Impulsivity is Associated with Uric Acid: Evidence from Humans and Mice

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Background: The ability to control impulses varies greatly, and difficulty with impulse control can have severe consequences; in the extreme, it is the defining feature of many psychiatric disorders. Evidence from disparate lines of research suggests that uric acid is elevated in psychiatric disorders characterized by high impulsivity, such as attention-deficit/hyperactivity disorder and bipolar disorder. The present research tests the hypothesis that impulsivity is associated with higher uric acid in humans and mice.

Methods: Using two longitudinal, nonclinical community samples (total $n = 6883$), we tested whether there is an association between uric acid and normal variation in trait impulsivity measured with the Revised NEO Personality Inventory. We also examined the effect of uric acid on behavior by comparing wild-type mice, which naturally have low levels of uric acid, with mice genetically modified to accumulate high levels of uric acid.

Results: In both human samples, the emotional aspects of trait impulsivity, specifically impulsiveness and excitement seeking, were associated with higher levels of uric acid concurrently and when uric acid was measured 3 to 5 years later. Consistent with the human data, the genetically modified mice displayed significantly more exploratory and novelty-seeking behavior than the wild-type mice.

Conclusions: Higher uric acid was associated with impulsivity in both humans and mice. The identification of biological markers of impulsivity may lead to a better understanding of the physiological mechanisms involved in impulsivity and may suggest potential targets for therapeutic intervention.

Key Words: Excitement seeking, impulse control, impulsivity, mouse model, personality traits, uric acid

Impulsivity is a key component of many psychiatric disorders, including pathological gambling, attention-deficit/hyperactivity disorder (ADHD), and substance abuse (1). Evidence from genetic (2,3) and neuroimaging (4) studies suggests a physiological basis for impulsivity, and there is interest in identifying additional biomarkers associated with this trait. Uric acid is a promising candidate. The end product of purine metabolism, uric acid is typically carried through the blood to the kidneys and then eliminated in urine. Perhaps most well-known for its role in an extremely painful type of arthritis known as gout, elevated uric acid levels have been linked to other medical conditions, including high blood pressure, cardiovascular disease, metabolic syndrome, kidney stones, and chronic kidney disease (5). It is also possible to have high levels of uric acid without any symptoms or medical complications. In addition, accumulating evidence suggests that uric acid may serve beneficial roles as an endogenous antioxidant and neuroprotectant (6,7).

Although it has not been directly associated with impulsivity, uric acid has been implicated in a number of psychiatric disorders characterized by impulsivity. In an experimental study of pathological gamblers, for example, uric acid concentrations increased while the gamblers played for money but not when they played checkers without betting (8). In a study of young children, uric acid correlated positively with teacher-rated hyperactive symptoms (9) and thus may play a role in hyperactivity (10). In a randomized control trial of ADHD compared with placebo, the impulsivity-related symptoms of ADHD participants taking the drug methylphenidate decreased over the course of 24 weeks. These same participants also had significantly lower levels of uric acid at the 24-week follow-up than did ADHD participants in the placebo group (11). In a study of drug-naïve bipolar patients, those suffering through their first manic episode had higher levels of uric acid than matched control subjects (12). Additional evidence for the role of uric acid in impulsivity comes from Lesch-Nyhan syndrome. Individuals with this syndrome have an enzyme deficiency that causes a buildup of uric acid throughout the body. Behavioral manifestations of Lesch-Nyhan syndrome include impulsivity and even individuals with less severe variants still manifest attention deficits (13).

Evidence for the association between uric acid and impulsivity has primarily come from analyses secondary to the principal question of interest. In the present research, we directly tested the role of uric acid in impulsivity in two distinct but complementary ways. First, we examined the association between uric acid and impulsivity-related personality traits. The clinical impulsivity manifested in psychiatric disorders may be the extreme end of variations in normal personality traits. Indeed, most conceptualizations of normal and abnormal personality include dimensions that capture different aspects of impulsivity. For example, Gray

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and McNaughton (14) and Corr (15) suggest that impulsivity-related traits map on to activation of the Behavioral Activation System and Behavioral Inhibition System. The fifth revision of the DSM proposes the broad dimension of disinhibition, which is characterized by a number of impulsivity-related facets (16). The present research uses the five-factor model of personality as an organizing framework. As operationalized by the Revised NEO Personality Inventory, impulsivity is measured by four traits (17,18): impulsiveness (the tendency to give in to temptation); excitement seeking (the tendency to crave stimulation); self-discipline (the tendency to follow through on intentions); and deliberation (the tendency to think before acting). Given that emotional temperaments (19) have been associated with elevated uric acid and that high arousal states increase uric acid (8), we hypothesized that individuals who score high in impulsiveness and excitement seeking will have higher levels of uric acid.

We tested for this association in two large longitudinal samples that included two assessments of uric acid measured approximately 3 to 5 years apart. We probed these associations in three additional ways. First, because smoking and body mass index (BMI) are associated with both impulsivity-related traits (20,21) and uric acid (22,23), we tested whether smoking and BMI contributed to the relation between impulsivity and uric acid. Second, we examined whether these associations differed by sex and age because of sex and age differences in both impulsivity-related traits (24) and uric acid (25). Third, to examine whether the associations were primarily driven by psychiatric illness, we controlled for psychiatric morbidity and repeated the analyses, removing participants with a history of psychiatric morbidity.

Impulsivity is a complex trait, and both impulsivity and uric acid are difficult to directly manipulate in humans. In study 2, we therefore compared the behavior of mice with elevated levels of uric acid (uricase-deficient mice) with that of wild-type mice. We expected that the mice with elevated uric acid levels would exhibit more impulsivity-related behavior than their wild-type siblings.

Methods and Materials

Study 1: Samples

SardiNIA. Participants were drawn from the SardiNIA project, a large multidisciplinary study of the genetic and environmental basis of complex traits and age-related processes, described in detail elsewhere (26,27). A total of 5663 participants (58% female; mean age = 42.63 [SD = 16.9]) had valid personality and uric acid data at Time 1 and 4764 participants had a second assessment of uric acid approximately 3 years later (time 2).

Baltimore Longitudinal Study of Aging. Participants were also drawn from the Baltimore Longitudinal Study of Aging (BLSA), a multidisciplinary cohort study administered by the National Institute on Aging. A total of 1220 participants (50% female, 63% white, mean age = 64.25 [SD = 13.56]) had valid personality and uric acid data at Time 1 and 798 participants had a second assessment of uric acid at Time 2, approximately 5 years later.

Study 1: Measures

Personality Traits. In both samples, personality was assessed with the Revised NEO Personality Inventory (18). In the SardiNIA sample, participants filled out the self-report questionnaire (88%) or chose to have the questionnaire read by a trained psychologist (12%). A variable (test administration) was used as a covariate in the analyses. All participants filled out the self-report questionnaire in the BLSA. We focused on the four impulsivity-related facets of the Revised NEO Personality Inventory: impulsiveness (alphas = .53 and .62, respectively for SardiNIA and BLSA); excitement seeking (alphas = .63 and .62), self-discipline (alphas = .62 and .80); and deliberation (alphas = .68 and .66).

Uric Acid. Blood samples were collected in the morning after participants had been fasting for at least 12 hours and after sitting for 15 minutes. Aliquots of serum were immediately obtained and stored at −80°C. Uric acid (mg/dL) was measured using enzymatic–colorimetric methods (Bayer, GmbH, Leverkusen, Germany). The lower limits of detection were .2 mg/dL, range .2 to 25.0 mg/dL, intra-assay and interassay coefficients of variation were equal to .5% and 1.7%, respectively.

Psychiatric Morbidity. During a medical history interview, participants in both SardiNIA and the BLSA reported psychiatric conditions, such as depression, anxiety, bipolar disorder, and schizophrenia.

Study 1: Analysis

We first examined the associations between the impulsivity-related traits and uric acid, controlling for basic demographic factors (age, sex, education, test administration [SardiNIA only], and ethnicity [BLSA only]) at Time 1 and Time 2 and at Time 2 controlling for baseline levels (i.e., change over time). We next controlled for smoking and body mass index and tested smoking and BMI as mediators of the personality–uric acid relations using bootstrapping techniques; we report the standardized indirect effects and their corresponding confidence intervals (28). We tested age and sex as moderators of these associations using the method by Aiken and West (29) for testing interactions. Additional analyses controlled for history of psychiatric illness and a diagnosis of gout (n = 54; 1% of the SardiNIA sample). Descriptive statistics for all human study variables are shown in Table 1.

Table 1. Mean (SD) or Percentage for all Human Study Variables

	SardiNIA		BLSA	
Variable	Time 1	Time 2	Time 1	Time 2
Age (Years)	42.63 (16.90)	46.06 (16.27)	64.25 (13.56)	65.14 (12.89)
Sex (Women)	58%	58%	50%	51%
Ethnicity (White)	–	–	63%	63%
Education (Years)	8.75 (4.07)	9.08 (3.92)	16.68 (2.34)	16.76 (2.39)
Current Smoker	21%	20%	3%	3%
BMI (m/kg^2)	25.23 (4.66)	25.26 (4.57)	27.16 (4.82)	27.02 (4.66)
Psychiatric Morbidity	6%	6%	17%	16%
Traits (T-Scores)				
Impulsiveness	4.80 (.94)	4.79 (.93)	4.80 (.95)	4.77 (.94)
Excitement seeking	4.75 (1.00)	4.73 (1.00)	4.72 (.96)	4.73 (.96)
Self-discipline	4.80 (.92)	4.82 (.91)	4.85 (1.05)	4.90 (1.04)
Deliberation	5.52 (1.10)	5.54 (1.09)	5.30 (.93)	5.30 (.95)
Uric Acid (mg/dL)	4.26 (1.46)	4.43 (1.52)	5.14 (1.37)	5.21 (1.40)

n = 5663 and n = 4764 for Time 1 and Time 2 in the SardiNIA sample and n = 1220 and n = 798 for Time 1 and Time 2 in the BLSA sample.

BLSA, Baltimore Longitudinal Study of Aging; BMI, body mass index.

Study 2: Mice

Mice heterozygous for a disrupted urate oxidase transgene (30) were obtained from Jackson Laboratories (Bar Harbor, Maine) and were interbred to generate wild-type (WT; $n = 6$–9) and urate oxidase null (UOX; $n = 6$–9) mice. Mice were maintained according to National Institutes of Health guidelines on a standard diet with free access to water that was supplemented with allopurinol (.3 mmol/L) for the UOX mice to prevent long-standing hyperuricemia. Allopurinol therapy was terminated 3 to 5 weeks before the behavioral assessment. All procedures on animals were approved by the Animal Care and Use Committee of the National Institute on Aging Intramural Research Program.

Study 2: Biochemical Analysis

Uric acid levels were routinely monitored in serum samples from the mice using a commercial kit (Randox, San Diego, California) and a Roche COBAS FARA II automated analyzer (Roche Diagnostic, Basel, Switzerland).

Study 2: Behavioral Tests

Open Field Test. Open field testing was performed using the MEDOFA-MS system (Med Associates, St. Albans, Vermont). Mice were placed in the center of an open field, and exploration was assessed for 15 minutes under dim light conditions (~400 lux). The dimensions of the arena were 40 cm × 40 cm, of which the external 10 cm were considered as the peripheral zone and the internal 30 cm were considered as the central zone. The following parameters were recorded for each session: horizontal activity (horizontal photobeam breaks or counts), number of stereotypical movements (e.g., grooming), and vertical activity (vertical photobeam breaks). Thus, spontaneous locomotor activity, stereotypical movements, and exploratory behavior were assessed.

Elevated Plus Maze. The movement of the mice was recorded for 5 minutes in an elevated (60 cm) plus-shaped maze consisting of two open arms (25 cm × 5 cm) with a clear 1 cm wall and two closed arms with 30 cm high dark walls. Each mouse was placed in the center of the maze facing the open arm. Arm preference was automatically analyzed using the ANYmaze video tracking software (Stoelting, Kiel, Wisconsin).

Novel Object Test. Mice were habituated to the experimental cage (25 cm × 25 cm with opaque walls) by 3 consecutive days of pre-exposure for 30 minutes. On the testing day, mice were placed in the experimental cage for 1 hour. After introduction of novel objects in the arena, the mice exploratory behavior was recorded for 30 minutes and analyzed using the ANYmaze video tracking software.

Statistical Analysis

Data were analyzed using GraphPad Prism (GraphPad Software Inc., La Jolla, California). To determine the effect of genotype on behavior, Student *t* test was used. To assess the correlation between uric acid levels and the various features of exploratory and novelty-seeking behavior, a Pearson correlation test was performed. Data are presented as means and standard error of the mean.

Results

SardiNIA

The correlations between uric acid and the impulsivity-related traits in the SardiNIA sample are shown in Table 2. Consistent with our hypothesis, individuals who were prone to give in to temptation (impulsiveness) and those who craved stimulation (excitement seeking) had higher levels of uric acid. Lower self-discipline and lower deliberation were also associated with higher uric acid. Across the 3-year follow-up period, higher scores on excitement seeking and lower scores on deliberation were associated with increases in uric acid.

Table 2. Associations Between Impulsivity-Related Traits and Uric Acid (SardiNIA)

	Time 1		Time 2	Change
Personality Traits	*r*	OR (95% CI)	*r*	*r*
		Model 1		
Impulsiveness	.07[a]	1.15 (1.07–1.23)[a]	.07[a]	.03[b]
Excitement Seeking	.02	1.08 (1.01–1.16)[b]	.04[a]	.03[b]
Self-Discipline	−.05[a]	.88 (.83–.95)[a]	−.04[a]	−.01
Deliberation	−.03[a]	.95 (.90–1.01)	−.04[a]	−.03
		Model 2		
Impulsiveness	.05[a]	1.09 (1.01–1.17)[b]	.04[a]	.02
Excitement Seeking	.04[a]	1.11 (1.03–1.20)[b]	.05[a]	.04[b]
Self-Discipline	−.05[a]	.89 (.82–.95)[a]	−.04[a]	−.02
Deliberation	−.04[a]	.95 (.89–1.00)	−.04[a]	−.03[b]

$n = 5663$ for Time 1 and $n = 4764$ for Time 2. Partial correlations and OR (95% CI). The OR contrast those with uric acid in the top 50% of the sample vs. the bottom 50% of the sample. The change analysis predicts Time 2 uric acid controlling for Time 1 levels and time interval between assessments. Model 1 controls for age, sex, education, and test administration. Model 2 controls for Model 1 covariates and body mass index and smoking.

CI, confidence interval; OR, odds ratio.

[a] $p < .01$.

[b] $p < .05$.

The correlation between impulsiveness and uric acid was slightly reduced when smoking and BMI were included in the model, which suggested that smoking and/or BMI partially mediated this association. And, indeed, the association between impulsiveness and uric acid was mediated, in part, by higher BMI at both time points (point estimate = .0364 [95% confidence interval = .0269–.0470] and point estimate = .0390 [95% confidence interval = .0287–.0509], respectively for Time 1 and Time 2). Smoking and BMI had a suppressor effect on the association with excitement seeking, such that when these factors were controlled for, the Time 1 association between excitement seeking and uric acid was now significant. The addition of smoking and BMI did not appreciably change the correlations between uric acid and self-discipline or deliberation and neither smoking nor BMI mediated these associations at either time point. Sex moderated the association between uric acid and self-discipline at both time points, such that this association was stronger for women than for men ($\beta_{N5 \times sex} = .04$, $p < .05$, for both Time 1 and Time 2). Age did not moderate any of these associations. Finally, additional analyses demonstrated the robustness of these associations: controlling for psychiatric morbidity or gout did not alter the results, nor did removing these participants from the analyses. In addition, although uric acid tends to be moderately correlated with inflammatory markers (31) that are also linked to impulsivity-related traits (32), all of the impulsivity–uric acid relations remained significant after controlling for interleukin-6, C-reactive protein, and white blood cell count (data not shown).

BLSA

Similar to the SardiNIA sample, those who gave in to their urges (impulsiveness) and those who craved excitement

Table 3. Associations Between Impulsivity-Related Traits and Uric Acid (BLSA)

Personality Traits	Time 1		Time 2	Change
	r	OR (95% CI)	*r*	*r*
	Model 1			
Impulsiveness	.09[a]	1.18 (1.03–1.35)[b]	.12[a]	.08[b]
Excitement Seeking	.06[b]	1.23 (1.07–1.41)[a]	.10[a]	.08[b]
Self-Discipline	.01	1.03 (.91–1.16)	−.04	−.06
Deliberation	.01	1.01 (.88–1.16)	−.01	.00
	Model 2			
Impulsiveness	.00	1.01 (.87–1.17)	.03	.05
Excitement Seeking	.05[c]	1.21 (1.05–1.39)[a]	.08[b]	.07[b]
Self-Discipline	.02	1.06 (.94–1.20)	−.02	−.05
Deliberation	.01	1.01 (.88–1.16)	−.01	.00

$n = 1220$ for Time 1 and $n = 798$ for Time 2. Partial correlations and OR (95% CI). The OR contrast those with uric acid in the top 50% of the sample vs. the bottom 50% of the sample. The change analysis predicts Time 2 uric acid controlling for Time 1 levels and time interval between assessments. Model 1 controls for age, sex, education, and ethnicity. Model 2 controls for Model 1 covariates and body mass index and smoking.

BLSA, Baltimore Longitudinal Study of Aging; CI, confidence interval; OR, odds ratio.

[a] $p < .01$.

[b] $p < .05$.

[c] $p < .05$, one-tailed.

(excitement seeking) had higher levels of uric acid at both Time 1 and Time 2 (Table 3). Controlling for BMI and smoking reduced the association between uric acid and impulsiveness; mediational analyses confirmed that this association was due to BMI (point estimate = .0116 [95% confidence interval = .0086–.0146] and point estimate = .0132 [95% confidence interval = .0098–.0183], respectively for Time 1 and Time 2). Controlling for smoking and BMI slightly reduced the association between uric acid and excitement seeking, but neither of these factors mediated the excitement seeking–uric acid relation. In contrast to SardiNIA, neither self-discipline nor deliberation was associated with uric acid at either time point, and none of the personality–uric acid associations were moderated by sex or age in the BLSA sample. Finally, similar to SardiNIA, after accounting for smoking and BMI, excitement seeking was associated with increases in uric acid over the follow-up period and controlling for psychiatric morbidity or removing participants with a history of psychiatric illness from the analyses did not alter the findings.

Mouse Study

The findings from study 1 supported the hypothesis that uric acid is associated with trait impulsivity in nonclinical populations. To further understand the relation between uric acid and impulsivity, we tested for behavioral differences between mice with elevated uric acid levels resulting from disruption of the urate oxidase gene (UOX mice) and wild-type mice. In contrast to primates, mice naturally have very low levels of uric acid due to urate oxidase-dependent conversion to allantoin. In homozygous urate oxidase-deficient mice (30), the loss of function of the urate oxidase enzyme results in the accumulation of uric acid (Figure 1A), unless they are maintained on allopurinol therapy. These mice thus have high levels of uric acid compared with WT mice.

We tested for behavioral differences between UOX and WT mice. Rodents have a natural tendency to avoid unfamiliar exposed areas where they could be subject to predators; in addition to low levels of anxiety, the increased exploratory activity in open areas and novelty-seeking behavior reflect higher levels of impulsivity (33,34). We thus tested UOX and WT mice in various free exploration paradigms to test the relation between elevated uric acid levels and behavior.

Across the three behavioral tests, the UOX mice had significantly more exploratory activity than the WT mice. First, in the open field test, UOX mice entered (Figure 1B) and spent significantly more time (Figure 1C) in the center of the arena compared with WT mice. No differences were observed between the two genotypes in terms of resting and stereotypical (e.g., grooming) behaviors, but the UOX mice traveled more often (Figure S1A in Supplement 1) and further (Figure 1D) in the open area compared with WT mice. While locomotion mainly reflects exploratory behavior, vertical activity in an open area relies both on exploratory activity and emotionality (35,36). We found that vertical activity, including rearing (Figure 1E; Figure S1B in Supplement 1) and jumping (Figure 1F), was significantly elevated in UOX mice compared with WT siblings. Notably, levels of uric acid were significantly positively correlated with each component of the exploratory and emotional behavior. Second, similar to what was observed in the open field, UOX mice in the elevated plus maze spent more time in the open arms, which was positively correlated with levels of uric acid (Figure 1G). Third, in the novel object test, upon introduction of novel objects in a familiar environment, UOX mice increased the frequency (Figure 1H) and time spent (Figure 1I) in the area containing the novel object. Similar to the exploratory activity, significant positive correlations between levels of uric acid and response to novelty were observed (Figure 1J). These findings suggest that elevated uric acid levels are sufficient to enhance exploratory and novelty-seeking behaviors in mice.

Discussion

Across two independent human samples, impulsivity-related traits, particularly the emotional aspects of trait impulsivity, were associated with higher levels of uric acid. Further, mice bred for high levels of uric acid displayed significantly more exploratory and novelty-seeking behavior than their wild-type peers. Thus, the present set of studies supports the hypothesis that impulsivity is associated with higher levels of uric acid.

Among the four impulsivity-related personality traits, uric acid was most consistently associated with excitement seeking. In both human samples, individuals high in this trait had higher uric acid levels when measured concurrently, when uric acid was measured 3 to 5 years later, and with increases in uric acid over this time interval. Individuals who score high in excitement seeking tend to seek out exciting and daring activities; are attracted to intense sensations, including bright colors and crowded environments; and engage in unnecessary risks for the thrill of it (18). As such, this trait is theoretically and empirically related to many psychiatric disorders in which impulsivity is a key component, including substance abuse (37), gambling (38), and ADHD (39). Of note, uric acid has also been associated with each of these disorders (10,40), which might be partly due to a shared association with impulsive tendencies manifested in normal populations.

The other emotional aspect of trait impulsivity, impulsiveness, was also associated with higher uric acid in both samples. This association was primarily through the shared association with BMI. Among the facets of personality, impulsiveness is the strongest personality predictor of obesity and weight gain (21),

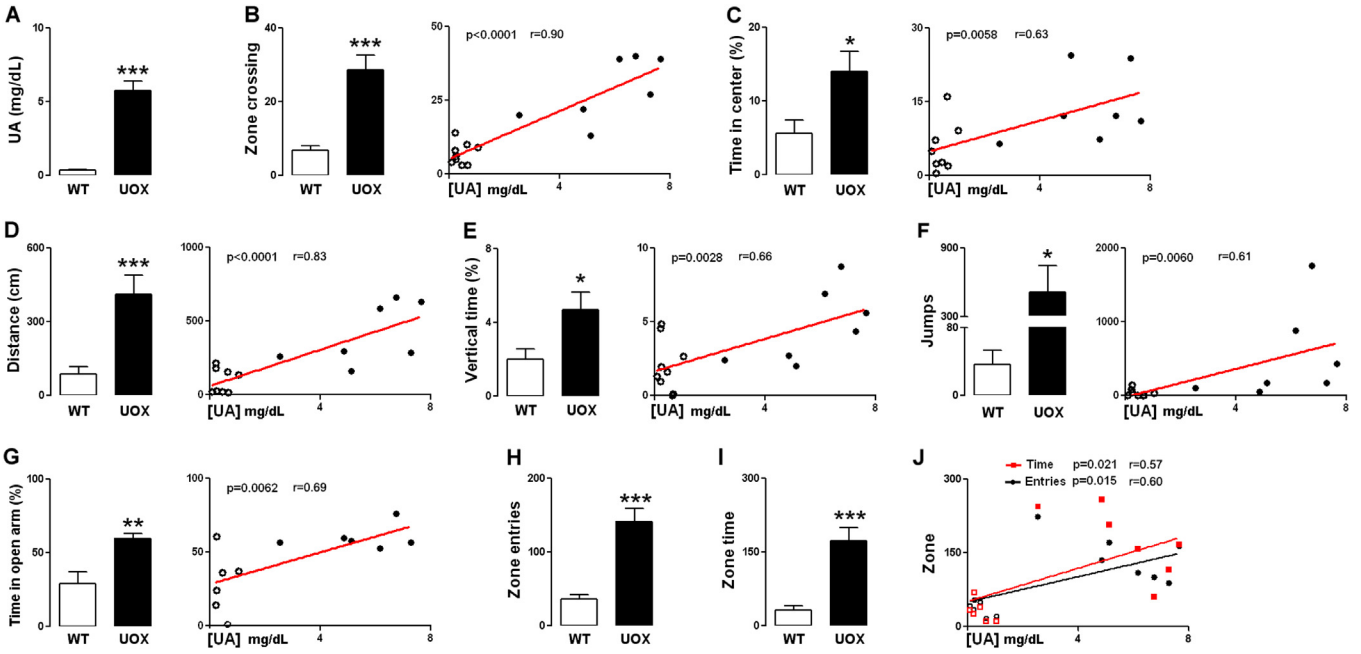

Figure 1. Urate oxidase null (UOX) mice showed increased exploration and novelty-seeking behaviors. **(A)** Urate oxidase null mice displayed a significant increase of serum uric acid (UA) levels compared with wild-type (WT) mice. In the open field, UOX mice accessed more often **(B)**, spent more time **(C)**, and traveled longer distance **(D)** in the center of the field. Urate oxidase null mice showed increased vertical time **(E)** and jumping behavior **(F)**. **(G)** In the elevated plus maze, UOX mice spent more time in the open arms. Significant positive correlations between levels of uric acid and each of the various features of exploratory/impulsive behavior are also shown. Urate oxidase null mice showed enhanced response to novelty than WT mice both as number of entries **(H)** and overall time spent in the object zone **(I)**. The increased behavioral response to novelty is positively correlated with levels of uric acid **(J)**. $^{*}p \leq .05$; $^{**}p \leq .01$; $^{***}p \leq .001$ ($n = 6–9$).

and obesity is a significant predictor of elevated uric acid (41). Impulsiveness is also associated with preference for foods high in fructose (42), and fructose consumption increases uric acid production (43). Impulsiveness may thus be linked to higher uric acid through dietary factors, whereas the association between excitement seeking and uric acid may be through other physiological channels. This association is also likely to be bi-directional: higher uric acid may contribute to more impulsive behavior, including consumption of alcohol and soda, which, in turn, may increase levels of uric acid.

In contrast to excitement seeking and impulsiveness, less evidence emerged for the relation between uric acid and the more constraint-related aspects of impulsivity. Although lower self-discipline and lower deliberation were associated with higher levels of uric acid in the SardiNIA sample, these associations did not replicate in the BLSA sample. The emotionality aspects of impulsivity typically refer to the inability to regulate cravings and urges, whereas the constraint aspects of impulsivity are more related to having the discipline to accomplish a goal despite difficulties or distractions. Uric acid may be more strongly related to the arousal aspects of impulsivity (19) than its constraint-related aspects.

Across both of the human studies, the associations between the impulsivity-related traits and uric acid were relatively modest. Impulsivity is a complex trait and it is likely the product of many genetic, environmental, and biological factors. Thus, any one aspect of these factors should have a small effect on this complex phenotype. These associations did replicate, however, across two independent samples that varied greatly in their genetic makeup and environment, which suggests that the impulsivity–uric acid relation is robust. In addition, modest associations can lead to clinically significant changes, particularly over time. For example, one study found that a small effect of impulsiveness on weight gain was associated with a difference of more than 20 pounds across adulthood (21).

The relation between uric acid, impulsive behavior, and food intake may have evolutionary origins. Johnson *et al.* (44) hypothesized that uric acid may be a physiological alarm signal that evolved to arouse animals to search for food. After periods of fasting, such as with hibernation, uric acid levels increase, and this rise is associated with increased foraging, food intake, and weight gain in a number of species (44). Early in our history, this process was advantageous and helped humans to survive periods of food shortages. With the abundance of food now available in Western societies, the function of uric acid to refill fat stores may contribute to the obesity epidemic. Further, the foraging/increased arousal that led to finding food during scarce times may be expressed in modern society through impulsive and novelty-seeking behavior.

The increased exploratory and novelty-seeking behaviors in the UOX mice suggest that uric acid acts as a driving force for foraging. Mechanistically, the behavior displayed by UOX mice is likely due to alteration of the serotonergic system. While both serotonin and/or dopamine alterations may account for impulsivity and locomotor hyperactivity, the peculiar exacerbation of jumping behavior we observed has been previously associated with serotonergic impairment. Decreased serotonin turnover is responsible for the explosive jumping behavior of the schizophrenia/bipolar disorder model of adenylate cyclase-activating polypeptide knockout mice (45,46). Similarly, Huntington's disease mouse models show enhanced jumping behavior and decreased serotonin turnover due to altered expression of serotonin receptors and transporters before dopaminergic and

motor impairments (47,48). Notably, altered expression of serotonin receptors has been observed in lymphocytes of Lesch-Nyhan patients (49) and in the corresponding mouse model (50), both characterized by elevated uric acid levels. The A/G polymorphism of the HTR2A promoter has been associated with hyperuricemia (51). The possible inverse correlation between uric acid levels and the serotonergic system could also account for its association with metabolic disorders and obesity. In addition to mood, sleep, and cognitive functions, brain serotonin levels are known to regulate appetite. In vertebrates, when brain serotonin signaling is decreased, food intake and weight gain are augmented (52).

The present research had several strengths, including two large longitudinal human samples and corroborating evidence from a mouse model of elevated uric acid levels. Future research could consider additional mediational factors. For example, we found that BMI partially mediated the association between impulsiveness and higher uric acid. We did not, however, test the role of diet in this association. A diet high in meats, alcohol, and soda is associated with increased production and decreased excretion of uric acid. Given that personality is associated with eating habits, particularly a preference for fructose, diet could be one mechanism through which impulsivity is associated with uric acid. Although our findings suggested that the UOX mice behaved more impulsively, the tasks we used to measure impulsivity also reflect anxiety. Thus, future research could consider other measures, such as delayed discounting or the go/no-go task. In addition, building on the evidence for the relation between uric acid and exploratory behavior from the mouse data, future research could elucidate the physiological pathways through which impulsivity and uric acid are linked. Finally, in psychiatric cases characterized by high impulsivity, it may be worthwhile to examine levels of uric acid. In cases that turn out to be hyperuricemic, it would be of interest to test whether an intervention on uric acid levels would also decrease impulsivity-related behavioral/psychiatric symptoms.

In sum, the present research found support for the relation between uric acid and trait impulsivity. Given the personal and societal costs associated with impulsivity, it is important to understand its biological and environmental basis. The identification of biological markers may lead to a better understanding of the physiological mechanisms involved, and it may suggest potential targets for therapeutic intervention. This research joins multiple lines of evidence drawn from the psychiatric, obesity, and comparative literatures that is now converging on the association between impulsivity-related traits and behaviors and elevated uric acid.

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