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

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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).

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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).