Childhood trauma and genetic factors in familial schizophrenia associated with the *NOS1AP* gene

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Abstract

There is some evidence that childhood adversity may be associated with the expression of schizophrenia but whether genetic risk affects this finding is unknown. We investigated the history of early trauma in 194 subjects from 24 multiply affected families where schizophrenia was previously shown to be associated with a functional allele in the *NOS1AP* gene. In subjects with schizophrenia (n=79), only events prior to the onset of psychosis were considered. Generalized estimating equation models that adjusted for familial clustering were used to estimate odds ratios (ORs) and 95% confidence intervals (CI). Subjects with narrowly defined schizophrenia were more likely than their unaffected family members to have a history of early trauma (adjusted OR=4.17, 95% CI=1.52, 11.44). The results were similar after adjusting for the *NOS1AP* risk genotype (adjusted OR=3.57, 95% CI=1.32, 9.65) and for maternal or paternal history of schizophrenia (adjusted ORs=3.27, 95% CI=1.45, 7.38; 4.38, 95% CI=1.61, 11.91, respectively). The results suggest that childhood trauma is associated with expression of schizophrenia independent of measured genetic susceptibility and may be a candidate for gene-environment research using genetic variants.

Keywords

Familial schizophrenia; Childhood adversity; Early trauma; Risk factor; Genetic predisposition

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Contributors

None.

Conflict of Interest

None of the authors have financial interests that might present a conflict of interest.

1. Introduction

Susceptibility to schizophrenia is believed to be due to multiple genetic and interacting non-genetic factors (Bassett et al., 2008; McGuffin et al., 1994). The search for non-genetic factors has focused on the period from conception through childhood and adolescence before onset of psychosis (Cannon et al., 2003). Longstanding theories related to heightened sensitivity to stress among individuals with schizophrenia have driven this research (Collip et al., 2008; Read et al., 2005). Several studies have identified severe early trauma such as abuse or neglect as a potentially relevant environmental exposure. However, the evidence to date is limited and inconclusive (Morgan and Fisher, 2007; Read et al., 2005; van Os et al., 2008; van Zelst 2008). These epidemiologic studies have the advantage of large numbers but the disadvantage of significant heterogeneity. Only one (Janssen et al., 2004) has examined the genetic context of childhood traumatic events.

A familial sample may facilitate the study of non-shared environmental factors in siblings, especially factors that are independent of genetic susceptibility (Reiss et al., 1991). Samples with enhanced genetic homogeneity show increased power to detect effects of non-genetic factors (AbdelMalik et al., 2003). Following up on highly significant linkage of schizophrenia to a region on chromosome 1q22-q23 in a set of Canadian families with familial schizophrenia (Bassett et al., 1994; Brzustowicz et al., 2004), we have identified the A allele of the single nucleotide polymorphism (SNP) rs12742393 within the nitric oxide synthase 1 [neuronal] adaptor protein gene (*NOS1AP*) to be a risk allele associated with schizophrenia in this and an independent sample (Wratten et al., 2009). Two SNPs in strong marker to marker linkage disequilibrium with rs12742393 have shown significant association in schizophrenia in another independent sample (Kremeyer et al., 2009).

Lifetime phenotypic data on these families and the *NOS1AP* data available provided an opportunity to investigate a non-genetic factor in conjunction with both a specific genotype and the general effects of other genetic predisposition.

We hypothesized that early trauma would be associated with the development of schizophrenia in this familial sample of enhanced genetic homogeneity. We predicted that individuals with schizophrenia would have a higher occurrence of childhood or adolescent trauma than their family members without schizophrenia. We also predicted that the effect of early trauma on schizophrenia would be independent of the measured genetic effects (AbdelMalik et al., 2003).

2. Methods

2.1. Sample and diagnostic assessment

Subjects were adults from 24 multigenerational Canadian families of Celtic (n=23) or German (n=1) descent, ascertained for an ongoing study of familial schizophrenia. The ascertainment and assessment procedures of the sample have been described elsewhere (Bassett et al., 1994; Brzustowicz et al., 2000; Wratten et al., 2009). Briefly, pedigrees were recruited for study because schizophrenia appeared to be segregating in a unilineal (one side of the family) dominant-like manner, and were selected if they had a proband and at least

one other relative with schizophrenia or with schizoaffective disorder, and if multiple affected and unaffected members were willing to participate. All participants were directly interviewed by a psychiatrist (ASB or EWC) using the Structured Clinical Interview for DSM-III-R (SCID-I), modified to obtain information on life history (including childhood and adolescence environmental exposures) and medical issues (AbdelMalik et al., 2003; Bassett et al., 1994). Collateral information, including extensive family history and medical records was also collected. After a review of all available information, lifetime DSM-III-R lifetime diagnoses were assigned (Bassett et al., 1994; Brzustowicz et al., 2000). Age at onset of psychosis in schizophrenia was determined from SCID-I and collateral information (Bassett et al., 2004). All phenotypic data were collected blind to genotypic data (see (Wratten et al., 2009) for details on DNA extraction and genotyping).

Genotypic and detailed lifetime phenotypic and interview data were available for 202 subjects (all members of a sibline with at least one affected sibling) from 24 multigenerational families. Eighteen subjects with missing or insufficient information on life history, including childhood environment and trauma, were excluded. The final sample of 184 subjects comprised 79 individuals with narrowly defined schizophrenia (DSM-III-R schizophrenia or chronic schizoaffective disorder), 98 subjects with broadly defined schizophrenia, comprising narrowly defined schizophrenia (n=79) and those with schizophrenia-spectrum disorders (i.e., non-affective psychotic disorders, or schizotypal or paranoid personality disorders) (n=19), and 86 unaffected subjects who did not meet narrow or broad criteria for schizophrenia and had no affective psychotic disorder (Brzustowicz et al., 2000). Written informed consent was obtained after complete description of the study to the subjects.

Protocols were approved by the institutional review boards of the University of Toronto, Rutgers University, University of Waterloo and the Centre for Addiction and Mental Health.

2.2. Assessment of early trauma

Consistent with others (Fisher et al., in press-b; Morgan and Fisher 2007; Schilling et al., 2008; Shevlin et al., 2007; Spauwen et al., 2006), childhood trauma was defined as a threat to physical, emotional and sexual integrity, a victim of serious injury or illness or a witness of violence. The primary data source for childhood trauma was the in-depth SCID-I interview. The modified SCID-I included a section on personal history, inquiring about childhood and adolescent home environment and adversity. Additional data sources included medical, social services and legal records, as well as collateral information provided by other family members. There was also SCID-I data from other family members. A major advantage of using multiple sources of information was the minimization of information bias (Morgan and Fisher, 2007). Using all sources of information trained research assistants coded the presence or absence of the following eight severe childhood adversities was coded for each subject: physical abuse (physically assaulted), neglect, sexual abuse, verbal abuse (verbally assaulted), victim of life-threatening accident, witness of violence/serious assault or accident, victim of disaster (e.g., flood, fire) and victim of physical assault (e.g., threatened with weapon or held captive) that excluded family violence. Information on age at occurrence and frequency was also coded. Although precise ages were unavailable for

several subjects, data were sufficient to determine whether events occurred in childhood or adolescence (19 years) and/or before age at onset of psychosis. We then derived a binary early trauma variable, where 0=no traumatic events at or younger than 19 years and 1=one or more traumatic events at or younger than 19 years. Only early trauma before onset of psychosis was considered for subjects with schizophrenia. Several studies have shown that retrospective reports of early trauma are reliable even when respondents with a history of psychosis were included (Briere and Zaidi 1989; Dill et al., 1991; Fisher et al., in press-a; Goodman et al., 1999; Meyer et al., 1996; Moffitt et al., 2005; Read et al., 2005; Shevlin et al., 2008).

2.3. Genetic factors

Individuals homozygous or heterozygous for the A allele of rs12742393 were coded as having the NOS1AP schizophrenia risk genotype and those homozygous for the C allele of rs12742393 were coded as not having the NOS1AP risk genotype (Wratten et al., 2009). To reflect additional non-specific genetic influences, maternal or paternal history of broadly defined schizophrenia was also considered. These parental diagnoses were determined using the same methods described above for siblings, including SCID-I, extensive family history and medical records where available.

2.4. Other potentially relevant variables

Others have identified cannabis use, urbanicity, and immigrant status as exposures that may be associated with schizophrenia or psychoses (van Os et al., 2008). The majority of the sample grew up in a rural environment and no subjects were recent immigrants, therefore urbanicity and immigrant status were not considered. However, there were two subjects with weekly and six with daily marijuana use before age 19 years in the unaffected group and one with weekly and seven with daily use prior to onset of psychosis in the narrow schizophrenia group. We previously reported a significant relationship between history of childhood (<11 years) head injury and narrow schizophrenia (AbdelMalik et al., 2003). We adjusted for cannabis use and for childhood head injury in secondary analyses. While all sibilines within the 24 families had at least one member with narrow schizophrenia, there was within-sibline variability in the number of affected and unaffected subjects. We therefore included number of siblings, in addition to age as continuous covariates, and gender and educational level achieved (high school and above or not) as categorical covariates, in all analyses.

2.5. Statistical analyses

The data from this familial schizophrenia sample represent “clusters” (families) of individuals affected with schizophrenia and therefore cannot be treated as independent for hypothesis testing. To adjust for this clustering, we used Generalized Estimating Equations (GEE) (Liang and Zeger 1986; Zeger and Liang 1986) as implemented in SAS Proc Genmod (SAS Institute Inc. 2003). In GEE, the standard errors of the regression coefficients are estimated in a way that accounts for correlated observations within families.

The main analyses compared subjects with narrow schizophrenia (n=79) to the unaffected group (n=86). Since the outcome variable was presence or absence of schizophrenia, we assumed a binomial distribution and used the logit link function for GEE analysis. Odds

ratios (OR) and 95% CI were used to assess the association between early trauma, genetic risk and expression of schizophrenia. Missing data were excluded from the analysis and assumed to be missing at random (Rubin 1976). All analyses were performed using the SAS 9.01 software (SAS Institute Inc. 2003).

3. Results

3.1. Sociodemographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics for the sample. The mean and median age at onset in the narrow schizophrenia group were 23.7 years (SD=8.6) and 22 years, respectively. Overall, the sample was through the peak period of risk of schizophrenia. In the unaffected group, only 22 (25.6%) subjects (n=8 males) in the unaffected group were younger than age 40 years and none were younger than age 22 years. As expected, a higher proportion of subjects in the schizophrenia groups carried the *NOS1AP* risk genotype than in the unaffected group. The gender distribution was similar (approximately 49% men and 51% women) in subjects with and without the *NOS1AP* risk genotype.

3.2. Early trauma characteristics

In the entire sample, 25 (13.6%) subjects (15 female, 10 male) had a reported history of early trauma, with a higher prevalence in subjects with narrow and broad schizophrenia compared with unaffected subjects (see Table 1). There were in total 53 traumatic events, with 56% of the subjects reporting two or more events. The most common were physical abuse (n=13), verbal abuse (n=12) and neglect (n=11). Of the remaining events, 8 pertained to threats to sexual integrity and 8 involved being a witness to violence. Approximately 23% of the events, primarily physical violence, were substantiated by medical records and/or family members.

3.3. Early trauma, genetic risk and expression of schizophrenia

Table 2 shows the univariate and multivariate relationships between history of early trauma, *NOS1AP* risk genotype and narrow schizophrenia. The unadjusted odds of experiencing an early traumatic event in the narrow schizophrenia group were significantly greater than those in the unaffected group. The association between schizophrenia and early trauma strengthened after adjusting for age, gender, educational level and number of siblings (OR=4.17, 95% CI=1.52, 11.44) and remained after adjustment for the potential confounding influence of the *NOS1AP* risk genotype (OR=3.57, 95% CI=1.32, 9.65). To assess whether the association between early trauma and schizophrenia was influenced by one family with eight traumatic events, we repeated the analyses excluding this family. The significant association remained after adjusting for the covariates and the *NOS1AP* risk genotype (OR=2.98, 95% CI=1.01, 8.84).

Further, the significant relationship between *NOS1AP* risk genotype and expression of narrowly defined schizophrenia was essentially unchanged after adjusting for early trauma and other covariates (Table 2). This result reflected the lack of an association between the *NOS1AP* risk genotype and history of early trauma ($\chi^2_1=0.86$; $p=0.357$).

There was no significant interaction between early trauma and gender ($\chi^2_1=0.11$; $p=0.74$). Further, the association between trauma and schizophrenia held after adjusting for covariates including early cannabis use and childhood head injury (OR= 4.43 95% CI = 1.65, 11.94). There was no observed association between age at onset of psychosis and early trauma. Repeating all analyses using broadly defined schizophrenia showed that the observed associations remained statistically significant but decreased in magnitude (data not shown).

The relationship between early trauma and narrow schizophrenia also remained significant after adjusting for paternal or maternal history of schizophrenia (OR=4.38, 95% CI=1.61, 11.91 and OR=3.27, 95% CI=1.45, 7.38, respectively). There were no statistically significant associations between expression of narrowly defined schizophrenia in the siblings studied and presence of schizophrenia in the subject's mother or father, therefore no further analyses using these factors were necessary. Similar results were observed for broadly defined schizophrenia.

4. Discussion

The current study investigated whether early trauma (i.e., a threat to physical, emotional or sexual integrity age 19 years) plays a role in the expression of schizophrenia in families demonstrating genetic predisposition to schizophrenia involving the *NOS1AP* gene (Brzustowicz et al., 2004; Wratten et al., 2009). As hypothesized, we found that early trauma was significantly associated with the expression of schizophrenia in this familial sample. The results suggested that the observed association was not due to genetic confounding by the *NOS1AP* risk genotype (or parental history of schizophrenia). In addition, there was no evidence to suggest that the *NOS1AP* risk genotype (or parental history of schizophrenia) increased the probability of exposure to early trauma. These findings offer some preliminary support for the proposition that early life trauma may be a non-genetic (environmental) factor, associated with expression of psychotic illness in individuals with genetic vulnerability to psychosis (Spauwen et al., 2006). Interestingly, early trauma was unrelated to age at onset of psychosis in this sample.

Our study findings are consistent with six large population-based studies (Bebbington et al., 2004; Fisher et al., in press-b; Janssen et al., 2004; Shevlin et al., 2007; Spauwen et al., 2006; Whitfield et al., 2005). The two longitudinal studies (Janssen et al., 2004; Spauwen et al., 2006) found that subjects who experienced trauma during early or mid-adolescence had a significantly increased risk for developing psychoses, even when adjusting for family history of psychosis (Janssen et al., 2004). One case-control study (Fisher et al., in press-b) reported that severe physical abuse from the mother that started before age 12 years was significantly associated with psychosis (adjusted OR=3.60) while paternal maltreatment and other types of adversity were unrelated to psychosis. The remaining studies (Bebbington et al., 2004; Shevlin et al., 2007; Whitfield et al., 2005) were cross-sectional and also reported significant associations between childhood physical, emotional and sexual abuse and lifetime prevalence of psychosis or hallucinations (adjusted ORs ranged from 1.7 to 2.9). The similarity of these results to ours, despite major differences in study design, argues for a generalized relationship between childhood trauma and expression of psychotic symptoms and major psychotic illness.

The main advantages of the present study relate to the familial sample used and genetic data unavailable to previous studies. Lifetime phenotypic data on these families, detailed family history and recent identification in these families of a risk allele of *NOS1AP* provided an opportunity to investigate a non-genetic factor in conjunction with both a specific genotype and general genetic factors. The methods facilitated the study of non-shared environmental factors in families, especially factors that are independent of measured genetic susceptibility (Moffitt et al., 2005). Further, the sample characteristics controlled for other environmental factors such as urbanicity and minority status with the results indicating that the association between trauma and schizophrenia was not significantly influenced by either early cannabis use or mild childhood head injury. A further advantage, in contrast to the majority of the literature in this area which has investigated the link between trauma and psychoses in general, was that the outcome investigated was well-defined schizophrenia. The comparability of the results to those of large population-based samples supports the enhanced power of more genetically homogenous samples to study non-genetic factors (AbdelMalik et al., 2003).

There are several limitations to this study. As with all retrospective studies in this area, the reliability of the history of early trauma is uncertain. Mitigating recall and information bias, the initial data gathering was performed blind to both the specific hypotheses of this study and to the genotypic data, and by including all available medical and collateral information. Nevertheless, we may have underestimated the prevalence of childhood trauma. We note however that in this familial sample approximately 14% of the subjects were reported to have a traumatic event prior to age 19 years, similar to the proportion found by Janssen et al. (Janssen et al., 2004) in their population-based study of childhood abuse prior to age 16 years and that in a Canadian population-based survey, where about 15% of respondents age 25–44 years reported a history of severe physical or sexual abuse (MacMillan et al., 1997). As in other studies, we also cannot rule out the possibility that early trauma may be more likely to be reported for affected than unaffected individuals. We attempted to minimize this potential source of recall bias by using multiple sources of information and assuring confidentiality (Morgan and Fisher, 2007). Others noting this limitation have argued that there is evidence suggesting that psychiatric patients may be more likely to under-report rather than over-report abuse (Fisher et al., in press-a; Janssen et al., 2004). Due to the small number of severe traumatic events, we were unable to assess the differential effects of trauma type, single versus multiple events, and specific timing of early trauma, which may be important factors in studying childhood adversity (Fisher et al., in press-b). Another limitation is that our assessment of early trauma is not exhaustive and it is difficult to predict how this may have influenced the estimated association between early trauma and narrow schizophrenia. Finally, despite the similarity of our results to other studies, the observed impact of early trauma on expression of familial schizophrenia may reflect the particular genetic factors present in our sample that may differ from those of other samples.

Several mechanisms by which early trauma could play a role in the expression of schizophrenia have been suggested. One mechanism involves gene-environment interactions. It has been proposed that there may synergistic effects of genes and early trauma on dopamine transmission that lead to lasting changes in the responsiveness of dopamine neurons in the mesocorticolimbic system, inducing sensitization of dopamine systems to

later life stressors (Collip et al., 2008; Read et al., 2005). Animal models suggest the glutamate system is also involved. Adverse events may also lead to synapse regression and loss of synaptic spines, a process thought to be mediated by glucocorticoids and the glutamate neurotransmitter system through post-synaptic NMDA receptors (Bennett, 2008). Given the role of *NOS1AP* in mediating NMDA receptor associated signaling (Brzustowicz et al., 2004) and the increased likelihood that glutamatergic abnormalities and synaptic connectivity are involved in the pathophysiology of schizophrenia, this is an attractive hypothesis for the current study (Arnold et al., 2005). Due to the small number of trauma events, this study could not test for interaction between the *NOS1AP* risk genotype and early trauma. Other studies, however, have reported significant gene-environment interactions influencing schizophrenia risk (Caspi et al., 2005; Nicodemus et al., 2008).

Another plausible mechanism is that genes influence the probability of exposure to environmental risk factors (i.e., gene-environment association) (van Os et al., 2008). Accordingly, early trauma could act as a marker of genetic predisposition. Studies of children at high risk for schizophrenia have shown that a subgroup of these children exhibit attentional dysfunctions, emotional instability, neuromotor disturbances, social withdrawal and/or conduct disorder (Done et al., 1994; Watt et al., 1984). This subgroup of genetically vulnerable children may be more likely recipients of early trauma than high risk children without such features. We, however, found no evidence that the *NOS1AP* risk genotype (or parental history of schizophrenia) was associated with probability of exposure to early trauma.

In summary, the results indicate that early trauma is associated with expression of schizophrenia, independent of measured genetic risk, and therefore may be a candidate for gene-environment research using specific genetic variants, especially those related to individuals' sensitivity to stress. Future studies should ensure the use of precise and sensitive measures of childhood and adolescent trauma.

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Table 1

Characteristics of the familial sample of affected and unaffected siblings (n=184).

Variable	Narrowly defined schizophrenia (n=79)		Broadly defined schizophrenia ^a (n=98)		Unaffected (n=86)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age in years	51.8	(14.1)	51.9	(14.1)	49.6	(11.8)
Number of siblings ^b	6.5	(4.6)	6.8	(4.5)	8.6	(3.8)
Male sex	n	(%)	n	(%)	n	(%)
	42	(53.2)	52	(53.1)	35	(39.5)
Educational level high school or above.	26	(32.9)	34	(34.7)	61	(70.9)
Genetic factors NOS IAP risk genotype	65	(82.3)	80	(81.6)	45	(52.3)
Paternal history of broadly defined schizophrenia	17	(21.5)	22	(22.5)	17	(19.8)
Maternal history of broadly defined schizophrenia	25	(31.7)	28	(28.6)	24	(27.9)
Trauma History of early trauma	16	(20.3)	18	(18.4)	7	(8.1)

^aBroadly defined schizophrenia comprised those with narrowly defined schizophrenia (n=79) and subjects with schizophrenia-spectrum disorders (non-affective psychotic disorders, schizotypal or paranoid personality disorders) (n=19).

^bThe mean number of siblings varied due to within-family variability in the number of affected and unaffected subjects.

Table 2

Associations between early trauma, NOS1AP risk genotype and narrow diagnosis of schizophrenia.

Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI), controlled for the effect of familial clustering				
	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	Adjusted OR ^b (95% CI)	Adjusted OR ^c (95% CI)
Early trauma				
Absent	1.00	1.00	1.00	-
Present	2.56 (1.08, 6.03)	4.17 (1.52, 11.44)	3.57 (1.32, 9.65)	-
NOS1AP risk genotype				
Absent	1.00	1.00	-	1.00
Present	4.19 (2.13, 8.25)	3.67 (1.57, 8.60)	-	3.36 (1.39, 8.15)

^a Estimate adjusted for age, gender, education, and number of siblings.

^b Estimate adjusted for age, gender, education, number of siblings and NOS1AP risk genotype.

^c Estimate adjusted for age, gender, education, number of siblings and early trauma.