Psychiatry Research 185 (2011) 402–407

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Familial influence of substance use disorder on emotional disorder across three generations

Adam M. Leventhal [a,*], Jeremy W. Pettit [b], Peter M. Lewinsohn [c]

[a] Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
[b] Department of Psychology, Florida International University, Miami, FL, USA
[c] Oregon Research Institute, Eugene, OR, USA

ARTICLE INFO

Article history:
Received 4 September 2009
Received in revised form 12 August 2010
Accepted 16 August 2010

Keywords:
Substance use disorder
Emotional disorder
Grandparental
Parental
Three generation study

ABSTRACT

The concomitant influence of grandparental (Generation 1; G1) and parental (G2) substance use disorder (SUD) on grandchild (G3) emotional disorder (EmD) across three generations is unclear. The present study addressed this in a sample of 284 families participating in the Oregon Adolescent Depression Project. Structured clinical interviews were used to collect psychiatric history data on a community cohort of G2 individuals and their G1 parents. G2 parents rated EmD symptoms in their G3 children (M age = 5 years, SD = 2.4). Results indicated that G1 SUD was associated with increased risk of G3 EmD symptom elevations, above and beyond the influence of comorbid G1 EmD. G2 SUD was associated with a similar independent increase in risk for G3 EmD symptoms. Also, G1 SUD conferred risk for G2 SUD. Mediational tests indicated that the influence of G1 SUD on G3 EmD was transmitted via its influence on G2 SUD. G1 and G2 SUD did not interact in predicting G3 EmD; rather results suggested an additive influence. There was no evidence that the influence of G1 SUD on G3 EmD was transmitted via G2 EmD. These findings shed light on the multigenerational processes through which SUD influences EmD.

1. Introduction

The familial influence of substance use disorder (SUD) on emotional disorder (EmD) has been well documented. Individuals with a SUD (versus those without) are more likely to have offspring who develop EmDs, such as depressive and anxiety disorders (Caraveo-Anduaga et al., 2005; Chassin et al., 1999; Clark et al., 2004, 1997; Diaz et al., 2008; Grillon et al., 2005; Harter, 2000; Merikangas and Low, 2005; Preuss et al., 2002; Westermeyer et al., 2006). Some evidence indicates that these associations remain, even after accounting for the effects of comorbid EmD in parent generations (Chassin et al., 1999; Diaz et al., 2008), although this has not always been replicated (Preuss et al., 2002; Clark et al., 1997). These effects can emerge during early childhood, with reports that children of parents with SUD are at increased risk for exhibiting internalizing symptoms indicative of EmD (e.g., social withdrawal, somatic complaints, and anxiety/depression) as early as 36 months of age (Edwards et al., 2006). This is notable because childhood EmD predicts a host of problems in adolescence and adulthood, including higher occurrence of substance abuse and mental disorders, greater prevalence of suicidal behavior, increased use of long-term psychiatric and medical services, and impaired functioning (Weissman et al., 1999b; Weissman et al., 1999a).

Previous studies of high-risk families have primarily focused on the effects of parental SUD on offspring EmD across two generations. However, recent evidence suggests that behavior problems can be transmitted across three generations (Bailey et al., 2006; Grillon et al., 2005; Hammen et al., 2004; Pettit et al., 2008; Olino et al., 2008; Warner et al., 2008, 1999; Weissman et al., 2005). For example, recent work indicates that depression in an older generation (G1; grandparents) not only predicts increased risk of mental disorders in the next generation (G2; parents), but also predicts behavior problems in the third generation (G3; grandchildren) (Hammen et al., 2004; Pettit et al., 2008). The intergenerational transmission of behavior problems from G1 and G2 to G3 can take several forms: (a) G1 psychopathology can influence G3 behavior problems, independent of effects on G2 psychopathology (Pettit et al., 2008); (b) G1 psychopathology can influence G3 behavior problems partially or entirely via intergenerational transmission through G2 psychopathology (Bailey et al., 2006; Warner et al., 1999; Hammen et al., 2004); (c) G1 and G2 psychopathology can interact, such that the risk of G3 behavioral problems are disproportionally higher in those with both parental and grandparental loadings for psychopathology (Olino et al., 2008); or (d) G1 and G2 psychopathology can interact, such that the presence of psychopathology in either G1 or G2 conveys the same risk as the presence of psychopathology in both G1 and G2 (Pettit et al., 2008).

* Corresponding author. Department of Preventive Medicine, University of Southern California Keck School of Medicine, 2250 Alcazar St., CSC 240, Los Angeles, CA 90033, USA. Tel.: +1 323 442 2732; fax: +1 323 442 2359.
E-mail address: adam.leventhal@usc.edu (A.M. Leventhal).

0165-1781/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2010.08.013

Extant data supports each of these potential pathways for the transmission of several forms of behavioral problems across three generations (Bailey et al., 2006; Grillon et al., 2005; Hammen et al., 2004; Pettit et al., 2008; Olino et al., 2008; Warner et al., 2008, 1999; Weissman et al., 2005). However, it remains unclear whether SUD influences risk of EmD across three generations, and how this familial risk pathway may be transmitted from G1 to G2 to G3. Studying the tri-generational effects of SUD on EmD is important for: (a) clarifying the mechanisms by which family history of SUD enhances vulnerability to EmD; (b) identifying high-risk families who may benefit most from preventive interventions; (c) elucidating whether interventions which target G2 SUD may (or may not) potentially disrupt the effects of G1 SUD on G3 EmD; and (d) ascertaining whether researchers and clinicians should obtain extended family pedigrees to evaluate risk in children.

There are several reasons why G1 SUD may increase risk of G3 EmD. Given that SUD and EmD potentially share overlapping genetic variance (Tambs et al., 1997; Prescott et al., 2000; Kendler et al., 1993), grandparents with SUD may transmit genetic vulnerability to EmD to their children, who may in turn transmit this genetic susceptibility to their offspring. Environmental factors may also play a role. Offspring of parents with SUD are at substantial risk of developing SUD when they enter into adulthood (Merikangas et al., 1998). Thus, when these offspring become parents themselves, they are likely to have a SUD. Evidence suggests that parents with SUD are more likely to engage in dysfunctional parenting practices which may mediate the link between parental SUD and child EmD (Edwards et al., 2006). Thus, the influence of G1 SUD on G3 EmD may be transmitted through G2 SUD because G3 offspring may be subject to considerable environmental risk in having a G2 parent with SUD.

The current study examined the familial influence of SUD on EmD across three generations. Because multiple forms of SUD have familial links with both the mood and anxiety disorders (Clark et al., 2004; Diaz et al., 2008) and there has been little specificity in familial clustering of subtypes of EmD in young children (Merikangas and Low, 2005), this initial analysis focused on the effect of any type of SUD on any type of EmD. The data for this report were collected from the Oregon Adolescent Depression Project (OADP), a longitudinal study of mental disorders that followed a community cohort of adolescents into adulthood (G2) that was later expanded to include assessment of the cohort's parents (G1) and their children (G3). In a previous analysis of subsample of the OADP, Olino et al. (2008) found that neither G1 nor G2 SUD predicted internalizing symptoms among 162 G3 grandchildren when they were 24 months of age. However, one study suggests that offspring of parents with SUDs may not exhibit elevated internalizing symptoms until 36 months of age (Edwards et al., 2006). In addition, Olino et al.'s analysis did not clarify how the risk carried by G1 and G2 SUD status may either overlap or interact to influence vulnerability to EmD among G3 offspring.

The current report addressed these issues using an expanded sample of 284 families who participated in the OADP. G3 grandchildren were aged 2 to 10 years-old (mean age of 5 years old). Given the potential genetic and environmental factors that may play a role within families across three generations, we hypothesized that G1 SUD would be associated with increased risk of elevated levels of EmD symptoms in G3 and that this association would be transmitted via G2 SUD. Therefore, we examined the influence of G1 SUD on G3 EmD symptoms, relevant intermediate familial links between G1 SUD and G3 EmD (i.e., G1 SUD → G2 SUD; G1 SUD → G2 EmD; G2 SUD → G3 EmD), and mediational models that tested whether the effects of G1 SUD on G3 EmD symptom elevations were carried by G2 SUD. We also investigated whether G1 and G2 SUD interacted to predict G3 EmD symptoms. Because previous research demonstrating interactive effects of G1 and G2 diagnostic status on grandchild outcomes have been mixed in the depression literature (Olino et al., 2008; Pettit et al., 2008; Weissman et al., 2005), we did not make any a priori hypotheses regarding the interactive effects of G1 and G2 SUD status.

2. Methods

2.1. Sampling strategy

2.1.1. G2 parents

Original OADP probands, who will be referred to as "G2" in this report, were randomly selected from nine high schools in western Oregon to be representative of the region. A total of 1709 sixteen-year-old adolescents (91.1% Caucasian) completed an initial (T1) psychiatric assessment between 1987 and 1989. The T1 participation rate was 61%. Approximately one year later, 1507 (53.7% female; 91.8% Caucasian) returned for a second evaluation (T2). Differences between the sample and the larger population from which it was selected, and between participants and those who declined or dropped out before T2, were small (Lewinsohn et al., 1993). At age 24, all probands with a history of Axis I psychiatric disorders and a random sample of probands with no history of psychopathology by T2 ($n=457$) were invited to a third (T3) evaluation. Of the 1101 probands selected for a T3 interview, 941 (57.3% female; 90.4% Caucasian) completed the evaluation. T2 diagnostic groups did not differ on the rate of participation at T3. At age 30, all T3 probands were invited to a T4 evaluation. Of the 941 T3 probands, 816 (59.3% female; 89.2% Caucasian) completed the T4 diagnostic interview. Among those invited to T3 and T4 assessments, women were more likely than men to complete evaluations, $X^2>5.99$, $ps<.05$; participation did not differ as a function of other status variables or previous diagnoses.

2.1.2. G3 grandchildren

Probands with children were asked to complete the Child Behavior Checklist (CBCL: Achenbach, 1991, 1992) parent ratings on their biological children (G3) near the time of the T3 interview, annually for up to seven years, and then again at T4. Out of the total 816 probands with data available, at least one CBCL rating was completed for biological children of 337 (41.3%) probands, who ranged in age from 2 to 18 years old. No Axis I diagnostic status differed as a function of proband parental status.

2.1.3. G1 grandparents

We assessed lifetime psychopathology in both of the biological parents (G1) of probands near the time of the T3 evaluation. Of the 337 G2 probands with available child data, 294 (87.2%) also had available data on G1 diagnostic status. Cases with missing G1 data ($n=43$, 12.8%) did not significantly differ from other cases on any measured variable.

2.1.4. Reference sample for the present report

As indicated above, all three generations of diagnostic data were available for 294 G2 probands, their G3 children, and both of their G1 parents. Of these 294 families, two cases in which G3 CBCL ratings were collected prior to G2 SUD onset were eliminated because of difficulty discerning temporal precedence of disorder onset across generations. Examination of the distribution of G3 ages indicated a natural break in the data in which only 8 cases were aged 11 to 18 years old. Thus, to reduce heterogeneity due to puberty and adolescent developmental processes, these cases were eliminated. The final dataset included 284 families (see demographic data for each generation in Table 1).

After a description of the study, written informed consent was obtained from G1 and G2 participants, and they were remunerated for their participation. This research was approved by an Institutional Review Board.

2.2. Measures

2.2.1. G2 parents

At T1, G2 probands were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Orvaschel et al., 1982), which included additional items to derive *DSM-III-R* diagnoses. At following assessment waves, probands were interviewed using the Longitudinal Interval Follow-up Evaluation (Keller et al., 1987), which elicited detailed information about the onset and course of psychiatric disorders since the previous evaluation.

2.2.2. G3 grandchildren

CBCL ratings of G3 children were completed by G2 probands at up to eight assessment points. Only G3 children born at least two years prior to the first CBCL administration were eligible for all eight ratings; the majority of G3 children were born during the course of the CBCL administrations. On average, 1.91 CBCL ratings were completed for each child, with 121 grandchildren being rated only once, 72 receiving two ratings, 86 receiving three ratings, and 5 receiving four or more ratings. For G3 children with multiple CBCL ratings, the rating with the highest Internalizing Scale score was selected in order to increase statistical power and to make G3 diagnoses consistent with our lifetime diagnostic approach used with G2 and G3 (Pettit et al., 2008; Olino et al., 2008). As in our prior reports (Pettit et al., 2008; Olino et al., 2008), we included ratings only for firstborn children in families with 2 or more G3 children to reduce potential biases associated with birth order and to increase the mean age of G3. Mean age of G3 children at the time of the CBCL rating was 4.74 ($SD=2.43$) years (range: 2–10).

The CBCL 2–3 (for children aged 2–3 years: Achenbach, 1992) consists of 99 items and the CBCL 4–18 (for children aged 4–18 years: Achenbach, 1991) consists of 113 items. Items are rated on a 3-point scale, corresponding to whether the behavior is not true, somewhat/sometimes true, or very true/often true of the target child. The CBCL factor structure consists of eight narrow-band problem scales and two broadband scales, Internalizing Problems and Externalizing Problems.

2.2.3. G1 grandparents

G1 grandmother and grandfathers were directly interviewed once using a version of the nonpatient edition of the Structured Clinical Interview for *DSM-III-R* that had been modified for *DSM-IV* criteria (Spitzer et al., 1992). Interviewers were unaware of probands' diagnoses. To ensure that some diagnostic data were available even for the portion of G1 participants who were not personally interviewed and to supplement the direct interviews, family history data on G1 were collected using the Family Informant Schedule and Criteria (FISC: Manuzza and Fyer, 1990), supplemented with items to derive *DSM-IV* diagnoses. The FISC was administered to the G2 probands and at least one first-degree relative from each family. Best estimate *DSM-IV* diagnoses (Leckman, 1982) were derived for G1 participants using all available data by two senior diagnosticians. Statistical controls for direct vs. informant interview status had no meaningful impact on any analysis.

2.3. Diagnostic classifications for the present report

G1 EmD status was rated positive if at least one grandparent had a lifetime history of any mood or anxiety disorder. Similarly, G1 SUD status was rated positive if at least one grandparent had a lifetime history of any alcohol or drug abuse or dependence diagnosis, other than nicotine. As with previous reports (Pettit et al., 2008; Olino et al., 2008), we selected this approach rather than examining the effects of grandmother and grandfather diagnostic status separately to increase power to detect effects.[1] G2 SUD or EmD status was rated positive if the proband had a lifetime history of the respective class of disorder across data collected from all 4 assessments. Independent review of randomly-selected audiotapes revealed moderate-to-excellent interrater reliability for SUD, mood disorder, and anxiety disorder diagnoses of G1 and G2 (Kappas .69 to .85: Pettit et al., 2008). The lifetime prevalence of psychiatric disorders outside of the EmDs and SUDs (e.g., psychotic disorders, eating disorders) in this sample was very low. For G1, there were 3 cases of eating disorders, 1 psychotic disorder, and 12 cases of disruptive behavior disorders (i.e., conduct disorder, oppositional defiant disorder, and attention deficit/hyperactivity disorder). For G2, there were 5 cases of eating disorders, 0 psychotic disorders, and 11 disruptive behavior disorders. None of these disorders for G1 or G2 were significantly associated with G3 EmD and were therefore not included as covariates in analyses (see Data analysis section).

G3 participants were rated positive for EmD symptoms if they demonstrated a borderline or clinical elevation (T-score>60: Achenbach, 1992) on the Internalizing scale, which measures various symptoms of childhood emotional disturbance (Social Withdrawal, Somatic Complaints, and Anxiety/Depression). Children above this cutoff score in the top 16% of the normative sample (Achenbach, 1992). Using this cutoff is consistent with recommendations (Achenbach, 1992) and demonstrates good concordance with *DSM*-based diagnoses of current (Keenan et al., 1997) and future (Mesman and Koot, 2001) EmD.

2.4. Data analysis

The primary approach involved conducting logistic regression analysis to examine whether SUD status predicted EmD status across generations (G1 to G2 to G3). To examine each relevant link from G1 SUD to G3 EmD status, four sets of logistic regression models were tested: (1) G1 SUD predicting G3 EmD; (2) G2 SUD predicting G3 EmD; (3) G1 SUD predicting G2 EmD; and (4) G1 SUD predicting G2 SUD. For each set of models, Model A included only the primary predictor, Model B added any demographic variable that was associated with the primary predictor and the outcome variable as a covariate (i.e., G3 age at CBCL rating for analyses predicting G3 EmD; G2 gender for analyses predicting G2 SUD/EmD), and Model C added the older generation's EmD status as a covariate to examine whether any intergenerational effect of SUD was specific or explained by within-generation SUD-EmD comorbidity. The third set of models examining if G1 SUD predicted G2 EmD also included a Model D that added G2 SUD as a covariate. Similarly, the fourth set of models examining if G1 SUD predicted G2 SUD also included a Model D that added G2 EmD as a covariate. These additional models help to disentangle overlap between EmD and SUD at the G2 generation.

To examine whether the effect of G1 SUDs on G3 EmD symptoms was transmitted through effects on G2 SUD, we re-assessed the initial models to see if the conditions for mediation were met (i.e., G1 SUD → G3 EmD, G1 SUD → G2 SUD, G2 SUD → G3 EmD) and then examined the significance of the indirect effect by performing a PRODCLIN asymmetric confidence intervals test (Fritz and MacKinnon, 2007; MacKinnon et al., 2008). PRODCLIN provides a product-of-coefficient test that does not rely on normal theory. It is a variation of the Sobel test that accounts for a non-normal distribution of the product term through the construction of asymmetric confidence intervals. Prior research suggests that PRODCLIN provides a more statistically powerful test and results in more accurate Type I error rates than other commonly-used mediation tests (MacKinnon et al., 2008).

To evaluate the concurrent and interactive effects of G1 and G2 SUD on G3 EmD, we tested a fifth set of models in which G1 SUD and G2 SUD were entered as simultaneous predictors (Model A), G3 age was added (Model B), G1 and G2 EmD were added (Model C), and the G1 SUD × G2 SUD interaction was added (Model D).

Results are reported as odds ratios (*ORs*) with 95% confidence intervals (*CIs*). All tests were two-tailed and statistical significance was set at .05.

Table 1
Sociodemographic characteristics of each generation.

Variable	
G1 ($n=284$ dyads)	
Grandfathers ($n=284$)	
Age, *M* (SD)	50.69 (5.47)
Married, *n* (%)	199 of 227 (87.7%)[a]
Caucasian, *n* (%)	209 of 223 (93.7%)[a]
Grandmothers ($n=284$)	
Age, *M* (SD)	48.71 (4.37)
Married, *n* (%)	196 (69.0%)
Caucasian, *n* (%)	255 (89.8%)
G2 ($n=284$)	
Age, *M* (SD)	27.38 (2.72)
Female, *n* (%)	186 (65.5%)
Married, *n* (%)	195 (69.4%)
Caucasian, *n* (%)	250 (88.0%)
G3 ($n=284$)	
Age at highest CBCL internalizing score, *M* (SD)	4.74 (2.43)
Female, *n* (%)	143 (50.4%)

G1 = grandparental generation; G2 = parental generation; G3 = grandchild generation.
[a] Information on marital status and race was not provided for approximately 60 G1 grandfathers.

3. Results

3.1. Prevalence of SUD and EmD

Of the total 284 G2 probands in this report, 157 (55.2%) had at least one G1 parent with a lifetime history of SUD. Similarly, 156 (54.9%) had at least one G1 parent with lifetime EmD. Within G2, 114 (40.1%) and 187 (65.8%) probands were positive for lifetime SUD and EmD, respectively. In G3, 39 (13.7%) firstborn children of G2 probands were positive for EmD in their highest CBCL Internalizing score rating and were therefore coded positive for G3 EmD status.

3.2. Are there linkages between G1 SUD and G3 EmD symptom elevations?

Prevalence rates of EmD and SUD, by parental and grandparental SUD status are presented in Table 2. Results of logistic regression analyses are reported in Table 3.

3.2.1. G1 SUD predicting G3 EmD symptoms

Positive G1 SUD status significantly predicted increased risk of G3 EmD symptom elevations with and without adjusting for covariates (see prevalence rates in Table 2 and Model Set 1 in Table 3).

3.2.2. G2 SUD predicting G3 EmD symptoms

Positive G2 SUD significantly predicted increased risk of G3 EmD symptom elevations with and without adjusting for covariates (Table 3; Model Set 2).

[1] To explore the potential influence of having 1 vs. 2 grandparents with SUDs, we compared rates of G3 EmDs between offspring of these two groups. Results showed that 18% of G3 offspring with 1 grandparent with SUD were positive for EmD, and 10% of offspring with 2 grandparents with SUDs were positive for EmD. These rates were not significantly different. Thus, the primary analyses use a binary classification of G1 SUD status, with a positive rating indicating at least one grandparent had a lifetime SUD.

Table 2
Prevalence rates of EmD and SUD, by parental and grandparental SUD status.

	G1 SUD status[a]		G2 SUD status[b]	
	SUD- ($n=127$)	SUD + ($n=157$)	SUD- ($n=170$)	SUD + ($n=114$)
G3 EmD, *n* (%)	11 (8.7%)	28 (17.8%)	16 (9.4%)	23 (20.2%)
G2 EmD, *n* (%)	80 (63.0%)	107 (68.2%)		
G2 SUD, *n* (%)	40 (31.5%)	74 (47.1%)		

Total $N=284$. SUD = Substance Use Disorder; EmD = Emotional Disorder; G1 = grandparental generation; G2 = parental generation; G3 = grandchild generation.
[a] Rated positive (+) if at least one grandparent has a lifetime history of SUD, and rated negative (−) if neither grandparent has lifetime history of SUD.
[b] Rated positive if G2 proband has lifetime history of SUD.

3.2.3. G1 SUD predicting G2 EmD

Positive G1 SUD status did not significantly predict increased risk of G2 EmD (Table 3; Model Set 3).

3.2.4. G1 SUD predicting G2 SUD

Positive G1 SUD status significantly predicted increased risk of G2 SUD with and without adjusting for covariates (Table 3; Model Set 4).

3.3. Is the influence of G1 SUD on G3 EmD symptoms transmitted through effects on G2 SUD?

As indicated above, G1 SUD predicted G3 EmD symptoms. Furthermore, G1 SUD predicted G2 SUD and G2 SUD predicted G3 EmD symptoms. Therefore, the initial conditions of mediation were met. To test whether the influence of G1 SUD on G3 EmD symptoms was transmitted indirectly through effects on G2 SUD, a mediation analysis was conducted using the PRODCLIN asymmetric confidence intervals test. The PRODCLIN test indicated that the 95% confidence interval of the product term did not overlap with zero: lower limit = .0569, upper limit = 1.442. This result therefore indicates an indirect effect of G1 SUD on G3 EmD via G2 SUD.

In a combined model which included G1 SUD and G2 SUD as simultaneous predictors of G3 EmD symptoms, the effect of G1 SUD was reduced to a non-significant trend, and the effect of G2 SUD was significant (Table 3; Model Set 5, Model A). This pattern of results was consistent after adjusting for relevant covariates (Table 3; Model Set 5, Models B and C). Overall, these results indicate that the effects of G1 SUD on G3 EmD were partially (but not entirely) transmitted through G2 SUD. In addition, the remaining trend-level effects of G1 and significant effects of G2 SUD are indicative of non-overlapping, additive effects on G3 EmD to some degree.

3.4. Do G1 SUD and G2 SUD interact to predict G3 EmD symptoms?

In the model which included the G1 SUD × G2 SUD interaction term, the interaction was non-significant (Table 3; Model Set 5, Model D).

4. Discussion

This study found that grandchildren who had at least one grandparent with a history of SUD were at greater than two-fold increase in risk for elevated levels of EmD symptoms, indicating that the familial effects of SUD on EmD may span three generations. Results from mediational analyses indicated that this effect was partially transmitted via increased prevalence of G2 SUD. There was not an interactive effect between G1 SUD and G2 SUD on risk of G3 EmD symptoms.

These results add to previous data supporting familial transmission of behavioral problems across three generations (Bailey et al., 2006; Grillon et al., 2005; Hammen et al., 2004; Pettit et al., 2008; Olino et al., 2008; Warner et al., 2008, 1999; Weissman et al., 2005), and extend them to the SUD-EmD link. Previous work has found that G1 depression predicts G3 anxiety (Weissman et al., 2005; Warner et al., 1999), G1 depression predicts G3 internalizing symptoms (Pettit et al., 2008; Hammen et al., 2004), G1 depression predicts G3 externalizing symptoms and disruptive behavior disorders (Warner et al., 1999; Pettit et al., 2008), and G1 substance use predicts G3 externalizing behavior (Bailey et al., 2006). To our knowledge, this was the first study to find evidence that the familial influence of SUD on EmD symptoms spans three generations. This result is in contrast of Olino et al. (2008), which did not find an influence of G1 SUD on G3 EmD symptoms in 166 OADP families with G3 grandchildren assessed at 24 months of age. In the current study, the sample was expanded to 284 families and the average age at G3 assessment was 5 years (range 2–10 years). The discordant findings across these investigations could be due to: (a) the greater statistical power provided by the larger sample; or (b) the possibility that risk for EmD that is carried by grandparental SUD may not be manifested until later in childhood. Indeed, a recent longitudinal study found that increased risk of EmD symptoms due to parental SUD was not expressed when offspring were 18 and 24 months of age, but was present when offspring reached 36 months of age (Edwards et al., 2006). However, the question of whether tri-generational effects of SUD on EmD differ between children who are older versus younger than 36 months of age remains an empirical question that should be addressed in future work.

Results revealed several intermediate intergenerational links between G1 SUD and G3 EmD symptom elevations, including G1 SUD → G2 SUD and G2 SUD → G3 EmD. Each of these linkages remained significant when adjusting for comorbid EmD within the older generation and relevant demographic variables. This raised the possibility that the effects of G1 SUD on G3 EmD could be transmitted via G2 SUD. A test of this hypothesis using meditational modeling yielded a statistically significant result, which indicates that the influence of grandparental SUD on grandchild EmD was transmitted through parental SUD. This finding is consistent with a previous study demonstrating that the influence of G1 substance use on G3 externalizing behavior was partially transmitted via G2 substance use (Bailey et al., 2006).

Unexpectedly, there was no evidence of an intermediate link from G1 SUD to G2 EmD, suggesting that G2 EmD did not transmit the effects of G1 SUD on G3 EmD symptom elevations. Although the direction of the *OR* in the model predicting G2 EmD from G1 SUD indicated an increase in risk, this effect was not statistically significant. This finding is in contrast with previous reports documenting a two-generation familial effect of SUD on EmD (e.g., Clark et al., 2004) and the current finding that G2 SUD predicted G3 EmD symptom elevations. Although a similar pattern has been demonstrated previously (e.g., Baily et al. demonstrated that the effects of G1 substance use on G3 externalizing behavior were stronger than the corresponding effects of G1 substance use on G2 externalizing behavior), the meaning of this finding is currently unclear.

We found no evidence of an interaction between G1 SUD and G2 SUD in predicting G3 EmD symptoms. The lack of interaction along with evidence that G1 SUD and G2 SUD had significant (or near-significant) unique effects on G3 EmD symptoms in combined models suggests that the risk of child EmD may increase with the presence of SUD in prior generations in an additive manner. This is in contrast with previous reports of interactive intergenerational effects in the depression literature, such that having two (versus one) generations of familial loading for depression results in a non-additive, disproportionate change in risk of EmD (Olino et al., 2008; Pettit et al., 2008; Weissman et al., 2005).

This study had several limitations. We were unable to obtain diagnostic information on all G1 and G2 participants. We relied on a single index of EmD in G3 children–parent report on the CBCL Internalizing scale. This measure does not indicate an EmD diagnosis per se; rather, it assesses symptoms indicative of EmD, which should be considered when interpreting the present findings. Although statistical control of comorbid EmD in G2 analyses predicting G3 EmD potentially limited the degree to which mood state may have biased parental

Table 3
Results of logistic regression models.

Predictors	Model A	Model B	Model C	Model D
Model set 1 (outcome: G3 EmD)				
G1 SUD, *OR* (95% *CI*)	2.34 (1.05, 5.21)*	2.26 (1.00, 5.09)*	2.26 (1.00, 5.14)*	N/A
G3 age, *OR* (95% *CI*)	–	1.24 (1.07, 1.43)**	1.24 (1.07, 1.43)**	N/A
G1 EmD, *OR* (95% *CI*)	–	–	0.99 (0.47, 2.10)	N/A
Overall Model Statistics	$\chi^2 = 4.70^*$, $R^2 = 0.02$	$\Delta\chi^2 = 8.79^{**}$, $\Delta R^2 = 0.03$	$\Delta\chi^2 = 0.01$, $\Delta R^2 < 0.01$	N/A
Model set 2 (outcome: G3 EmD)				
G2 SUD, *OR* (95% *CI*)	2.43 (1.22, 4.84)*	2.36 (1.17, 4.73)*	2.03 (1.00, 4.15)*	N/A
G3 age, *OR* (95% *CI*)	–	1.19 (1.04, 1.36)*	1.18 (1.03, 1.36)*	N/A
G2 EmD, *OR* (95% *CI*)	–	–	2.22 (0.92, 5.38)	N/A
Overall Model Statistics	$\chi^2 = 6.53^*$, $R^2 = 0.02$	$\Delta\chi^2 = 6.00^*$, $\Delta R^2 = 0.02$	$\Delta\chi^2 = 3.48^{\dagger}$, $\Delta R^2 = 0.01$	N/A
Model set 3 (outcome: G2 EmD)				
G1 SUD, *OR* (95% *CI*)	1.26 (0.77, 2.06)	1.34 (0.80, 2.25)	1.25 (0.74, 2.12)	1.07 (0.62, 1.85)
G2 gender, *OR* (95% *CI*)	–	0.26 (0.15, 0.44)***	0.26 (0.15, 0.43)***	0.18 (0.10, 0.33)***
G1 EmD, *OR* (95% *CI*)	–	–	1.83 (1.08, 3.10)*	1.84 (1.07, 3.17)*
G2 SUD, *OR* (95% *CI*)	–	–	–	3.68 (1.98, 6.83)***
Overall Model Statistics	$\chi^2 = 0.83$, $R^2 < 0.01$	$\Delta\chi^2 = 26.36^{***}$, $\Delta R^2 = 0.09$	$\Delta\chi^2 = 5.18^*$, $\Delta R^2 = 0.02$	$\Delta\chi^2 = 19.13^{***}$, $\Delta R^2 = .07$
Model set 4 (outcome: G2 SUD)				
G1 SUD, *OR* (95% *CI*)	1.94 (1.19, 3.16)**	1.94 (1.18, 3.18)**	1.92 (1.17, 3.16)**	1.92 (1.15, 3.22)*
G2 gender, *OR* (95% *CI*)	–	1.98 (1.20, 3.29)**	1.99 (1.20, 3.29)**	3.19 (1.78, 5.74)***
G1 EmD, *OR* (95% *CI*)	–	–	1.08 (0.66, 1.77)	0.93 (0.55, 1.55)
G2 EmD, *OR* (95% *CI*)	–	–	–	3.78 (2.02, 7.06)***
Overall Model Statistics	$\chi^2 = 7.22^{**}$, $R^2 = 0.03$	$\Delta\chi^2 = 7.11^{**}$, $\Delta R^2 = 0.03$	$\Delta\chi^2 = 0.09$, $\Delta R^2 < 0.01$	$\Delta\chi^2 = 19.60^{***}$, $\Delta R^2 = .07$
Model set 5 (outcome: G3 EmD)				
G1 SUD, *OR* (95% *CI*)	2.05 (0.91, 4.64)†	2.00 (0.89, 4.57)†	2.02 (0.87, 4.72)†	2.20 (0.64, 7.60)
G2 SUD, *OR* (95% *CI*)	2.45 (1.16, 5.18)*	2.43 (1.13, 5.20)*	2.16 (1.00, 4.72)*	2.43 (0.59, 10.01)
G3 age, *OR* (95% *CI*)	–	1.24 (1.07, 1.43)**	1.24 (1.07, 1.43)**	1.23 (1.07, 1.43)**
G1 EmD, *OR* (95% *CI*)	–	–	0.88 (0.41, 1.91)	0.88 (0.41, 1.92)
G2 EmD, *OR* (95% *CI*)	–	–	1.79 (0.71, 4.53)	1.78 (0.70, 4.51)
G1 SUD × G2 SUD, *OR* (95% *CI*)	–	–	–	0.85 (0.16, 4.52)
Overall Model Statistics	$\chi^2 = 10.38^{**}$, $R^2 = 0.02$	$\Delta\chi^2 = 8.40^{**}$, $\Delta R^2 = 0.03$	$\Delta\chi^2 = 1.62$, $\Delta R^2 < 0.01$	$\Delta\chi^2 = 0.04$, $\Delta R^2 < 0.01$

Total $N = 284$. Dash indicates that predictor was not included in model. N/A = not applicable. SUD = substance use disorder; EmD = emotional disorder; G1 = grandparental generation; G2 = parental generation; G3 = grandchild generation.

† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

ratings of children adjustment, future analyses should extend these findings to non-parental informants and other assessment methods (Grillon et al., 2005). Because only a portion G2 participants with no history of psychopathology at T2 were invited to be reassessed as part of the T3 evaluation, a larger than normal proportion of G2 probands had psychopathology, which may have increased the rates of psychopathology in G1 and G3 generations. As a result, this sample may not be representative of the general population. Different tools were used to assess EmD and SUDs for G1, G2, and G3, which complicates comparisons across generations. Information on the timing, onset, and course of disorders was not considered due to the paucity of multi-time point data; thus, future multi-generational research examining the course of disorder progression should be a priority. Because we utilized the highest internalizing problems score to identify cases indicative of EmD, potential biases could be introduced as participants with more G3 assessments have more opportunities to score above the Internalizing Problems cutoff. However, there were no significant differences in the prevalence of G1 or G2 EmD or SUDs between families with different numbers of G3 CBCL ratings available (all χ^2s < 3.97 and *p*s = ns). The age range of G3 was limited ($M = 5$ years, rage 2–10), thus G3 offspring are yet to pass through their peak risk period for EmD onset. The study provides heritability information on only 50% of the G2 parents and G1 grandparents who transfer genetic material to the G3 children, which poses difficulty interpreting the mechanisms underlying intergenerational transmission in the current study, as assortive or biased mating at G1 and G2 could be contributing the heritability of EmD at G3. Finally, because of the limited sample size, there was insufficient power to examine whether risk differed depending on the gender of grandchildren. Given that familial effects of SUDs can differ according to gender (Puttler et al., 1998), this should be addressed in future work.

In sum, the present study found that grandparental SUD was associated with increased risk of grandchild EmD symptoms, and that this effect was in part transmitted through parental SUD. These findings highlight the importance of obtaining extended family pedigrees in both parental and grandparental generations to identify high risk children who may benefit most from preventive interventions. They also suggest that grandchildren of individuals with SUDs may be included in high-risk research designs evaluating individuals with a familial liability to EmD. Future research should explore the genetic mechanisms by which grandparental SUD may exert risk of offspring EmD across several generations. In addition, studies that examine environmental factors (e.g., parenting behavior) that transmit risk are needed to inform preventive interventions which might buffer the familial effects of substance misuse on offspring emotional disturbance from generation-to-generation.

Acknowledgements

This research was supported by NIH awards MH40501, MH50522, and MH52858 to Peter M. Lewinsohn, MH75744 to Jeremy W. Pettit, and DA02041 to Adam M. Leventhal. The authors report no competing interests.

References

Achenbach, T.M., 1991. Child Behavior Checklist: 4–18 Years (CBCL/4–18). University of Vermont Department of Psychiatry, Bulrington.
Achenbach, T.M., 1992. Manual for the Child Behavior Checklist/2–3 and 1992 Profile. University of Vermont Department of Psychiatry, Burlington.

Bailey, J.A., Hill, K.G., Oesterle, S., Hawkins, J.D., 2006. Linking substance use and problem behavior across three generations. Journal of Abnormal Child Psychology 34 (3), 273–292.
Caraveo-Anduaga, J.J., Nicolini-Sanchez, H., Villa-Romero, A., Wagner, F.A., 2005. Psychopathology across three family generations: an epidemiological study in Mexico City. Salud Pública de México 47 (1), 23–29.
Chassin, L., Pitts, S.C., DeLucia, C., Todd, M., 1999. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. Journal of Abnormal Psychology 108 (1), 106–119.
Clark, D.B., Moss, H.B., Kirisci, L., Mezzich, A.C., Miles, R., Ott, P., 1997. Psychopathology in preadolescent sons of fathers with substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry 36 (4), 495–502.
Clark, D.B., Cornelius, J., Wood, D.S., Vanyukov, M., 2004. Psychopathology risk transmission in children of parents with substance use disorders. The American Journal of Psychiatry 161 (4), 685–691.
Diaz, R., Gual, A., Garcia, M., Arnau, J., Pascual, F., Canuelo, B., et al., 2008. Children of alcoholics in Spain: from risk to pathology. Results from the ALFIL program. Social Psychiatry and Psychiatric Epidemiology 43 (1), 1–10.
Edwards, E.P., Eiden, R.D., Leonard, K.E., 2006. Behaviour problems in 18- to 36-month old children of alcoholic fathers: secure mother-infant attachment as a protective factor. Developmental Psychopathology 18 (2), 395–407.
Fritz, M.S., MacKinnon, D.P., 2007. Required sample size to detect the mediated effect. Psychological Science 18 (3), 233–239.
Grillon, C., Warner, V., Hille, J., Merikangas, K.R., Bruder, G.E., Tenke, C.E., et al., 2005. Families at high and low risk for depression: a three-generation startle study. Biological Psychiatry 57 (9), 953–960.
Hammen, C., Shih, J.H., Brennan, P.A., 2004. Intergenerational transmission of depression: test of an interpersonal stress model in a community sample. Journal of Consulting and Clinical Psychology 72 (3), 511–522.
Harter, S.L., 2000. Psychosocial adjustment of adult children of alcoholics: a review of the recent empirical literature. Clinical Psychology Review 20 (3), 311–337.
Keenan, K., Shaw, D.S., Walsh, B., Delliquadri, E., Giovannelli, J., 1997. DSM-III-R disorders in preschool children from low-income families. Journal of the American Academy of Child and Adolescent Psychiatry 36 (5), 620–627.
Keller, M.B., Lavori, P.W., Friedman, B., Nielsen, E., 1987. The longitudinal interval follow-up evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Archives of General Psychiatry 44 (6), 540–548.
Kendler, K.S., Heath, A.C., Neale, M.C., Kessler, R.C., Eaves, L.J., 1993. Alcoholism and major depression in women. A twin study of the causes of comorbidity. Archives of General Psychiatry 50 (9), 690–698.
Leckman, J.F., 1982. Best estimate of lifetime psychiatric diagnosis: a methodological study. Archives of General Psychiatry 39 (8), 879–883.
Lewinsohn, P.M., Hops, H., Roberts, R.E., Seeley, J.R., Andrews, J.A., 1993. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III–R disorders in high school students. Journal of Abnormal Psychology 102 (1), 133–144.
MacKinnon, D.P., Fritz, M.S., Williams, J., Lockwood, C.M., 2008. Distribution of the product coefficient limits for the indirect effect: Program PRODCLIN. Behavior Research Methods 39, 384–389.
Manuzza, S., Fyer, A., 1990. Family informant schedule and criteria (FISC), July 1990 revision. Anxiety Disorders Clinic, New York State Psychiatric Institute, New York.
Merikangas, K.R., Low, N.C., 2005. Genetic epidemiology of anxiety disorders. Handbook of Experimental Pharmacology 169, 163–179.
Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton, B., et al., 1998. Familial transmission of substance use disorders. Archives of General Psychiatry 55 (11), 973–979.
Mesman, J., Koot, H.M., 2001. Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. Journal of the American Academy of Child and Adolescent Psychiatry 40 (9), 1029–1036.
Olino, T.M., Pettit, J.W., Klein, D.N., Allen, N.B., Seeley, J.R., Lewinsohn, P.M., 2008. Influence of parental and grandparental major depressive disorder on behavior problems in early childhood: a three-generation study. Journal of the American Academy of Child and Adolescent Psychiatry 47 (1), 53–60.
Orvaschel, H., Puig-Antich, J., Chambers, W.J., Tabrizi, M.A., Johnson, R., 1982. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-E. Journal of the American Academy of Child and Adolescent Psychiatry 21, 392–397.
Pettit, J.W., Olino, T.M., Roberts, R.E., Seeley, J.R., Lewinsohn, P.M., 2008. Intergenerational trasmission of internalizing problems: effect of parental and grandparental major depressive disorder on child behavior. Journal of Clinical Child and Adolescent Psychology 37 (3), 640–650.
Prescott, C.A., Aggen, S.H., Kendler, K.S., 2000. Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of US twins. Archives of General Psychiatry 57 (8), 803–811.
Preuss, U.W., Schuckit, M.A., Smith, T.L., Barnow, S., Danko, G.P., 2002. Mood and anxiety symptoms among 140 children from alcoholic and control families. Drug and Alcohol Dependence 67 (3), 235–242.
Puttler, L.I., Zucker, R.A., Fitzgerald, H.E., Bingham, C.R., 1998. Behavioral outcomes among children of alcoholics during the early and middle childhood years: familial subtype variations. Alcoholism, Clinical and Experimental Research 22 (9), 1962–1972.
Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B., 1992. The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. Archives of General Psychiatry 49 (8), 624–629.
Tambs, K., Harris, J.R., Magnus, P., 1997. Genetic and environmental contributions to the correlation between alcohol consumption and symptoms of anxiety and depression. Results from a bivariate analysis of Norwegian twin data. Behavior Genetics 27 (3), 241–250.
Warner, V., Weissman, M.M., Mufson, L., Wickramaratne, P.J., 1999. Grandparents, parents, and grandchildren at high risk for depression: a three-generation study. Journal of the American Academy of Child and Adolescent Psychiatry 38 (3), 289–296.
Warner, V., Wickramaratne, P., Weissman, M.M., 2008. The role of fear and anxiety in the familial risk for major depression: a three-generation study. Psychological Medicine 38 (11), 1543–1556.
Weissman, M.M., Wolk, S., Goldstein, R.B., Moreau, D., Adams, P., Greenwald, S., et al., 1999a. Depressed adolescents grown up. JAMA 281 (18), 1707–1713.
Weissman, M.M., Wolk, S., Wickramaratne, P., Goldstein, R.B., Adams, P., Greenwald, S., et al., 1999b. Children with prepubertal-onset major depressive disorder and anxiety grown up. Archives of General Psychiatry 56 (9), 794–801.
Weissman, M.M., Wickramaratne, P., Nomura, Y., Warner, V., Verdeli, H., Pilowsky, D.J., et al., 2005. Families at high and low risk for depression: a 3-generation study. Archives of General Psychiatry 62 (1), 29–36.
Westermeyer, J., Yoon, G., Thuras, P., 2006. Psychiatric morbidity and parental substance use disorder. The American Journal of Drug and Alcohol Abuse 32 (4), 607–616.