Published in final edited form as:

Pers Individ Dif. 2015 August ; 82: 96–101. doi:10.1016/j.paid.2015.03.001.

Temperament disturbances measured in infancy progress to substance use disorder 20 years later

Michelle S. Horner^{a,b,*}, Maureen Reynolds^{b,c}, Betty Braxter^{b,d}, Levent Kirisci^{b,c}, and Ralph E. Tarter^{b,c}

Michelle S. Horner: Michelle.Horner@gmail.com; Ralph E. Tarter: Tarter@pitt.edu

^aUniversity of Pittsburgh School of Medicine, Department of Psychiatry, Pittsburgh, PA, USA

^bCenter for Education and Drug Abuse Research (CEDAR), Pittsburgh, PA, USA

^cUniversity of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA

^dUniversity of Pittsburgh School of Nursing, Pittsburgh, PA, USA

Abstract

Objective—This prospective study determined whether temperament before two years of age predicts transmissible risk for substance use disorder (SUD) up to a decade later and SUD outcome in adulthood.

Method—Boys between 10 and 12 years of age ($N = 482$) were tracked to age 22. The previously validated *transmissible liability index* (TLI) was administered at baseline, and temperament prior to two years of age was retrospectively rated. The Structured Clinical Interview for DSM-III-R (SCID) was administered to document presence/absence of SUD for parents at baseline and sons at age 22.

Results—Path analysis revealed that number of parents with SUD predicted severity of temperament disturbance in their sons which in turn predicted TLI score at age 10–12, presaging SUD. Temperament before age two did not predict SUD at age 22. The association between number of SUD parents and transmissible risk was mediated by severity of temperament disturbance.

Conclusion—Temperament disturbance in early childhood, reflecting quality of behavioral and emotion regulation, comprise psychological antecedents of transmissible risk for SUD.

Keywords

Temperament; Development; Infancy; Substance use disorder (SUD); Transmissible liability; Longitudinal

1. Introduction

Substance use disorder (SUD) frequently persists across generations consequent to genetic vulnerability and parental rearing environment (Agrawal & Lynskey, 2008; Hopfer,

*Corresponding author at: Center for Education and Drug Abuse Research, PARKV-226, 3520 Forbes Avenue, Suite 203, Pittsburgh, PA 15213, USA. Tel.: +1 412 864 2460; fax: +1 412 864 2464.

Crowley, & Hewitt, 2003). Biological children of SUD parents have up to sevenfold heightened risk to develop SUD (Johnson & Leff, 1999; Tarter, Horner, & Ridenour, 2012). Compared to children whose parents do not have SUD, offspring of SUD parents initiate substance use at a younger age (Hill, Shen, Louters, & Locke, 2000) and more rapidly progress to SUD (Trim, Schuckit, & Smith, 2010; Warner, White, & Johnson, 2007). Notably, the transmissible component of risk encompassing both genetic and parental environment influences accounts for over 40% of variance underlying cannabis dependence (Hopfer et al., 2003).

Research has shown that the psychological characteristics comprising transmissible risk for SUD are indicators of a unidimensional interval construct (Vanyukov, Tarter et al., 2003; Vanyukov et al., 2009). This trait, termed the *transmissible liability index* (TLI), predicts SUD in adulthood, and, consistent with the common liability model of SUD etiology (Vanyukov, Tarter et al., 2003), predicts all SUD categories in the DSM-IV (Ridenour, Kirisci, Tarter, & Vanyukov, 2011). Twin studies demonstrate that 75% (Hicks, Iacono, & McGue, 2012) to 85% (Vanyukov et al., 2009) of TLI variance is genetic, and the genetic component accounts for approximately 50% of variance underlying development of SUD (Vanyukov et al., 2015). Furthermore, TLI score in childhood covaries negatively with age of first substance use and interval between initial substance exposure and SUD diagnosis (Kirisci et al., 2013). Conforming to the theory that SUD is a developmental outcome (Tarter, 2002; Tarter & Horner, in press; Tarter et al., 2012), five age-specific versions of the TLI have been validated to quantify transmissible risk between childhood and adulthood using a Web-based computer-adaptive test format (Kirisci et al., 2012).

Inspection of the TLI in Table 1 indicates that the items mainly denote various aspects of behavior and emotion dysregulation. Considering that several items in the TLI correspond to traits posited by Thomas and Chess (1977), and that low inhibitory control in early childhood, conceptualized within a temperament framework, predicts SUD in adulthood (Caspi, Moffitt, Newman, & Silva, 1996), it was hypothesized that higher parental loading for SUD predicts temperament disturbances in infancy and higher TLI score in childhood, which in turn predicts SUD in adulthood. Furthermore, TLI score is hypothesized to mediate the relationship between number of SUD affected parents and SUD manifested in the offspring at 22 years of age. To determine whether temperament disturbance constitutes the psychological phenotype of transmissible risk in young children, it is hypothesized that temperament mediates the association between number of SUD parents and severity of transmissible risk. Confirming these hypotheses would provide important evidence that temperament disturbance in early childhood contributes to the transmissible risk for SUD that is conferred from parent to child.

2. Methods

2.1. Participants

Participants were 482 10–12 year-old boys having biological fathers who either qualified for DSM-III-R diagnosis of SUD consequent to use of an illicit drug (SUD+, $N = 245$) or had no adult psychiatric disorder (SUD–, $N = 237$). The sample was confined to boys because the TLI is still undergoing development and validation in females. Multiple recruitment

procedures were required due to the low prevalence of men diagnosed with lifetime SUD consequent to use of illegal drugs who have a healthy son in the designated age range and current or past spouse willing to participate in this longterm project. The families were recruited using random digit telephone calls, advertisement and public service announcements. Approximately 20% of the SUD+ fathers were recruited from substance abuse treatment programs. Exclusion criteria for the fathers were any history of neurological disorder, psychosis or uncorrectable sensory incapacity. Boys with any history of psychosis, uncorrectable sensory incapacity, chronic physical disability, neurological disorder requiring hospitalization, or an IQ less than 80 (Wechsler, 1991) were excluded from study. This project was approved by the University of Pittsburgh Institutional Review Board.

Attrition between enrollment and age 22 was 37%. Incarceration, military deployment overseas, and relocation to other regions in the U.S. hampered efforts to conduct the outcome assessment at age 22. Table 2 compares the retained and attrited subjects on the predictor variables (temperament, TLI), ethnicity, IQ and SES. As can be seen, the attrited subjects scored on average six points lower than the retained subjects on the intelligence test. The mean score in both groups is, however, in the normal range of intelligence. Socioeconomic status (SES) measured by the two factor Hollingshead index was on average three points lower in the attrited participants.

2.2. Instrumentation

2.2.1. Substance use disorder (SUD)—Lifetime SUD diagnoses in the fathers and mothers were formulated using the Structured Clinical Interview for Diagnosis (SCID; Spitzer, Williams, Gibbon, & First, 1992). The SCID was administered privately to each parent by trained clinical research associates. A diagnostic committee chaired by a psychiatrist certified in addiction medicine and another psychiatrist or psychologist along with the clinical associates who conducted the interviews consensually assigned SUD diagnoses employing DSM-III-R criteria. The DSM-III-R taxonomy was used because this longitudinal project was initiated prior to publication of the DSM-IV.

Current SUD (abuse or dependence) in the sons at age 22 consequent to consumption of any compound other than tobacco was also determined by this committee. The most frequent diagnoses were alcohol use disorder (27.6%) and cannabis use disorder (26.2%).

2.2.2. Temperament (<2 years of age)

The primary caregiver (mother in 97.4% of the sample) retrospectively rated their son's temperament using the *Developmental and Health History Questionnaire Form* (Garmezzy, 1981). Seven aspects of temperament were recorded: (1) easy/difficult, (2) active/passive, (3) regular/irregular routines (sleep, bowel movement, eating), (4) positive/negative reaction to new experiences, (5) friendly/unfriendly, (6) low/high arousability threshold, and (7) low/high distractibility. Items 3 and 5 required a binary response in which “regular” and “friendly” were scored 0 and “irregular” and “unfriendly” were scored 1. The remaining items had three response choices. For example: *When people describe babies they sometimes say: Oh so and so is an “easy” baby or a “difficult” baby. What kind of an infant was (child’s name)?* Answer options: *Easy, Moderate, Difficult, or Don’t Know*. “Easy” was

assigned a score of zero, moderate = 1, and difficult = 2. Hence, higher scores reflect greater temperament disturbance. All of the questions included a “don’t know” option, thereby limiting scored responses to items that the mother confidently provided a rating. The “don’t know” responses were not included in the scoring. Notably, the rate of “don’t know” responses was low, namely 0.4%, 0.8%, 0.6%, 0.6%, 0.8%, 1.6% and 2.6% for items 1 through 7. To obtain the overall temperament score, the items were first transformed to a z -scale. The z -scores were summed and averaged to derive each participant’s temperament score.

2.2.3. Transmissible liability index (TLI)

The TLI has documented construct, discriminative and predictive validity (Kirisici et al., 2009; Vanyukov et al., 2009). Sons of SUD+ fathers score on average approximately 0.5 SD higher on the TLI than sons of SUD– fathers (Vanyukov et al., 2009). Moreover, each unit (1 SD) increment in TLI increases risk for SUD by 70%. Internal consistency of the TLI is .93.

The TLI was developed using a multistage procedure (Vanyukov, Kirisici et al., 2003; Vanyukov, Tarter et al., 2003). At the outset, faculty in the Center for Education and Drug Abuse Research (CEDAR) reviewed the empirical literature and catalogued the psychological traits implicated to presage SUD. Items selected from CEDAR’s protocols consisting of parent reports, teacher reports and self-reports were provisionally assigned to the traits. Exploratory factor analysis was performed on the provisional traits yielding a complement of constructs. Items in the constructs having loading less than 0.4 were removed. The constructs that were subsequently shown to be unidimensional by confirmatory factor analysis were retained. Next, the sons of SUD+/- fathers were compared on the constructs using analysis of variance. The constructs that discriminated the boys in the two groups were then submitted to exploratory factor analysis from which a single major factor was derived. Items having loading less than .40 were removed and confirmatory factor analysis was performed on the remaining set to verify unidimensionality of the construct. Using this procedure, the initial pool of 441 items assigned to 34 constructs was reduced to one construct consisting of 45 items. Twelve items involved self-report, 23 items parent report and 10 items teacher report. Lastly, a two parameter item response theory model was used to calibrate the items. Detailed description of the theory and method of TLI development can be found in Vanyukov et al. (2003).

2.3. Procedure

The project details were reviewed with the family upon arrival at the laboratory. Parents provided written informed consent and the child provided verbal assent. Before implementing the research protocol, the child confirmed that he was not coerced into participation. A urine drug screen was conducted at the outset to ensure that validity of the data was not compromised by the acute effects of abusable substances. None of the boys tested positive. The boys were also given the WISC-III to assess IQ for study inclusion prior to protocol administration. The research protocol was administered in fixed order in sound-attenuated private rooms. Upon conclusion of the research protocol, the boys and parents

were debriefed and monetary compensation to each family member was provided at a rate of \$10 per hour.

2.4. Statistical analysis

Two ANOVAs were conducted to contrast number of parents with SUD (0, 1, or 2 SUD parents) on child's temperament and TLI score. Significant between-group differences were further examined with post-hoc pairwise comparisons. Next, path analysis using MPLUS (Muthen & Muthen, 1998–2006) was conducted to examine the association between parental SUD, temperament before two years of age, TLI score at age 10–12, and SUD at age 22. The hypotheses that temperament mediates the association between number of SUD parents and TLI score, and TLI score mediates the relationship between number of SUD parents and offspring SUD at 22 years of age were tested using the formula described by Sobel (1982). Specifically, mediation was evaluated using the formula:

$z = b_1 b_2 / \sqrt{b_2^2 \sigma_{b_1}^2 + b_1^2 \sigma_{b_2}^2}$, where b_1 is the regression coefficient between predictor and mediator, b_2 is the regression coefficient between mediator and dependent variable, and σ^2 is the square of the estimate of the standard error of the corresponding regression coefficient. The standard error of mediated paths was estimated using the bias-corrected bootstrap procedure described by MacKinnon and colleagues (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). The overall model was evaluated using the weighted least-square parameter estimation method with diagonal weight matrix and robust standard errors. This method uses all available observations and does not exclude any subject from the analysis due to missing data. Four indices of model-data fit were used: (1) χ^2 goodness-of-fit index, (2) root mean square error of approximation (RMSEA), (3) comparative fit index (CFI), and, (4) Tucker-Lewis index. A non-significant χ^2 value ($p > .05$) indicates that the model aligns with the data. RMSEA values greater than .08 reflect poor model-data fit whereas values between .05 and .08 indicate acceptable fit and values less than .05 reflect good fit. Values greater than .90 and .95 for the CFI and Tucker–Lewis index indicate good model-data fit.

3. Results

Results of the ANOVA are shown in Table 3. A significant main effect of parental SUD group on temperament disturbance and TLI was found at the .05 level. Post-hoc pairwise group comparisons indicate that boys with two SUD parents scored significantly higher on temperament disturbance than boys who had zero SUD parents. A significant temperament difference was not observed between boys who had zero SUD parents and one SUD parent at the .05 level. Post-hoc pairwise comparisons also revealed that boys who had two SUD parents scored significantly higher on TLI than boys who had one and zero SUD parent. Furthermore, boys who had one SUD parent scored significantly higher on TLI than boys who had no SUD parent. Effect size is .02 for temperament and .08 for TLI score.

Path analysis revealed satisfactory model-data fit ($\chi^2 = 1.91$, $df = 1$, $p = .17$, RMSEA < .001, TLI = .99, CFI = .92). As can be seen in Fig. 1, number of SUD parents predicted offspring temperament before two years of age and TLI score at 10–12 years of age which, in turn, predicted SUD at age 22. However, neither temperament nor number of SUD parents significantly predicted SUD in the boys. Notably, temperament mediated the association

between number of SUD parents and transmissible risk ($\beta = .03, z = 2.59, p = .01$). Furthermore, TLI mediated the association between number of parents with SUD and son's SUD ($\beta = .04, z = 2.43, p = .01$). Thus, whereas temperament before age 2 did not predict SUD two decades later, it forecasts transmissible risk in late childhood which, in turn, predicts SUD.

4. Discussion

This study demonstrated that number of biological parents having lifetime SUD is related to severity of temperament disturbances in their sons during infancy (<2 years of age) and severity of transmissible risk for SUD in late childhood (10–12 years of age), which in turn predicts offspring SUD outcome at age 22. Temperament also mediates the association between parental SUD and sons' transmissible risk at age 10–12, suggesting that early temperament disturbances may comprise the liability phenotype of transmissible risk for SUD in young children. Considering that a substantial portion of the variance in temperament (Saudino, 2005) and TLI score (Hicks et al., 2012; Vanyukov et al., 2009) is genetic, it is likely that each trait constitutes age-specific characteristics of SUD liability having strong genetic basis.

The developmental pathway observed in this study linking temperament in infancy to transmissible risk and SUD informs prevention. Temperament disturbances frequently precede antisocial behavior, particularly among boys with parental SUD (Giancola, 2000). Proneness toward social deviance is prominent in children who develop SUD and non-normative socialization during adolescence mediates the relationship between transmissible risk in childhood and SUD in adulthood (Horner, Tarter, Kirisci, & Clark, 2013). Considering that first exposure to drugs usually occurs in the context of social interactions with peers, and psychologically dysregulated youths form friendships with peers having similar disposition (Trucco, Colder, & Wieczorek, 2011), it would appear important to exercise oversight of friendships in youths who are at high risk for SUD.

Children with difficult temperaments are more likely to experience avoidance and harsh discipline from parents (Berg-Nielsen, Vikan, & Dahl, 2002) which heightens the child's propensity for early age disengagement from the family, increasing risk factors for developing substance abuse. Also, a parent burdened with SUD is often hampered by psychopathology, inadequate social support, and chronic stress (e.g. single parenting, abusive partner, limited emotional resources, etc.; Moses-Kolko, Horner, Phillips, Hipwell, & Swain, 2014; Pokorni & Stanga, 1996). These factors impede consolidating positive affective synchrony between parent and child. Notably, home visitations by nurses to socioeconomically disadvantaged mothers improves parenting and reduces the child's future risk for substance abuse (Olds, 2002).

Psychological dysregulation, constituting a component of SUD liability, may reflect a heritable neurobiological process. For example, functional neuroimaging studies document prefrontal cortex dysfunction in youths at high risk for SUD (Clark et al., 2013; Goldstein & Volkow, 2011) and may provide a target for prevention of SUD (Perry et al., 2011). Numerous studies have shown that exercise improves psychological self-regulation (e.g.,

Gapin, Labban, & Etnier, 2011; Medina et al., 2010; Pontifex, Saliba, Raine, Picchietti, & Hillman, 2013) and frontal parietal cortex connectivity (Chaddock, Erickson, Prakash, Kim et al., 2010; Chaddock, Erickson, Prakash, VanPatter et al., 2010). Considering that substance abusing youths are less inclined toward exercise (e.g., Collingwood, Reynolds, Kohl, Smith, & Sloan, 1991; Kristjansson, James, Allegrante, Sigfusdottir, & Helgason, 2010), it is possible that effective intervention may involve increasing participation in recreational physical activities (Werch, Moore, DiClemente, Bledsoe, & Jobli, 2005). It is also noteworthy that breastfeeding promotes neuromaturation during infancy (Brazelton & Cramer, 1991; Herba et al., 2012; Isaacs et al., 2010), and is well-known to strengthen affectional bonding between mother and infant, thereby facilitating the child's acquisition of psychological self-regulation.

Several limitations of this study are noted. Because prospective tracking of the boys began at age 10–12, the temperament ratings were necessarily retrospective. Recall bias could have, therefore, threatened the validity of the results. It is notable, however, that each item on the temperament scale had a “don't know” option. Hence, mothers rated their children on only the traits for which they felt knowledgeable. Also, because this study was confined to boys, the results cannot be assumed to generalize to girls. Lastly, the sample was accrued using the family high-risk paradigm. Whereas it is conceivable that the obtained results are not representative of the general population, other investigators (Hicks, Iacono, & McGue, 2012) have used the TLI and obtained results similar to our sample (Vanyukov et al., 2009).

In summary, this study demonstrated that parental SUD predicts severity of temperament disturbances in boys prior to two years of age. In addition, temperament mediates the association between parental SUD and transmissible risk for SUD measured in late childhood that, in turn, forecasts SUD a decade or more later. These findings demonstrate that temperament disturbances in early childhood may be indicators of transmissible (intergenerational) risk for SUD.

Acknowledgments

Supported by grants P50DA05605, K05DA031248 and K12DA000357. Content is solely the responsibility of the authors and does not represent official views of NIH or NIDA.

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Fig. 1. Temperament in infancy mediates the association between number of biological parents with lifetime SUD and transmissible liability index (TLI) in childhood, presaging SUD in adulthood.

Table 1

Items comprising the transmissible liability index (TLI).

<i>Parent as respondent</i>	
Characteristics of child prior to age 13	
1. Lying	
2. Stealing	
3. Impulsive	
8. Did he often do things to annoy people like grabbing another child's hat?	
9. Did he often annoy people on purpose to get even?	
10. Did he have difficulty staying in line in the supermarket or waiting for his turn while he was playing with other children?	
11. Did he blurt out answers to questions before they had been completed or did he get into trouble because he would rush into things without thinking?	
12. Did he get into trouble a lot for talking out of turn in school or talking without the teacher calling on him or for bothering people?	
13. Did he get into trouble because he would do things without thinking about them first, for example running into the street without looking?	
15. He/she interrupts on people when they are speaking	
Describes your child now or within the past 6 months...	
21. Impulsive or acts without thinking	
22. Destroys things belonging to his/her family or others	
23. Disobedient at school	
24. Steals at home	
25. Bites fingernails	
26. Picks nose, skin or other parts or body	
38. My child moves a great deal in his/her sleep.	
39. In the morning, my child is still in the same place as he/she was when he/she fell asleep (reverse-coded)	
40. My child doesn't move around much at all in his/her sleep (reverse-coded)	
41. It takes my child a long time to get used to a new thing in the home (reverse-coded)	
42. It takes my child a long time to adjust to new schedules (reverse-coded)	
43. Changes in plans make my child restless (reverse-coded)	
44. My child resists changes in routine (reverse-coded)	
<i>Child as respondent</i>	
4. Did you often annoy people on purpose to get even?	
5. Did you often do things to annoy people like grabbing another child's hat?	
6. Did you blurt out answers to questions before they had been completed or did you get into trouble because you would rush into things without thinking?	
7. Were things so bad that you were thinking a lot about death or that you would be better off dead?	
14. I interrupt on people when they are speaking	
32. I move a great deal in my sleep	
33. I don't move around much at all in my sleep (reverse-coded)	
34. I get hungry about the same time each day (reverse-coded)	
35. I usually eat the same amount each day (reverse-coded)	
36. I eat about the same amount at supper from day to day (reverse-coded)	
37. My appetite seems to stay the same day after day (reverse-coded)	
45. Did you skip classes or school without an excuse?	

Teacher as respondent

16. Excitable, Impulsive best describes the child

The behavior of the child is best described as ...

17. ...often engages in physically dangerous activities without considering possible consequences (not for the purpose of thrill-seeking), e.g. runs into street without

looking

18. ...has difficulty awaiting turn in games or group situations

19. ...often blurts out answers to questions before they have been completed

20. ...often interrupts or intrudes on others, e.g., butts into other children's games

Describes the pupil now or within the past 2 months...

27. Impulsive or acts without thinking

28. Talks out of turn

29. Aches or pains (not stomach or headaches) (without known medical causes)

30. Headaches (without known medical causes)

31. Deliberately harms self or attempts suicide

Table 2

Comparison of retained and attrited segments of the sample.

	Retained (N = 303)		Attrited (N = 179)		Equivalence test between groups		Probability of equivalence (%)
	M	(SD)	M	(SD)	Difference	95% CI	
Full scale WISC-III IQ	110.36	15.84	103.71	15.36	6.65	(3.75, 9.55)	1
Socioeconomic status	42.01	13.51	39.12	12.80	2.89	(.47, 5.31)	35
Transmissible liability index (z-score)	.19	.93	.32	1.00	-.13	(-.30, .05)	99
Temperament	.001	.49	.001	.50	<.001	(-.30, .29)	99
	N	%	N	%			
European-American	231	76.2	133	74.3	1.9	(-5.76, 10.16)	96
African American	65	21.5	38	21.2			
Other	7	2.3	8	4.5			

Table 3

Mean score on temperament and TLI in relation to number of parents with SUD.

Number of parents with SUD					
	0 Mean (SD)	1 Mean (SD)	2 Mean (SD)	df	F (p) η^2_p
Temperament ^a	-.06 (.46)	.03 (.50)	.11 (.58)	2	3.61 (.03) .02
TLI ^b	.04 (.93)	.27 (.95)	.82 (.82)	2	18.52 (<.001) .08

^a Only the comparison between the zero-SUD group and the two-SUD parent group was significant at the .05 level.

^b All pairwise comparisons are significant on TLI at .05 level.

^c Partial eta-squared presents effect sizes for temperament and TLI.