, and overall higher KYNA levels were observed in the subgroup of patients with distress intolerance.
Post hoc tests confirmed the pattern as follows: (1) analysis of simple effects exclusively for patients revealed that individuals with distress intolerance had significantly higher salivary KYNA levels than distress-tolerant patients across time ($F_{1,54} = 6.25, P = .02$) but showed no significant time × distress intolerance interaction ($P = .35$); (2) patients with distress intolerance also had a significantly greater KYNA response than controls across time ($F_{1,74} = 6.02, P = .02$); and (3) in comparison, analysis of simple effects for controls showed no significant main effect ($P = .84$) or distress intolerance × time interaction ($P = .26$). These results reveal a different pattern of KYNA change in patients with schizophrenia displaying the behavioral phenotype of distress intolerance. Thus, compared with patients without distress intolerance, these patients had significantly higher salivary KYNA levels following the stress challenge (Cohen $d = 0.61$). This effect was more robust in patients with schizophrenia because distress intolerance in controls was not significantly associated with KYNA elevations compared with controls without this phenotype (Cohen $d = 0.18$).

The correlation between salivary KYNA baseline level or ΔKYNA (difference between levels at baseline and 20 minutes after challenge) and chlorpromazine dosage equivalent of antipsychotic medication was not statistically significant ($p = 0.18, P = .19$ and $p = 0.073, P = .63$, respectively). Moreover, patients taking an antipsychotic drug did not have significantly different baseline KYNA levels (Mann-Whitney $U$ test, $U = 219, P = .34$) or a significantly different ΔKYNA (Mann-Whitney $U$ test, $U = 189, P = .82$) than patients not receiving medication.

**Basal KYNA Without Anticipation of Stress**

One possibility accounting for the high baseline level of KYNA in patients with distress intolerance (Figure 3B) is that these individuals were so much more sensitive to stress that merely the anticipation of the coming stress test caused elevations in KYNA. This is possible based on data seen in one human study in which anticipation of surgery, rather than the surgery itself, appeared sufficient to increase KYNA formation.20 This post hoc hypothesis was tested by recollecting saliva for a repeated KYNA measurement at rest. This was done on a separate day when participants were instructed to sit comfortably for 1 hour after arrival and then provided a saliva sample by passive drool before being discharged without stress test. A total of 39 partici-
pants (15 controls and 24 patients, including 12 distress-intolerant patients and 12 distress-tolerant patients) completed this additional experiment. Of these, saliva samples from 1 control and 1 patient were not of good quality, and KYNA could not be assayed. In the remaining 37 samples, KYNA levels were positively skewed (Kolmogorov-Smirnov test, $z = 1.81; P = .003$). Therefore, nonparametric statistical analyses were used. Patients with schizophrenia ($n = 23$) had higher KYNA levels than controls, although the values were not significantly different (mean [SEM], 5.74nM [1.64nM] vs 2.83nM [0.22nM], respectively; Mann-Whitney $U$ test, $U = 124.5; P = .25$). Importantly, the KYNA levels of patients with ($n = 11$) and without ($n = 12$) distress intolerance were no longer statistically different (Mann-Whitney $U$ test, $U = 61.0; P = .79$) when KYNA was measured at rest without anticipation of stress. Finally, there was a positive Spearman correlation of baseline KYNA levels between this second sample set and the original set ($r = 0.52; P = .003$), suggesting some stability in individual salivary KYNA levels despite the fact that the conditions of collection were not the same (1 with and 1 without stress test immediately after).

**Discussion**

Patients with schizophrenia were found to be significantly more likely than controls to exhibit distress intolerance as assessed by our laboratory-based stress-inducing paradigm. Different from controls or patients showing no distress intolerance, patients with this behavioral phenotype showed elevated KYNA levels at baseline and following the stressor. Notably, this KYNA elevation was not correlated with subjectively reported NA, suggesting that the elevated KYNA levels primarily marked an inability to persist in tasks while stressed rather than the subjective experience of stress. Therefore, in individuals with schizophrenia, elevated salivary KYNA levels may provide a quantitative biomarker indexing an inability to persist in tasks under stressful conditions.

The observation that patients with schizophrenia with distress intolerance had increased salivary KYNA baseline levels is intriguing and may be related to previous findings of increased concentrations of KYNA in postmortem brain tissue and cerebrospinal fluid. Alternatively, it may reflect a particular sensitivity to stress in these individuals, such that even the preparatory phase of the experiment, including anticipation of the stress test, already induced an increase in KYNA. This alternative explanation would be consistent with a report showing that the stress of anticipating surgery can induce an upregulation of TDO or IDO. This hypothesis was supported by our finding that individuals who were distress intolerant did not have significantly higher salivary KYNA levels at rest when they were not anticipating a stressful task. Regardless of the underlying mechanisms, which clearly require further investigation, it appears that patients with schizophrenia and distress intolerance have increased KYNA levels, which can be captured by a simple salivary assay.

Overall, salivary KYNA levels at baseline were in agreement with published data. It was also reported that dental abscess is associated with elevated salivary KYNA, similar to those seen in patients with schizophrenia and distress intolerance (Figure 3). Without performing dental examination, we cannot categorically exclude that poor oral health contributed to the elevated KYNA levels seen in our study. Another potential confound is the possibility that stress can decrease salivary flow, causing dry mouth and concentrating analytes of interest. However, our data indicate that flow rate was not reduced following exposure to the brief stressful tasks. Furthermore, previous studies have found that acute mental stress can increase protein concentration without decreasing salivary flow rate.

Levels of KYNA were found to be elevated in patients with schizophrenia but only weakly elevated in controls showing...
distress intolerance. This suggests that KYNA reactivity was not associated with distress intolerance per se but appeared to be an aberrant physiological response associated with a subset of patients with schizophrenia who exhibited this behavioral phenotype. This observation illustrates one of the underlying concepts in the National Institute of Mental Health Research Domain Criteria approach in that mapping biological processes to functional constructs rather than to diagnoses may uncover “mechanisms that can illuminate the marked heterogeneity” in our patients.

Our clinical data also revealed that increased KYNA levels were associated with more severe psychiatric symptoms in patients with distress intolerance. As KYNA does not readily pass the blood-brain barrier, one may argue that measurement of salivary KYNA may not reflect KP changes in the brain. Indeed, the relationship of KYNA in saliva to levels of KYNA in the brain, cerebrospinal fluid, plasma, or other tissues has not been comprehensively evaluated. However, in animals, stress increases both kynurenine and KYNA in the brain as well as in the periphery, suggesting that an increased KYNA level in response to stress is generalized, probably related to the fact that circulating kynurenine readily penetrates the blood-brain barrier. The physiological mechanism underlying the KYNA response to stress and distress intolerance in schizophrenia remains to be determined. Alone or jointly, possibilities include glucocorticoid production by stress and subsequent TDO activation, relative serotonin depletion accompanying increased tryptophan catabolism, and stress-induced immune activation leading to IDO induction. We attempted to initiate a mechanistic inquiry by measuring salivary cortisol response along with KYNA response to stress. Unexpectedly, we found no significant correlation between KYNA and cortisol levels, suggesting that the mechanism(s) underlying the responses of the 2 analytes to acute stress may be somewhat segregated. This supposition clearly requires further exploration.

A caveat of this study is the relatively small number of distress-intolerant controls. We were therefore unable to adequately assess whether healthy individuals with this phenotype also have increased salivary KYNA levels following a stress challenge. Furthermore, we considered that antipsychotic medication may have influenced the results of our study. Antipsychotics have been reported to reduce peripheral kynurenine levels in medication-naïve or medication-free patients with schizophrenia, but it is quite possible that this effect was secondary to symptom changes after medicating untreated patients. Notably, a recent trial of quetiapine fumarate and escitalopram oxalate showed that neither drug significantly altered KYNA levels, although both decreased kynurenine levels, in the blood of patients with major depressive disorder. Rodents treated with antipsychotics or antidepressants also failed to show a substantial effect on peripheral KYNA. We did not find a clear relationship between dose of antipsychotics and salivary KYNA level, nor did salivary KYNA level differ between patients treated vs not treated with antipsychotics. It is therefore unlikely that the pattern of increased KYNA levels in patients with distress intolerance can be explained by effects of antipsychotics.

Conclusions

Measuring KYNA in the saliva in context of a brief stress challenge represents a new approach with many potential applications in psychiatric research. Acute psychological stress using this paradigm increased salivary KYNA by an average of about 40% of baseline levels within 20 minutes of applying the stressor. This effect was replicable across groups (Figure 3A and B). Importantly, we have uncovered a potential biomarker segregating a subgroup of patients with schizophrenia displaying a particular maladaptive behavior. The need to reduce heterogeneity within diagnosis has increasingly been recognized as a necessity for advancing research and improving treatment outcomes. However, it has been difficult to operationalize heterogeneity reduction in research and clinical practice, in part owing to the lack of biological mechanism–based biomarkers that have direct clinical relevance. Our study suggests that combined investigations of distress intolerance and salivary KYNA levels reveal a novel behavioral-biological dimension in schizophrenia pathology that may lead to more effective treatment target identification and personalized intervention.


