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TECHNICAL NOTE

PSYCHIATRY/BEHAVIORAL SCIENCES

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Alcohol Dependence and Criminal Behavior: Preliminary Results of an Association Study of Environmental and Genetic Factors in an Italian Male Population

ABSTRACT: The aim of this study is to propose an innovative approach evaluating the connection between alcohol use disorders and criminal behavior. The research, structured as a case–control study, was based on the analysis of environmental (social variables) and genetic factors (single nucleotide polymorphisms of glutamic acid decarboxylase) in a population (N = 173) of Italian alcohol-dependent men. Group 1 (N = 47, convicted subjects) was compared with Group 2 (N = 126, no previous criminal conduct). Grade repetition, work problems, and drug problems were statistically associated with criminal behavior. Having daily family meals together and having children were inversely related to convictions. The genotype distribution of the two groups was similar. The association between environmental factors and antisocial behavior confirms previous findings in the literature. The lack of genetic association does not exclude the role of the gamma-aminobutyric acid (GABA) system in determining antisocial behavior; further studies with larger samples are needed, together with investigation of other components of the GABA pathway.

KEYWORDS: forensic science, glutamic acid decarboxylase, criminal behavior, γ-aminobutyric acid, alcohol dependence, violent crime

Alcohol dependence (AD) (1) has been considered an important contributing factor to felonies like homicides, intimate partner violence, rape, abuse of children, road deaths, and unintentional harm (2,3). According to the hypothesis of Cloninger (4), alcoholics are divided into type 1, men and women, late onset, and type 2, male-limited, early onset, and impulsive and antisocial behavior. Reported differences may reflect dissimilar environmental and genetic influences on the development of AD and related antisocial conduct.

In recent years, some authors (e.g., [5]) have highlighted the integrated role of social and genetic factors in delinquency. According to informal social control theories, an individual is more likely to commit a crime when that person's bonds with society are weak or broken (5,6). Family and school represent the dominant institutions of informal social control in adolescence, marriage and employment in adulthood (5). Religion is another factor that has been widely studied in relation to the deterrence of criminal conduct (7,8), with varied and contested results (9). Divergences in results are probably due to differences in conceptual and methodological approaches (9).

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According to some authors, the social propensity to delinquency can produce effects only in individuals with genetic predisposition, understood as the presence of genes playing a susceptibility role or the absence of genes playing a protective role in subjects who develop such a propensity.

Several gene regions and neurotransmitter systems have been studied in relation to aggressive behavior (10–15). The gamma-aminobutyric acid (GABA) system may reveal interesting results in the study of antisocial behavior of alcoholics (2). GABA has indeed been related to both AD (16) and aggressiveness (17). The involvement of the GABA system in acute and chronic effects of ethanol (18), the many behavioral effects attributable to acute alcohol consumption (e.g., impaired motor coordination) by GABA A receptor agonists (16) and the role of the GABA B receptor in alcohol-seeking and drinking behavior (19) are all indications of a link between the GABA system and AD. The same association is suggested by the involvement of the GABA A receptor in symptoms observed during withdrawal from ethanol (20,21).

GABA may also play an important role in inhibiting aggressive behavior (17). Pharmacological treatment which decreases impulsivity-related symptoms such as impulsive aggression (22) and behavioral dyscontrol (23) includes pro-GABAergic mechanisms. Low GABA levels in plasma have been associated with impulsivity (24).

Some authors have gone into further depth regarding the specific relation between alcohol, GABA, and aggressiveness (2). In particular, it has been established that administration of alcohol, like other allosteric modulators of the GABA A receptor

complex, such as benzodiazepines, barbiturates, or neurosteroids, can lead to heightened aggression in a variety of animal species and in a range of conditions (25). The relation between alcohol intake and GABA aggressiveness is again suggested by the observation of the aggression-heightening effects of low alcohol doses concurrently administered with the neurosteroid allopregnanolone (26). These findings suggest that alcohol, benzodiazepines, and neurosteroids can lead to aggression through a similar mechanism (2).

The fact that GABA levels can play a role in the development of AD and aggressiveness (24) led us to consider the potential interest of glutamate decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis. In particular, the isoform GAD1, responsible for maintaining basal GABA levels (27,28), appears to be the most interesting isoform of GAD.

According to the above assumptions and to provide novel insights into understanding of antisocial behavior related to AD, we conducted an environmental (institutions of informal social control) and genetic (GAD1 gene) study on a relatively homogeneous sample of Italian men.

Materials and Methods

Subjects and Phenotype Assessment

This research was structured as a case–control study. The total cohort analyzed was composed of 173 Italian subjects, meeting DSM-IV-TR criteria for AD. They were divided into two groups, according to their positive or negative history of criminal conduct.

Group 1, $n = 47$, history of criminal conduct, recruitment from prison or therapeutic communities in the Veneto Region (northeast Italy).
Group 2, $n = 126$, no history of criminal conduct, recruitment from alcohol abuse treatment centers in Dolo, Rovigo and Cittadella (Veneto) and from the Section of Forensic Toxicology, University of Padova.

Participants were all male Italians with grandparents born in Italy, over 25 years of age, and with a history of development of AD before the age of 40. Exclusion criteria were psychiatric, neurological, and/or medical disorders. In particular, subjects with major psychiatric conditions such as bipolar or psychotic disorders, in possible correlation with aggressive or impulsive behavior, were excluded from our sample.

Subjects' informed written consent was obtained after an explanation of the study, including mention of the strict confidentiality of all data collected, anonymity, and the absence of any juridical or treatment-related implications. Examination of medical records (including chemico-toxicological analyses), anamnesis, clinical-behavioral examination (Audit and Cage tests), and objective general and toxicological clinical examinations were carried out for all subjects. Demographic, social, and criminological data (Table 1), gathered by means of interviews and examination of available records (medical and legal), were recorded in a database.

Following literature on delinquency (29–31), felonies were subdivided into type of crime (Table 1) and into nonviolent and violent acts. Stealing amounts larger or smaller than Euro 50, breaking and entering, and selling drugs were not considered as violent crimes. Serious physical fighting resulting in injuries requiring medical treatment, use of weapons to obtain something forcibly from someone, involvement in physical fighting between groups, shooting or stabbing someone, deliberately damaging property, and pulling a knife or gun on someone were considered violent crimes. At the end of the interviews, EDTA anticoagulated peripheral blood samples were obtained from each participant for DNA extraction. The study protocol was approved by the local Ethics Committee; procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

TABLE 1—*Demographic, social, and criminological data.*

Demographic and Social Data			
		Yes	No
Age			
Place of birth			
Place of residence			
Family	More than 4 persons per family		
	More than 8 years of education of at least one of the 2 parents		
	Daily family meals		
	Parent jobless		
	Parents divorced/separated		
Substance use disorders in the family	Alcohol use disorder		
	Substance use disorder other than alcohol		
School	Repetition of one or more grade		
Compulsory military service	Problems during military service		
Marital status	Single		
	Married		
	Separated/divorced		
Offspring			
Employment	Work problems related to alcohol consumption		
Religiosity	Religious preference		
	Attendance of services		
Comorbidity with substance use disorders			
AA membership	Prior to conviction		
Criminological Data—Type of Felony			
		Yes	No
Crime against person	Homicide		
	Sexual violence (including child abuse)		
	Personal injuries		
Family crime	Family violence		
Property crimes	Burglary, theft, arson, shoplifting, and vandalism		
Drug-related crimes	Drug dealing		

AA, alcoholics anonymous.

Selection of Single Nucleotide Polymorphisms

Information on single nucleotide polymorphism (SNP) selection was retrieved from both the dbSNP database of NCBI (http://www.ncbi.nlm.nih.gov) and the literature findings (32–35).

In total, 23 SNPs spanning the promoter region of the GAD1 gene to 3′ UTR were tested for association with criminal behavior in alcohol-dependent subjects. For preliminary screening of polymorphisms in GAD1, first of all nonsynonymous SNPs in the coding regions were selected, bearing in mind that SNPs changing amino acids located within exonic regions may affect

protein structure and/or function. Exonic SNPs responsible for silent mutation without amino acid changes were also included in the study. In addition, SNPs in intronic and promoter regions were selected, because they may affect mRNA splicing and gene expression, respectively. The markers turned out to be classified as follows: five SNPs were located in coding regions (rs11542313, rs1049736, rs1049731, rs17857149, and rs769402), 11 in intronic regions (rs3791850, rs3791872, rs41393845, rs3791853, rs45510198, rs3791876, rs3828275, rs10179059, rs3791864, rs1420385, and rs3828274), and five in promoter regions (rs3762554, rs4667659, rs6755102, rs1978340, and rs872123) of the gene. One SNP (rs769395) was located in the 3′ UTR region and one (rs3749034) in the 5′ UTR region. Autoprimer software (www.autoprimer.com) was used to analyze the sequences and to design specific primers and probes for each SNP.

All SNPs were analyzed by GenomeLab SNPStream genotyping system technology (Beckman Coulter, Fullerton, CA) according to methods previously described (36). Briefly, genomic DNA was extracted in automated 96-well plates by means of the MultiPROBE II HTFEX automated system (Perkin Elmer, Shelton, CT). Multiplex polymerase chain reactions (PCRs) were performed in 25 μL volumes with 5 ng of DNA, 75 μM dNTPs, 50 nM each primer, and 5 mM MgCl2, 0.5 U TaqGold (Applied Biosystems, Foster City, CA) in 1X PCR buffer.

Cycling conditions (GeneAmp PCR System 9700 thermal cycler; Applied Biosystems) were 94°C for 10 min, followed by 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 1 min, with a final elongation step at 72°C for 4 min. Five microliters of PCR products were purified by ExoSAP IT chemistry (USB Corporation, Cleveland, OH) (37) and genotyped with the GenomeLab SNPStream genotyping system. Data obtained with SNPStream analysis were confirmed by direct sequencing on a model ABI Prism 3130xl Genetic Analyzer (Applied Biosystems).

Statistical Analysis

The association between belonging groups and social variables (education, family, religious beliefs and church attendance, marital status, and work) was assessed with the chi-square test. The role of sociodemographic characteristics, as risk factors for criminal behavior (information categorized as "yes" if subjects belonged to Group 1 and "no" if they were in Group 2) was investigated by multiple logistic regression analysis: odds ratios and their 95% confidence intervals were determined (38).

Statistical analysis of genetic data was performed with Power Marker (39) and Haploview (40) software. Deviations of genotypes from Hardy–Weinberg equilibrium and comparisons of differences in allele and genotype frequencies between alcoholics and prison inmates were evaluated by the chi-square test with Power Marker. Haploview was used to analyze which SNPs were in linkage disequilibrium. These data were indispensable for applying Bonferroni's correction and for evaluating the significance of results.

SNPs with minor allele frequencies (MAF) ≤ 0.05 in the two groups were excluded from the statistics. This choice was based on the number of subjects included in the study. For SNPs with MAF <0.05, the *p*-value could not always be exact, because estimation of allele frequency was performed on a relatively small number of subjects.

Results

In Groups 1 and 2, respectively, subjects' mean age was 40.70 ± 10.95 years (range 25–66 years) and 43.80 ± 9.83 years (range 25–69 years). The two groups were compared in relation to social variables with the chi-square test. The single characteristics in the two groups are listed in Table 2. The variable religious beliefs and church attendance were not further considered in statistical analysis, because of incomplete data collection.

As regards the distribution of crimes in Group 1, convictions were related to violent crimes in 33 cases (70.2%) and to serious crimes in 14 cases (29.7%). Crimes against the person were involved in 20 cases (42.5%), family crime was encountered in only two cases (4.3%), and property and drug-related crimes, respectively, in 26 (55.3%) and seven (14.9%) cases.

The chi-square test verified the association between each characteristic and group. As the above characteristics are all linked in some way, the role of each in terms of risk of criminal conduct, net of the influence of all the others, was evaluated by a logistic regression model. In addition, to estimate the model which includes only those factors with statistical significance, multiple logistic regression analysis with a criterion for stepwise selection of variables was performed.

The odds ratios of the risk factors for criminal behavior, determined by multiple logistic regression, are listed in Tables 3 and 4. Our results reveal the statistical association between grade repetition (OR = 12.7; 95% CI, 4.5–36.4; $p < 0.0001$), work problems (OR = 4.4; 95% CI, 1.6–12.8; $p = 0.0049$), drug problems (OR = 3.9; 95% CI, 1.1–13.9; $p = 0.0343$), and criminal behavior. Daily family meals (OR = 0.095; 95% CI, 0.02–0.36; $p = 0.0006$) and having children (OR = 0.298; 95% CI, 0.11–0.80; $p = 0.0162$) were inversely associated with convictions. No significant association was found between antisocial behavior and variables concerning features of the family other than daily family meals, compulsory military service, and marital status. Examination of each type of felony revealed an association

TABLE 2—*Chi-square analysis.*

	Group 1 *N* = 47		Group 2 *N* = 126		
	N	%	*N*	%	*p*-Value*
More than 4 persons per family	33	70.2	61	48.4	0.0104
More than 8 years of education of at least one of the 2 parents	5	10.6	14	11.1	0.9295
Daily family meals	30	63.8	121	96.0	<0.0001
Parent jobless	19	40.4	10	7.9	<0.0001
Parents divorced/separated	9	19.1	13	10.3	0.1209
Alcohol use disorder	19	40.4	23	18.2	0.0025
Substance use disorder other than alcohol	7	14.9	5	4.0	0.0119
Repetition of one or more grade	25	53.2	10	7.9	<0.0001
Problems during military service	6	12.8	11	8.7	0.4276
Single	26	55.3	36	28.6	
Married	15	31.9	77	61.1	0.0019
Separated/divorced	6	12.8	13	10.3	
Offspring	15	31.9	78	61.9	0.0004
Work problems related to alcohol consumption	22	46.8	15	11.9	<0.0001
Comorbidity with substance use disorders	15	31.9	16	12.6	<0.0001
AA membership	24	51.1	81	64.3	0.1132

AA, alcoholics anonymous.
*Chi-square test.

TABLE 3—*Odds ratios of the risk factors for antisocial behavior using multiple logistic regression model.*

Parameters		d.f.	Estimate	Error	Chi-Square	*p*-Value	OR	95% CI
Intercept		1	0.9572	1.2795	0.5596	0.4544		
More than 4 persons per family	Yes vs. No	1	0.2879	0.2938	0.9601	0.3272	1.778	0.562–5.626
More than 8 years of education of at least one of the 2 parents	Yes vs. No	1	−0.5173	0.4539	1.2987	0.2544	0.355	0.060–2.106
Parent jobless	Yes vs. No	1	0.6295	0.3407	3.4140	0.0646	3.522	0.926–13.389
Daily family meals	Yes vs. No	1	−1.2436	0.3942	9.9528	0.0016	0.083	0.018–0.390
Parents divorced/separated	Yes vs. No	1	−0.0576	0.4024	0.0205	0.8862	0.891	0.184–4.316
Alcohol use disorder	Yes vs. No	1	0.1731	0.2848	0.3694	0.5433	1.414	0.463–4.316
Repetition of one or more grade	Yes vs. No	1	1.1679	0.3043	14.7302	0.0001	10.339	3.136–34.081
Problems during military service	Yes vs. No	1	−0.3369	0.4293	0.6158	0.4326	0.510	0.095–2.743
Married	Yes vs. No	1	−0.6323	0.4579	1.9068	0.1673	0.282	0.047–1.700
Separated/divorced	Yes vs. No	1	−0.3498	0.4457	0.6159	0.4326	0.497	0.087–2.851
Offspring	Yes vs. No	1	−0.2159	0.3966	0.2963	0.5862	0.649	0.137–3.073
Work problems related to alcohol consumption	Yes vs. No	1	0.8590	0.3166	7.3617	0.0067	5.573	1.611–19.277
Comorbidity with substance use disorders	Yes vs. No	1	1.1382	0.4180	7.4163	0.0065	9.742	1.893–50.138
AA membership	Yes vs. No	1	0.4462	0.2820	2.5049	0.1135	2.441	0.808–7.372

AA, alcoholics anonymous.

TABLE 4—*Stepwise selection procedure.*

Parameters		d.f.	Estimate	Error	Chi-Square	*p*-Value	OR	95% CI
Intercept		1	1.2301	0.4730	6.7637	0.0093		
Repetition of one or more grade	Yes vs. No	1	1.2730	0.2677	22.6141	<0.0001	12.757	4.467–36.431
Work problems related to alcohol consumption	Yes vs. No	1	0.7517	0.2674	7.9034	0.0049	4.497	1.577–12.827
Comorbidity with substance use disorders	Yes vs. No	1	0.6831	0.3228	4.4788	0.0343	3.920	1.106–13.894
Daily family meals	Yes vs. No	1	−1.1760	0.3442	11.6712	0.0006	0.095	0.025–0.367
Offspring	Yes vs. No	1	−0.6052	0.2517	5.7800	0.0162	0.298	0.111–0.800

between crimes against the person and alcohol-related work problems (OR = 4.000; 95% CI, 1.166–13.728; $p = 0.0276$), property crimes and, again, alcohol-related work problems (OR = 7.225; 95% CI, 1.961–26.617; $p = 0.0030$), drug dealing and substance use disorder other than alcohol (OR = 7.500; 95% CI, 1.253–44.885; $p = 0.0273$).

As regards genetic data analysis, the 23 SNPs selected from the GAD1 gene were genotyped. All nine polymorphic SNPs (rs3791850, rs3791872, rs769395, rs11542313, rs1420385, rs3828275, rs3749034, rs1978340, and rs872123) were in Hardy–Weinberg equilibrium. The observed allele and genotype distributions are shown in Table 5. After Bonferroni's correction for multiple testing, considering that two SNPs were in linkage disequilibrium, no significant single-marker association was observed for any of the analyzed SNPs.

Discussion

AD has been widely associated with antisocial behavior and violent acts (2,3,41). Although alcohol consumption increases the risk of criminality (42), only a few subjects with alcohol use disorders become delinquents (41). The reason for this variability is largely unknown but may be related to genetic susceptibility conditioned by environmental factors (5).

For further understanding of these relations, we compared two groups of alcohol addicts, characterized, respectively, by the presence or absence of previous criminal conduct, from the genetic and environmental points of view.

In proposing the study, we were aware of the low sample size in examining the low risk associated with common variants in psychiatric disorders. Taking into account sample size, statistical tests at $\alpha = 0.05$ have sufficient power (at least 80%) to demonstrate differences of 15–20% compared with the proportion in control groups, around 60%.

The two groups of Italian male subjects had well-defined environmental and social histories. Criminal conduct was assessed by means of official records, avoiding possible bias caused by factors such as denial of illicit behavior or answering in socially desirable ways. Data concerning alcohol consumption and diagnosis of AD may both be considered accurate. The literature suggests an acceptable level of accuracy in self-reports of substance use (43) and this validity is also judged by the consistency of various measures (as in our study) such as biomarkers and criminal justice records. Genetic analysis was performed on 23 SNPs of the GAD1 gene, none of which had previously been studied in relation to antisocial behavior.

As regards environmental factors, our results reveal a statistical association between grade repetition, alcohol-related work problems, drug problems, and convictions. Daily family meals (OR = 0.095; 95% CI: 0.02–0.36; $p = 0.0006$) and having children (OR = 0.298; 95% CI: 0.11–0.80); $p = 0.0162$) were inversely associated with convictions.

The association between grade repetition and antisocial behavior was consistent with the results of other studies (5). One explanation of this finding is that repetition can weaken social control. Repeating students feel frustration, humiliation, shame, and failure (44), and a teacher with negative perceptions and low expectations can disorganize social bonds; in turn, weakened bonds toward school may increase exposure to deviant peers (5).

The relation between work problems and antisocial behavior has already been described in the literature (45). In particular, unemployment has been found to be significantly associated with violent crimes (homicide rates in North America [46], Australia [47], and Europe [48]) and serious crimes (45) (property crimes). The hypothesis stressing an association with property crimes, as found in our sample, was put forward after a significantly positive effect of unemployment on rates of this kind of crime had been reported. Similarly, the decline in property crime rates

TABLE 5—*Values of allele and genotype frequencies of prisoners (Group 1) and alcoholics (Group 2) for the SNPs resulted polymorphic (MAF > 0.01). Allele and genotype χ^2 values and allele and genotype* p*-values, calculated by χ^2 test, are also reported.*

			Allele Frequencies		Genotype Frequencies			χ^2		*p*-Value	
ID SNPs	Location	Group	C	T	CC	CT	TT	Allele	Genotype	Allele	Genotype
rs3791850	Intron 12	1	0.755	0.245	0.553	0.404	0.043	0.0805	0.8930	0.7766	0.6399
		2	0.770	0.230	0.603	0.333	0.063				
rs3791872	Intron 3	1	0.734	0.266	0.490	0.490	0.021	2.0505	3.2137	0.3587	0.3598
		2	0.693	0.306	0.476	0.435	0.089				
rs769395	3′ UTR	1	0.319	0.681	0.043	0.553	0.404	2.7405	3.0539	0.2540	0.3834
		2	0.244	0.756	0.032	0.424	0.544				
rs11542313	Exon 3	1	0.468	0.532	0.128	0.681	0.191	6.0539	9.1871	0.0139	0.0101
		2	0.615	0.385	0.365	0.500	0.135				
rs1420385	Intron 3	1	0.457	0.542	0.191	0.532	0.276	0.0071	0.2180	0.9329	0.8967
		2	0.452	0.547	0.206	0.492	0.301				
			A	G	AA	AG	GG				
rs3828275	Intron 3	1	0.447	0.553	0.170	0.553	0.276	0.0567	0.4039	0.8118	0.8171
		2	0.432	0.567	0.182	0.500	0.317				
rs3749034	5′ UTR	1	0.128	0.872		0.255	0.745	4.4570	4.7402	0.0347	0.0935
		2	0.230	0.770	0.071	0.317	0.611				
rs1978340	Promoter	1	0.638	0.362	0.638		0.362	0.5321	0.2660	0.4657	0.6060
		2	0.595	0.405	0.595		0.404				
rs872123	Promoter	1	0.819	0.181	0.681	0.276	0.042	1.2966	1.2012	0.2548	0.5485
		2	0.762	0.238	0.595	0.333	0.071				

SNPs, single nucleotide polymorphisms; MAF, minor allele frequencies.

during the 1990s was attributable, according to some authors (e.g., [45]), to a reduction in the unemployment rate.

The association of substance use disorder other than alcohol and antisocial behavior is not surprising, especially according to the types of felony evidenced (drug dealing); this observation may be explained by various theories of drug-related crime (49). In particular, drug use may lead to criminal behavior owing to direct (adverse effects of substances, intoxication, and craving) or indirect effects (economic reasons—drug users need money to buy drugs—and social context). In our cases, drug dealing was probably related to the two latter effects.

The direct effects of drugs or alcohol at the time of the crime were not considered in our study. This aspect is one which should be extended, as in most cases the data could be evaluated according to subjects' answers, which may be often missing, inaccurate, or deliberately misleading.

Daily family meals and the fact of having children were found to be "protective factors" against criminal behavior. These results, consistent with the literature (50), are a form of family tie, an indication of the existence of a structure which can support a person in time of need.

The genotype distribution of the two groups was similar. No statistical differences in the 23 SNPs were detected. In particular, considering that two SNPs (rs872123 and rs3749034) were in linkage disequilibrium, Bonferroni's correction for multiple testing to evaluate statistical significance turned out to be 0.05/8 = 0.0062. No genetic marker associated with antisocial behavior was found in our sample. These results do not confirm any involvement of the GABA system in antisocial behavior. Before excluding the possible role of GABA, we are currently implementing our sample and carrying out further genetic analyses in other parts of this neurotransmitter system.

Although only males are the subject of this study, we are also collecting female DNA samples, with a view to investigating gender differences. In particular, the role played by androgens and cortisol should be taken into consideration as a factor regulating human aggression (51).

In conclusion, our results highlighted an association between some environmental variables and antisocial behavior. Future studies will aim at better understanding of the connection between genes and crime-related factors (also by the analysis of other components of the GABA pathway); an integrated G × E evaluation will also be performed, after enlargement of the sample. It will be interesting to analyze genetic regions playing a protective or susceptibility role. In other words, some genes may contribute to increasing the risk because of social variables or protecting certain groups from developing aggressive behavior, even in cases of environmentally negative conditions.

The rationale for studies of this kind has been previously described (52) and may be mainly identified in better estimation of the mechanisms of behavioral problems and the designation of new preventive and therapeutic strategies.

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