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Association of the Val158Met Polymorphism of the *COMT* Gene with Measures of Psychophysiological Status in Athletes

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Resistance to psychological stress, motivation, physical work capacity, and fatigue are genetically determined characteristics which are important for successful competitive activity in athletes. Polymorphism of the catechol-O-methyltransferase (*COMT*; regulates the function of the dopaminergic system) gene can generate individual differences in the development and manifestation of psychophysical qualities. The present study assessed the influences of the rs4680 polymorphism of the *COMT* gene on the psychophysiological status of 146 athletes of different specialties and qualifications. Athletes carrying the Met allele were found to have high psychological stability in the critical flicker fusion frequency test, which reflects the ability to form a task-appropriate functional system and maintain it for a longer period of time, as compared with carriers of the Val allele. Females (aged 10–19 years) showed higher rates of sensorimotor reactions in a simple visuomotor reaction test and a smaller number of accurate reactions in a moving object reaction test. Males (aged 12–19 years) carrying the Met allele were characterized by higher levels of personal anxiety on the Spielberger–Hanin anxiety scale. Thus, these studies demonstrate that the rs4680 polymorphism of the *COMT* gene influences the psychophysiological status of athletes.

Keywords: psychogenetics of sport, psychophysiological measures, anxiety, athletes, dopaminergic system, catechol-O-methyltransferase, *COMT* gene.

Most studies of the heritability of psychological, psychophysiological, neurodynamic, and sensorimotor measures conventionally address individual electroencephalogram measures or groups of measures, reflecting some proposed cryptic variable, such as properties of the nervous system [1]. However, there is a clear need for a complex approach to studies of psychophysiology addressing human personality and bodily characteristics and assessing the capacity to realize abilities to carry out particular requirements, especially in professional sports.

Resistance to psychological stress, temperament and character features, the ability to cooperate, the ability to receive and process information, and mental capacity are parts of a very incomplete list of genetically determined signs of higher nervous activity with various levels of importance for successful sporting careers. As these signs manifest differently in different people (individual differences), it is important to identify polymorphism in the genes associated with different mental qualities (memory, thinking speed, attention, anxiety) and measures of emotional status in athletes (anxiety, affective arousal, fatigue). The biochemical variability of proteins, including enzymes, involved in the functioning of the neurotransmitter system, may also be determined genetically, which in turn is probably associated in some way with psychophysiological differences [2].

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The catechol-O-methyltransferase gene (*COMT*) is a member of the dopaminergic system gene family and plays a key role in degrading dopamine in the prefrontal cortex of the brain [3]. The fourth exon of the *COMT* gene contains a guanine-to-adenine substitution (rs4680), which leads to substitution of a valine residue for methionine at position 148 of the enzyme (Val158Met).

Data from a number of authors show that the Met allele is associated with lower (by a factor of 4) enzyme activity as compared with the Val allele, and thus with a higher dopamine concentration in the prefrontal cortex [4]. The Val allele is associated with the appearance of more aggressive (physically and verbally aggressive) behavior and with impaired attention and working memory, and less anxious behavior [4–6]. This polymorphism is also associated with the risk of developing various mental disorders, such as schizophrenia [7–10].

At the same time, data from a genome-wide association study (GWAS) have not confirmed an association of the rs4680 polymorphism of the *COMT* gene with cognitive or personality characteristics. Data from most meta-analyses indicate that only a few studies have revealed a significant connection between the Val allele in the European population with various metal disorders, particularly attention deficit hyperactivity disorder (ADHD), panic disorders, and major depressive disorder [11, 12], while other studies have not found a link with ADHD [13]. These contradictions can arise as a result of assessment of smaller numbers of case and control patients included in the meta-analyses. Studies with analysis of larger cohorts of healthy volunteers have demonstrated an association between the Met allele of the rs4680 polymorphism of the *COMT* gene with positive responses to reward on training [14], which may be due to the decrease in the activity of the enzyme catechol-O-methyltransferase [15].

There are also quite contradictory data on the contribution of genetic polymorphism of the *COMT* gene to the psychophysiological status of professional athletes [16, 17]. Abe et al. showed that the Met allele is positively associated with cognitive capacities and competitiveness in swimmers in this sporting category [18]. Another study involving Iron Man triathletes showed that ultraendurance athletes with the Met/Met genotype demonstrated high novelty-seeking behavior, which the author explained in terms of the association found in the ability of the enzyme to increase dopamine neurotransmission in carriers of the Met allele [16].

Considering the importance of COMT enzyme in regulating dopamine in the prefrontal cortex of the brain and that dopaminergic neurons take part in triggering movement acts [19], the effect of the Val158Met phenotype can be apparent as interindividual differences in psychophysiological characteristics.

Thus, the aim of the present work was to analyze the association between the Val158Met polymorphism of the *COMT* gene and measures of psychophysiological status in Russian athletes with different specialties and qualifications.

Methods. The study included a total of 146 athletes (62 female, 84 male, mean age 16.6 ± 3.4 and 19.4 ± 5.1 years old, respectively) of different sporting specializations and qualifications: cyclic sports (n = 49), game sports (n = 30), speed/strength sports (n = 33), complex coordination sports (n = 17), and single combat sports (n = 17). All subjects gave signed informed consent to take part in the study.

Psychophysiological and psychological testing of athletes was carried out using an NS-PsychoTest programmable system (Neurosoft, Ivanovo) in the morning hours in the state of rest using methods proposed in the I. N. Mantrova Methodological Guidelines [20].

Psychophysiological testing of athletes included the following tests:

– simple visuomotor reaction (SVMR), during which the sensorimotor reaction time (msec) was measured, along with the number of misses, the number of premature reactions, the total number of errors, the stability of attention and operative memory, the functional level of the system (FLS), reaction stability (RS), the functional potential (FP), and the Whipple coefficient of accuracy; work capacity was assessed in terms of FLS, RS, and FP. SVMR gives information on the characteristics of the functional state of the CNS;

– the moving object reaction (MOR), including measurement of the mean reaction time, the number of accurate reactions, the coefficient of variation of errors, the number of premature reactions, the number of late reactions, the total duration of early and late reactions, and the number of positive reactions. MOR characterizes the equilibrium of neural processes and work capacity;

– critical flicker fusion frequency (CFFF), including measurement of the mean frequency of light flashes and the mean frequency of signals on rising and dropping. CFFF identifies the mobility of neural processes in the cortical area of the visual analyzer;

– the tapping test, which assesses the number of taps, the mean movement speed, the initial speed, the mean difference in speed, the intertap interval, the magnitude of deviations from the work capacity curve from the initial level (a measure of nervous system strength), the number of taps in the first part of the test, and the extents of lability and endurance. The tapping test is used for diagnosis of the strength of neural processes, which reflects overall work capacity in humans.

Psychological testing was conducted using the Spielberger questionnaire (Hanin adaptation), including assessment of situational personal anxiety.

Materials for genotyping were DNA specimens extracted from whole venous blood using a commercial DNA-Express-Blood kit following the manufacturer's protocol (Litekh, Moscow). Analysis of the *COMT* genetic polymorphism used the real-time polymerase chain reaction with primers and probes produced at SibDNA (Novosibirsk).

Statistical analysis was run in GraphPad InStat. Groups were compared using the two-tailed t test for independent

TABLE 1. Results of Simple Visuomotor Reaction and Critical Light Flash Frequency Tests in Athletes Depending on the Val158Met Polymorphism of the *COMT* Gene (data for parameters showing statistically significant differences)

Test	COMT genotype			*p*	*F*	Magnitude of effect**
	Val/Val (n = 32)	Val/Met (n = 66)	Met/Met (n = 48)			
Simple visuomotor reaction						
Assessment of work capacity from the functional level of the system, U	4.4 (0.4)	4.4 (0.4)	4.6 (0.4)	0.02	3.9	0.23
Assessment of work capacity from reaction stability, U	1.8 (0.4)	1.8 (0.4)	2.1 (0.5)	0.001*	8.1	0.34
Assessment of work capacity from the level of functional capacities, U	3.4 (0.5)	3.4 (0.5)	3.7 (0.5)	0.001*	7.02	0.31
Critical light flash frequency						
Mean frequency, Hz	41.6 (4.3)	39.7 (4.8)	39.0 (4.2)	0.03	3.5	0.16
Mean frequency on rising, Hz	38.2 (5.3)	36.1 (5.5)	34.9 (6.1)	0.04	3.3	0.10

Mean values and standard deviations (parentheses) are shown. n is the number of subjects. Actual p values were computed using the Bonferroni correction for the total number of tests performed, $p \le 0.01$. *Significant differences between tests; **magnitude of effect compared between the Val/Val and Val/Met genotypes and the Met/Met genotype.

sets. Differences were taken as significant taking account of the Bonferroni correction.

The correspondence between allele frequencies and genotype to Hardy–Weinberg equilibrium (HWE) was assessed using the χ^2 test, online version [21]. Associations between genotypes and psychophysiological test results were evaluated by unifactorial analysis of variance.

Results. The distribution of allele and genotype frequencies for the Val158Met polymorphism of the *COMT* gene in the study group corresponded to PXB (χ^2 = 1.7; p = 0.19). Both males and females showed a predominance of the heterozygous Val/Met genotype (51% and 56%, respectively). The genotype frequencies obtained here are typical of most European populations (as compared with data from the 1000 Genome project) [22].

Significant results were obtained using the simple visuomotor reaction and the critical flicker fusion frequency tests (Table 1). An association between the Val158Met polymorphism of the *COMT* gene and measures of psychophysiological status was established. Thus, athletes with the Met/Met genotype, as compared with carriers of the Val allele, had a tendency to increases in measures such as "Assessment of work capacity in terms of the functional level of the system" (FLS), significantly high measures for "Assessment of work capacity in terms of reaction stability" (RS), and "Assessment of work capacity in terms of the level of functional potential (FP)" in the simple visuomotor reaction test. FLS characterizes the rate of voluntary reactions, which depend on CNS arousability. Our data indicate that Met/Met homozygotes had elevated FLS values, which can be explained by the low catechol-O-methyltransferase activity.

The theoretical basis of the critical flicker fusion frequency method is the supposition that the individual CFFF is due to the mobility of neural processes in the cortical component of the visual analyzer in understanding mobility as the speed with which the neural processes of arousal and inhibition arise and disappear [23]. Data from this test in athletes homozygous for the Met allele showed a tendency to decreases in the mean frequency and mean frequency on rising, which presumptively indicates a trend for neural processes to have greater inertia in homozygous Met/Met carriers (Table 2). No significant differences were found among athletes for the other tests.

The study group was then divided into age groups: group I – the early adolescent and adolescent period in females aged 10–19 years (48 subjects) and males aged 12–19 years (53 subjects); group II – females aged 20–30 years (14 subjects) and 20–41 years in males (31 subjects) [24].

Analysis of test results stratified by sex showed several significant differences. Males of group I showed a tendency to greater FLS in the simple visuomotor reaction test as compared with females, though the sensorimotor reaction speed in males was significantly lower than that in females (p = 0.0002).

In males, the tapping test showed a large number of taps, indicating a high working capacity for the nervous system, though these differences were seen only for group I. In the moving object reaction test, the total anticipation by females in group II indicates early reactions, which can be explained from the more marked predominance of the excitatory process; this was also supported by the fact that females showed smaller numbers of accurate reactions (p = 0.0004) in group I, and this trend persisted into group II (p = 0.01). In the critical flicker fusion frequency test, males showed tendencies to a higher mean light flash frequency (p = 0.05 and p = 0.02 in groups I and II, respectively) and on dropping of the frequency (p = 0.007) in group I as compared with females, which points to a greater degree of lability (Table 2).

TABLE 2. Values for Various Indicators from Psychogenetic Testing Stratified by the Sex of Athletes

Indicator/sex	Males (n = 84)		Females (n = 62)		p	t
	I (n = 53)	II (n = 31)	I (n = 48)	II (n = 14)		
Simple visuomotor reaction						
Sensorimotor reaction speed, msec	216.5 (23.2)	215.6 (28.0)	237.2 (30.0)	216.7 (16.0)	0.0002*	3.9*
Functional level of the system, U	4.53 (0.39)	4.54 (0.40)	4.34 (0.35)	4.39 (0.24)	0.01*	2.6*
Tapping test						
Number of taps, taps	206.3 (21.1)	202.5 (21.3)	193.3 (27.9)	209.6 (20.3)	0.009*	2.7*
Mean tap frequency, taps	7.0 (0.7)	7.1 (0.7)	6.6 (0.9)	6.8 (0.7)	0.01*	2.6*
Initial speed	7.7 (1.0)	7.8 (1.2)	7.3 (1.0)	7.5 (0.8)	0.01*	2.5*
Intertap interval, msec	145.9 (14.3)	143.6 (14.4)	157.6 (29.8)	148.3 (13.6)	0.01*	2.6
Number of taps in first part of test	36.3 (4.8)	37.7 (3.9)	38.8 (4.9)	38.9 (5.9)	0.01	2.6*
Endurance, U	8.4 (1.5)	8.8 (1.7)	7.5 (2.3)	8.0 (1.9)	0.02*	2.3*
Lability, U	7.0 (1.6)	7.1 (1.8)	6.4 (1.7)	6.7 (1.4)	0.048*	2.0*
Moving object reaction						
Number of accurate reactions, U	26.7 (5.9)	25.2 (7.0)	22.7 (5.0)	19.5 (4.1)	0.0004* 0.01**	3.6* 2.6**
Total anticipation time, msec	–794.8 (546.3)	–841.0 (533.4)	–1060.6 (656.6)	–1437.3 (705.1)	0.03* 0.004**	2.2* 3.1**
Number of anticipations, U	10.4 (6.2)	11.0 (6.2)	11.8 (5.4)	16.2 (7.7)	0.02**	2.3**
Critical light flash frequency						
Mean light flash frequency, Hz	39.9 (4.5)	42.9 (4.4)	38.1 (4.3)	39.7 (2.3)	0.05* 0.02**	2.0* 2.5**
Mean frequency on dropping, Hz	46.2 (0.8)	46.2 (10.5)	41.0 (6.5)	44.1 (3.7)	0.007*	2.8*

Group I – females aged 10–19 years, males aged 12–19 years; group II – females aged 20–30 years, males aged 20–41 years. *Differences between males and females in age group I; **differences between males and females in age group II; actual p values were computed using the Bonferroni correction for the total number of tests run, $p \le 0.003$.

These sex differences led us to study associations between polymorphisms of the *COMT* gene with test results stratified by sex only in age group I, as no significant differences were seen in group II. Results from the Spielberger–Hanin anxiety scale, which is used for diagnosis of situative and long-term mental status in humans, showed that male carriers of the Met allele in group I demonstrated high levels of personal anxiety ($p = 0.04$) as compared with carriers of the Val/Val genotype (Table 3). No associations were found for the simple visuomotor reaction test, the critical flicker fusion frequency test, the movement object reaction test, or the tapping test.

No further division into subgroups depending on type of sport and intensity of sporting load and their associations with the polymorphism of interest was carried out because of the small numbers of the resulting groups.

Our studies showed that in the overall group of athletes, assessment of reaction stability and the level of functional potentials were greater in athletes with the Met-Met genotype, group I male carriers of the Met allele being characterized by greater personal anxiety on the Spielberger–Hanin anxiety scale. Group I females showed a greater sensorimotor reaction speed in the simple visuomotor reaction test and a smaller number of accurate reactions in the moving object reaction test, though particular genotypes were not found to have any influences on these parameters.

Discussion. Little is known regarding genetically determined individual differences in mental status of elite athletes [12]. Various psychophysiological parameters, such as resistance to psychological stress, temperament and character features, coordination ability, information intake and processing ability, mental capacity, and many others are known to be due not only to external factors, but also to genetic polymorphisms. Such polymorphisms have now been found in tens of genes belonging to different neurotransmitter systems in the brain (for example, *DOMT*, *DRD1*, *DRD2*, *DRD3*, *DRD4*, *DBH*, *SLC6A3*, *SLC6A4*, *DBH*, *SLC6A3*, *SLC6A4*, *TPH1*, *TPH2*, *HTR2A*, *HTR2B*, and *MAOA*) [25–30].

One of these brain neurotransmitter systems may be the monoaminergic neurotransmitter system, which is responsible for the synthesis of biologically active amines – catecholamines, particularly dopamine and serotonin. In psy-

TABLE 3. Association of the Val158Met Polymorphism of the *COMT* Gene with Psychophysiological Test Results in Athletes Stratified by Gender in Age Group I

Indicator/genotype	Males			Females		
	Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met
	(n = 11)	(n = 24)	(n = 18)	(n = 6)	(n = 25)	(n = 17)
Simple visuomotor reaction						
Sensorimotor reaction speed, msec	211.0 (22.2)	220.7 (20.8)	214.3 (20.5)	236.6 (28.5)	233.9 (30.7)	242.3 (30.6)
FLS, U	4.5 (0.4)	4.6 (0.2)	4.6 (0.2)	4.3 (0.3)	4.2 (0.4)	4.2 (0.4)
Assessment of work capacity from reaction speed, U	211.0 (22.2)	210.5 (20.9)	212.3 (20.6)	236.6 (28.4)	238.9 (30.6)	237.9 (30.5)
Tapping test						
Number of taps, taps	213.0 (25.2)	211.5 (26.8)	206.2 (28.0)	181.3 (24.4)	184.0 (19.1)	191.8 (24.2)
Mean tap frequency, taps	7.2 (0.9)	7.1 (0.9)	7.0 (1.0)	6.1 (0.8)	6.2 (0.7)	6.5 (0.8)
Initial rate	7.8 (0.9)	7.8 (1.0)	7.5 (0.8)	7.0 (1.1)	7.0 (1.0)	7.4 (1.1)
Intertap interval, U	141.6 (16.4)	142.9 (17.8)	146.9 (18.9)	167.0 (25.7)	163.4 (18.1)	157.5 (21.2)
Number of taps in first part of test, U	34.5 (5.4)	35.7 (5.6)	35.8 (5.6)	40.7 (6.8)	36.7 (3.7)	35.9 (4.4)
Mean for example, Hz	7.2 (0.8)	6.8 (0.6)	7.0 (0.7)	5.6 (1.2)	6.6 (0.9)	6.5 (0.7)
Endurance, U	8.6 (1.5)	8.4(1.7)	8.1 (1.7)	6.6 (2.3)	7.8 (2.4)	7.3 (2.1)
Lability, U	7.2 (1.5)	7.1 (1.7)	6.6 (1.5)	5.8 (2.0)	6.6 (1.7)	6.1 (1.6)
Moving object reaction						
Number of accurate reactions, U	25.5 (4.9)	25.7 (6.9)	28.9 (4.6)	24.3 (4.3)	23.0 (5.0)	21.8 (5.1)
Total anticipation time, msec	–1020.6 (520.2)	–837.9 (594.0)	–599.3 (447.4)	–886.5 (328.3)	–978.4 (647.9)	–1242.9 (738.7)
Number of anticipations, U	14.0 (6.3)	10.8 (6.8)	7.7 (4.0)	9.9 (2.9)	11.1 (4.9)	13.4 (2.4)
Critical light flash frequency						
Mean light flash frequency, Hz	39.1 (4.1)	40.4 (4.8)	39.7 (4.5)	39.2 (2.9)	38.7 (4.8)	37.0 (3.9)
Mean frequency on dropping, Hz	43.8 (3.9)	44.8 (4.5)	43.7 (5.9)	38.8 (7.5)	41.5 (4.5)	41.0 (6.3)
Spielberger–Hanin anxiety scale						
Personality anxiety, U	33.4 (5.6)	39.1* (8.2)	37.0* (5.4)	33.8 (4.4)	36.7 (8.8)	39.0 (9.2)

*$p < 0.05$ compared with the group of males carrying the Val/Val allele.

chogenetic studies, the dopamine system is associated with reinforcement or "reward," while the serotonin system is associated with inhibitory effects on certain types of activity, particularly those leading to anxiety or aggression [31].

Polymorphism of the catechol-O-methyltransferase gene (*COMT*; regulates the functions of the dopaminergic system) can produce individual differences in the development and manifestation of psychophysiological qualities. The Val158Met polymorphism (rs4680) of the *COMT* gene has long been studied, though there are insufficient studies of this polymorphism in athletes. Nonetheless, there is ever more evidence that the key variants of genes can alter the activity of neuronal circuits and, as a result, influence psychophysiological status. The activity of the enzyme COMT has different influences on dopamine transmission in the prefrontal cortex of the brain, and as the existence of the Met allele of the rs4680 polymorphism significantly decreases the activity of this enzyme, this can lead to a decrease in dopamine metabolism [32].

Current views hold that genetically determined variability in brain structure and function can influence the individual variability of mental qualities in humans. In the context of neuropsychology, different types of sport impose different demands on athletes. For example, in golf, where the player controls his or her own rate of taking decisions, there is a preference for self-training, in contrast to hockey, basketball, etc., where there is a high requirement for adaptability and the skill of rapid decision-taking [33]. Vestberg

et al. have shown that time-limited tests for executive functions allow selection of the athletes with the greatest potential for football [34].

The battery of test methods assembled here serves one purpose – determination of the psychophysiological status of athletes, i.e., identifying the strengths, mobility, and balance of neural processes in the sportsman's nervous system by conducting psychomotor tests – and is a widely used practice [35–39]. In particular, results from the SVMR test can yield conclusions regarding the time parameters of the more complex components of behavior in humans; they provide for assessment of the integral characteristics of the CNS, as these involve both the main analyzer systems of humans and particular parts of the brain and top-down neural tracts. The SVMR assesses the work capacity and mobility of the nervous system [20].

The MOR assesses reaction accuracy, the inclination to risk, the equilibrium of neural processes, and the functional state and work capacity of the CNS.

The tapping test is used to evaluate the ability of nerve cells to mount rapid transfers from the state of inhibition to the state of arousal and vice versa, and for determining the potential speed of the movement analyzer. The test results can be used in assessing the strengths of the nervous system [40]. Teplov and Nebylitsyn took the view that the strength of neural processes reflects the sensitivity of the analyzers: a person with a strong nervous system is less sensitive and can respond to stimuli of higher intensity than a person with a weak nervous system [23]. These results provide evidence that the initial speed in carriers of the Met allele was lower, as was the number of taps.

The CFFF characterizes the functional state of the cortical compartment of the visual analyzer and the CNS, as well as the levels of inertia in mental processes. This test is a very important integral indicator in assessing psychoaffective tension, which is a factor in psychophysiological maladaptation [41].

Data from twin studies have shown that the rate of the simple visual motor reaction shows 22–86% inheritance [42–44]. The better developed a person's visuomotor (movement) (VMR) reaction speed, the greater the person's chance of making greater achievements in team sports. The VMR time depends on the ratio of inhibitory and excitatory processes in the cerebral cortex.

For example, published data indicate that carriers of the Met allele behave as more restless individuals, are occupied by exploratory activity, and are more susceptible to stress; carriers of the Val allele are characterized by higher thresholds and greater resistance to stress [45–47].

Our data lead to the suggestion that athletes with the Met allele are more inclined to personal anxiety. High anxiety is a negative personality trait and is a condition for the formation of negative personality states and conflict relationships; it creates the grounds for aggressive behavior, so this factor does not have any positive influences on future sporting achievements. On the other hand, increased anxiety can increase activity and the ability to foresee possible dangers, and can give rise to the feelings of helplessness and uncertainty [48, 49].

Wahlstrom et al. established that children and adolescents aged 9–17 years with the Val/Met genotype produced better results in various psychological and motor tests (measures of memory, attention, movement coordination, motor reaction speed) [50]. In addition, studies of the association of the Val158Met polymorphism of the *COMT* gene with emotional manifestations in Russian women demonstrated a link between the Val allele and higher physical aggressivity [51].

It is known from published data that carriers of the Met allele have high cognitive capacity, more gray matter in the brain, a low risk of developing depression, and lower physical aggressivity [52, 53]. Thus, increases in these parameters (FP and RS) typical of the Met genotype allow the rather higher productivity of nervous system functioning to be assessed.

Conclusions. Athletes with the Met/Met genotype of the *COMT* gene had higher values for a number of measures on the SVMR test (the functional level of the system, reaction stability, and level of functional capacities) than carriers of the Val allele. Females (aged 10–19 years) showed a higher sensorimotor reaction speed in the SVMR test and smaller numbers of accurate reactions in the MOR test as compared with males of the same age group. Males (aged 12–19 years) with the Met allele had higher levels of personal anxiety than Val/Val homozygotes.

The data obtained here are of value in psychological correction and for the individual training process and use of the personal approach.

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