Association of Adverse Childhood Environment and *5-HTTLPR* Genotype With Late-Life Depression

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Objective: Neurobiological and clinical studies suggest that childhood maltreatment may result in functional and structural nervous system changes that predispose the individual to depression. This vulnerability appears to be modulated by a polymorphism in the serotonin gene–linked promoter region (*5-HTTLPR*). Little is known, however, about the persistence of this vulnerability across the life span, although clinical studies of adult populations suggest that gene-environment interaction may diminish with aging.

Method: Depressive symptomatology and adverse and protective childhood events were examined in a population of 942 persons aged 65 years and older, taking into account sociodemographic characteristics and proximal competing causes of depression (widowhood, recent life events, vascular and neurologic disorder, and disability). Subjects were recruited between March 1999 and February 2001 and were diagnosed as depressed if they met 1 of 3 criteria: a diagnosis of major depression on the Mini-International Neuropsychiatric Interview, a score higher than 16 on the Center for Epidemiologic Studies-Depression Scale, or current treatment with an antidepressant.

Results: Exposure to traumatic events in childhood doubled the risk of late-life depression and increased the risk of repeated episodes. Not all events were found to be pathogenic; significant risk was associated with excessive sharing of parental problems, poverty or financial difficulties, mental disorder in parents, excessive physical punishment, verbal abuse from parents, humiliation, and mistreatment by an adult outside the family. Interactions were observed between the *5-HTTLPR* long (L) allele, poverty, and excessive sharing of parental problems.

Conclusions: Certain types of childhood trauma continue to constitute risk factors for depression in old age, outweighing more proximal causes. Gene environment vulnerability interaction is linked in older age to the L-carrying genotype, modulating the effects of general environmental conditions rather than aggressive acts on the individual, perhaps due to increased cardiac reactivity.

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Neurobiological studies have demonstrated that childhood maltreatment may alter brain development by programming the glucocorticoid, noradrenergic, and vasopressin stress response systems to overreact to new stressors,[1–3] thus rendering the individual increasingly vulnerable to psychiatric disorder. These effects appear to be long-lasting,[4] inducing structural and functional changes, notably reduced development of the hippocampus and amygdala, and abnormal frontotemporal electrical activity.[2] As these brain structures have also been implicated in the etiology of depression, it is not surprising that child abuse has been associated with increased risk for depression during childhood and also in early adulthood.[5,6]

Not all children exposed to traumatic experiences subsequently develop psychopathology, and accumulating evidence suggests that vulnerability for depression is influenced by variation in the serotonin transporter gene (*5-HTT*).[7,8] A functional insertion/deletion polymorphism in the serotonin gene–linked promoter region (*5-HTTLPR*) has been shown to modify the association between stressful life events and depression onset.[7] The *5-HTTLPR* short (S) allele appears to reduce in vitro transcriptional activity of *5-HTTLPR*, resulting in decreased expression of *5-HTT*. Most replication studies have confirmed this original finding, although a few have not, particularly when older subjects have been included.[9] It has also been observed that a supportive early environment appears to reduce symptomatology in S/S homozygous subjects exposed to childhood trauma.[8,10]

Clinical studies of child abuse have focused on the implication of these events in childhood and adolescence on the assumption of a proximal effect of life events on psychological health. Little is known about the persistence of this vulnerability across the life span and whether adverse childhood events continue to constitute a significant risk factor for depression in old age. The role of the *5-HTTLPR* genotype in mediating the late-life impact of child abuse is also uncertain. In a small community sample of 194 elderly

subjects, depressive symptoms were observed to be associated with abuse and neglect in childhood[11]; however, the sample size was too small for adjustment for other possible causes of depression. A study by Surtees et al[12] combining childhood and adult life events in a sample with an age range of 41 to 80 years found a strong relationship between childhood events and recent episodes of major depression. No interaction effect was found with *5-HTTLPR* genotype; however, a trend was observed in the opposite direction, with the long (L) allele constituting the interactive risk factor in men. Taylor et al[13] noted that, in elderly persons with depression, smaller hippocampal volume was associated with earlier depression onset and the S/S genotype, as opposed to late-onset (over 50 years) depression, in which reduced hippocampal volume was associated with the L/L genotype. Traumatic events were not examined.

Studies to date thus suggest that gene-environment interaction in the genesis of depression may not be the same in elderly populations as in childhood and young adults. Furthermore, while candidate environmental pathogens are generally considered to have greater impact when they are proximal to depression onset,[14] biologic evidence suggests that childhood trauma, occurring at critical stages of brain development, may lead to more permanent structural and functional changes. The present study aims to examine the relationship between childhood trauma and late-life depression in an elderly general population cohort, taking into account other more proximal risk factors for late-life depression, and *5-HTTLPR* genotype interaction. Adverse childhood events are examined individually along with potential environmental protective factors.

METHOD

Sample

Community-dwelling persons, 65 years and older, were recruited by random selection from the 15 electoral roles of the Montpellier District, France, between March 1999 and February 2001 as part of the Esprit study of late-life psychiatric disorder.[15] Refusers (of whom 3.3% were excluded due to severe disability) were replaced by another subject drawn at random from the same electoral division such that each division was equally represented. Subjects refusing were slightly older and more likely to live alone than nonrefusers. Subjects were subjected to a baseline examination and reexamined on 2 further occasions at 2-year intervals.

Measures

Participants were asked to attend a half-day examination by a neurologist and a center interviewer (nurse or psychologist) at the Gui de Chauliac Neurology Hospital (Montpellier, France). Disabled subjects unable to come to the study center were interviewed in their homes. The following procedures were carried out:

Standardized health interview. The health interview covered the participant's present state of health, individual and family medical history, and medication use—subjects were asked to bring their medication to the center and the type of medication was noted according to the World Health Organization's Anatomic Therapeutic Chemical Classification.[16] Disability was assessed by the Lawton Scale for Instrumental Activities of Daily Living (IADL).[17] Exposure to adverse life events in the past year was assessed using the Gospel Oak questionnaire,[18] a 12-item list of major adverse events covering bereavement, rupture in significant relationships, financial and legal problems, dismissal, severe illness, and loss of a highly valued object.

Standardized neurological examination. The neurological examination was based on *International Classification of Diseases*, Tenth Revision criteria[19] and was designed to detect neurologic and cardiovascular comorbidity, including measures of sitting and standing blood pressure. It was carried out at baseline and at each follow-up examination.

Standardized psychiatric interview. The Mini-International Neuropsychiatric Interview (MINI) (French version 5.00)[20] was used to record lifetime and current DSM-IV Axis I psychiatric disorder.[21] The MINI has been validated within the French general population setting.[21] Positive cases were reviewed by a panel of psychiatrists. The Center for Epidemiologic Studies-Depression Scale (CES-D)[22] was used to detect high levels of depressive symptomatology. Case-level late-life depression was defined as a MINI diagnosis of current major depression, a score above the 16-point cutoff on the CES-D, or current treatment with an antidepressant at baseline or at each follow-up examination.

Childhood environment self-report. A retrospective self-report questionnaire examining traumatic experiences during childhood and adolescence based on a review of existing instruments and covering 25 adverse and 8 protective factors was given to subjects for completion in the third wave of the study (4 years after recruitment), by which time the study interviewers had established close relationships with the cohorts, facilitating the request for sensitive information. Subjects were asked to respond yes or no to each item. Subjects were also given an opportunity to discuss the questionnaire contents with interviewers in case of doubt as to whether specific experiences corresponded with the items. Adverse factors included verbal abuse from parents and physical and sexual abuse, conflict at home, strict education, mental cruelty, neglect, mental disorder in parents, excessive sharing of parental problems, illness, poverty, mistreatment at school, separation, and war or natural catastrophe. Protective factors included maternal and paternal affection, availability of an adult friend, impression of having had a happy childhood, parents perceived as doing their best, feeling happy at school, and having been raised by both parents.

Subjects were reexamined on 2 further occasions at 2-year intervals. At follow-up, the neurological and psychiatric examinations were repeated and medication use and incident illness were recorded. The Gospel Oak questionnaire was used to record life events occurring since the last examination. The present study was carried out on the 942 subjects for whom complete information was available on all variables used in the analyses (clinical examinations at all time points, childhood environment, genotype, depression measures, and all potential confounding variables). Ethics approval for the study was given by the national ethics committee. All subjects gave their signed consent for participation in the study.

DNA collection. Blood samples for DNA collection for *5-HTTLPR* genotyping were taken after the baseline clinical interview. *5-HTTLPR* insertion/deletion polymorphisms were assayed in 2 stages. Genomic DNA was extracted from white blood cells harvested from 15 mL ethylenediaminetetraacetic acid blood samples using DNA extraction kits from Amersham-Pharmacia Biotech (Buckinghamshire, United Kingdom). Subsequently, amplification of *5-HTTLPR* was carried out using the primers HTTLPRF (GGCGTTGCCGCTCTGAATTGC) and HTTLPRR (GAGGGACTGAGCTGGACAACCCAC) in reaction mixtures with a total volume of 25 μL, with 200 ng of genomic DNA, 10 pM of the primers, 120 nM dNTP, containing 7-deaza-dGTP instead of dGTP (Roche, Rotkreuz, Switzerland), 5% dimethyl sulfoxide (Sigma, Buchs, Switzerland), 1.5 mM $MgCl_2$, and 1.25 U Taq polymerase (Eurobio, Brunschwig; Basel, Switzerland). Temperatures were 60°C for 30 seconds for annealing and 72°C for 1 minute for extension. PCR products (8 μL) were subjected to 45 mn electrophoresis at 120V in a PCR CheckIT gel (Elchrom Scientific AG, Cham, Switzerland) before being viewed under ultraviolet light to assess the *5-HTTLPR* genotypes. An adenosine/guanine (A/G) single nucleotide polymorphism (SNP; rs25531), located in the close vicinity of *5-HTTLPR*, has recently been reported to modify transcriptional activity.[23] On the basis of these in vitro functional data, it has been proposed to recode the *5-HTTLPR*/rs25531 allele as S' or "low-expressing allele" (S_A, S_G, and L_G) and L' or "high-expressing allele" (L_A).[24] As this new allelic dichotomy still awaits replication in in vivo studies, we initially examined both allelic systems (S/L and S'/L') within the present study. Recoding did not significantly alter results, so we report here only analyses relating to S and L.

Statistical Analysis

Univariate logistic regression was used to determine differences in unadjusted social and clinical characteristics between participants with and without depressive symptomatology. Variables found to be associated with current depression were used as adjustment variables in analyses relating to the association between childhood events and current depression. Polytomous logistic regression models were used to model the relationship between the number of depressive episodes (0, 1, 2 or more) and individual childhood events (binary) and to calculate the odds ratio and its 95% confidence interval (CI) for lifetime onset of a major depressive episode in relation to childhood events. The distribution of *5-HTTLPR* was tested by χ^2 for Hardy-Weinberg equilibrium.

We tested the hypothesis that *5-HTTLPR* genotype might modify the relationship between depressive symptomatology and childhood events using a logistic regression model. We therefore stratified our analysis by *5-HTTLPR* genotype and then added the interaction term to the full model and tested for its significance using Wald χ^2 test given by the logistic regression model. Significance level was set at $P < .05$. The statistical analysis was carried out using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The median (range) age of the sample was 72 (65–92) years. In this study, 38.4% of subjects scored over the cutoff point on the CES-D either at recruitment or at 1 of the 2 follow-up examinations, 23.5% had been diagnosed with major depression during their lifetime, and 12.6% were taking antidepressant medication at some point during the study. All subjects with diagnosed major depression scored over 16 on the CES-D, and 27 subjects (2.9%) taking antidepressant treatment did not meet either MINI or CES-D criteria for depression. These subjects were included as depressed on the assumption that a depressive episode had occurred but had been effectively treated and thus was not detected by the MINI or CES-D. The period prevalence (over the 4-year observation period) of significant depressive symptomatology in this cohort is estimated at 41.3%. The sociodemographic and clinical characteristics of subjects with significant levels of depressive symptomatology are given in Table 1.

Depressed subjects compared to those without depression were more likely to be female (OR = 2.92, 95% CI = 2.21 to 3.86), to be older than 75 years (OR = 1.60, 95% CI = 1.11 to 2.31), to have medium-low education (OR = 2.07, 95% CI = 1.44 to 2.96), to be divorced/separated (OR = 1.87, 95% CI = 1.17 to 2.99) or widowed (OR = 2.15, 95% CI = 1.56 to 2.96), and to have lower rates of hypertension (OR = 0.59, 95% CI = 0.45 to 0.76). Experiencing adverse life events recently (in the year before and during follow-up) and before the onset of the depressive symptoms showed a significant *P* value trend. Subsequent analyses were thus adjusted for these competing causes of depression. No significant relationship was found between depression and dementia or other neurologic disorders, disability, recent cardiovascular or cerebrovascular disorder, or *5-HTTLPR* allele.

Previous research on child maltreatment and depression has principally highlighted personally threatening events

Table 1. Relationship Between Sociodemographic Variables, Clinical Characteristics, and Late-Life Depression

	Late-Life Depression						
	No (n = 553)		Yes (n = 389)				
Variable	n	%	n	%	Odds Ratio	95% CI	*P* value[a]
Gender							
Men	289	52.26	106	27.25	1		
Women	264	47.74	283	72.75	2.92	2.21 to 3.86	< .0001
Age group, y							
≤ 68.5	150	27.12	89	22.88	1		
68.6–71.5	144	26.04	88	22.62	1.03	0.71 to 1.50	.0440
71.6–75.4	137	24.77	96	24.68	1.18	0.82 to 1.71	
> 75.4	122	22.06	116	29.82	1.60	1.11 to 2.31	
Education							
High	170	30.74	76	19.54	1		
Medium-high	113	20.43	101	25.96	2.00	1.37 to 2.93	.0002
Medium-low	145	26.22	134	34.45	2.07	1.44 to 2.96	
Low	125	22.60	78	20.05	1.40	0.94 to 2.06	
Marital status							
Married or living together	399	72.15	219	56.30	1		
Single	21	3.80	19	4.88	1.65	0.87 to 3.13	< .0001
Divorced/separated	39	7.05	40	10.28	1.87	1.17 to 2.99	
Widowed	94	17.00	111	28.53	2.15	1.56 to 2.96	
History of stroke, myocardial infarction, angina pectoris, or arteritis							
No	501	90.60	363	93.32	1		
Yes	52	9.40	26	6.68	0.69	0.42 to 1.13	.1377
Systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or intake of antihypertensive drugs							
No	201	36.35	192	49.36	1		
Yes	352	63.65	197	50.64	0.59	0.45 to 0.76	< .0001
Dementia							
No	546	98.73	383	98.46	1		
Yes	7	1.27	6	1.54	1.22	0.41 to 3.66	.7206
Disability							
No	505	91.32	366	94.09	1		…
Yes	48	8.68	23	5.91	0.66	0.40 to 1.11	.1153
Recent life events[b]							
0	126	22.78	90	23.14	1		
1	238	43.04	130	33.42	0.76	0.54 to 1.08	.0052
≥ 2	189	34.18	169	43.44	1.25	0.89 to 1.76	
5-HTTLPR							
LL	156	28.21	110	28.28	1		
SL	274	49.55	200	51.41	1.04	0.76 to 1.40	.7572
SS	123	22.24	79	20.31	0.91	0.63 to 1.32	

[a]For variables with more than 2 categories, the *P* value of the test for trend is given.
[b]Life events occurring in the past year at baseline.
Abbreviations: *5-HTTLPR* = serotonin gene–linked promoter region, L = long, S = short.

(items 1–6, including physical, sexual, and verbal abuse; Table 2) as being the most pathogenic.[25] In this older population, we found that exposure to at least 1 of these events significantly increased risk of late-life depression (OR = 2.28, 95% CI = 1.53 to 3.41). Exposure to a major protective factor (maternal or paternal affection, availability of an adult friend; items 26–28, Table 2) conversely decreased overall risk (OR = 0.54, 95% CI = 0.28 to 1.01).

We also examined the effects of childhood events on the number of depressive episodes occurring during the study period. Exposure to at least 1 adverse childhood event significantly increased the risk of having 1 episode of depression, with an OR = 1.72 (95% CI = 1.04 to 2.86), and for 2 or more episodes, with an OR = 2.89 (95% CI = 1.83 to 4.57) (*P* value for heterogeneity between these 2 ORs was .05). The presence of at least 1 protective factor gave a risk of OR = 1.03 (95% CI = 0.42 to 2.53) for 1 depressive episode and a protective effect of OR = 0.34 (95% CI = 0.17 to 0.69) for 2 or more episodes (*P* value for heterogeneity was .02) (data not shown).

The relationship between late-life depression and individual childhood life events was also examined using a logistic regression model. No significant sex interaction effects with individual childhood life events and depressive symptomatology were observed, so analyses were not gender stratified. Table 2 shows that a significant risk was associated with excessive sharing of parental problems with children (OR = 1.53, 95% CI = 1.04 to 2.27); poverty or financial difficulties (OR = 1.65, 95% CI = 1.17 to 2.31); mental disorder experienced by the father (OR = 2.13, 95% CI = 1.32 to 3.44) and mother (OR = 2.52, 95% CI = 1.65 to 3.85); excessive physical punishment for misbehavior

Table 2. Relation Between Individual Childhood Events and Late-Life Depression Adjusting for Age, Gender, Education, Marital Status, Hypertension, and Recent Life Events

	Late-Life Depression					
	No (n = 553)		Yes (n = 389)			
Item	n	%	n	%	Odds Ratio	95% CI
Traumatic factors	55	9.95	77	19.79	2.28**	1.53 to 3.41
1. Neglect	25	4.52	27	6.94	1.50	0.83 to 2.74
2. Verbal abuse from my parents	19	3.44	34	8.74	2.90**	1.57 to 5.38
3. Humiliation, harassment or mental cruelty	9	1.63	23	5.91	4.31**	1.87 to 9.93
4. Physical and/or sexual abuse	5	0.90	13	3.34	2.67	0.90 to 7.90
5. Excessive physical punishment for misbehavior	16	2.89	27	6.94	2.77**	1.41 to 5.46
6. Other mistreatment by an adult outside the family	3	0.54	13	3.34	6.71**	1.80 to 25.0
7. Father experienced mental problems	38	6.87	47	12.08	2.13**	1.32 to 3.44
8. Mother experienced mental problems	45	8.14	74	19.02	2.52**	1.65 to 3.85
9. Father had problems with alcohol, drugs	37	6.69	33	8.48	1.30	0.77 to 2.20
10. Conflict, nervous stress at home	86	15.55	79	20.31	1.42	0.98 to 2.04
11. Parents divorced or separated	35	6.33	26	6.68	1.19	0.67 to 2.09
12. Parents hospitalized, prisoner for extended period	77	13.92	73	18.77	1.38	0.94 to 2.00
13. Parents had serious illness	87	15.73	58	14.91	0.96	0.65 to 1.41
14. Strict, authoritarian education	267	48.28	198	50.90	1.11	0.84 to 1.47
15. Serious childhood illness	56	10.13	54	13.88	1.44	0.94 to 2.20
16. Poverty, financial difficulties	113	20.43	103	26.48	1.65**	1.17 to 2.31
17. Parents too often shared their problems with children	67	12.12	67	17.22	1.53*	1.04 to 2.27
18. Mistreatment at school by teacher	13	2.35	17	4.37	2.01	0.92 to 4.40
19. Mistreatment at school by schoolmates	8	1.45	10	2.57	2.22	0.81 to 6.08
20. No mistreatment but disliked school	74	13.38	47	12.08	0.97	0.63 to 1.47
21. Experienced adverse war events or natural catastrophe	298	53.89	217	55.78	1.22	0.92 to 1.62
22. Suicide attempt by family member	22	3.98	14	3.60	0.71	0.34 to 1.46
23. Death of a parent	97	17.54	64	16.45	0.99	0.68 to 1.43
24. Sent to a foster family	9	1.63	10	2.57	2.00	0.76 to 5.26
25. Witnessed abuse of other family members	5	0.90	8	2.06	2.22	0.67 to 7.33
Protective factors	532	96.20	363	93.32	0.54	0.28 to 1.01
26. Paternal affection	461	83.36	319	82.01	0.87	0.60 to 1.26
27. Maternal affection	510	92.22	326	83.80	0.45**	0.29 to 0.70
28. Had an adult friend outside the family	146	26.40	119	30.5	1.08	0.80 to 1.47
29. Raised by both parents	495	89.51	353	90.75	1.07	0.67 to 1.72
30. Happy childhood	519	93.85	343	88.17	0.45**	0.27 to 0.74
31. Happy at school	494	89.33	348	89.46	1.00	0.64 to 1.57
32. Impression that parents did their best	525	94.94	356	91.52	0.53*	0.30 to 0.92
33. Normal education	527	95.30	364	93.57	0.77	0.42 to 1.41

*$P < .05$, **$P < .01$.

(OR = 2.77, 95% CI = 1.41 to 5.46); verbal abuse from parents (OR = 2.90, 95% CI = 1.57 to 5.38); humiliation, harassment, or mental cruelty (OR = 4.31, 95% CI = 1.87 to 9.93); and other mistreatment by an adult outside the family (OR = 6.71, 95% CI = 1.80 to 25.0). A protective effect was observed for maternal affection (OR = 0.45, 95% CI = 0.29 to 0.70) and having the overall impression that parents had done their best (OR = 0.53, 95% CI = 0.30 to 0.92).

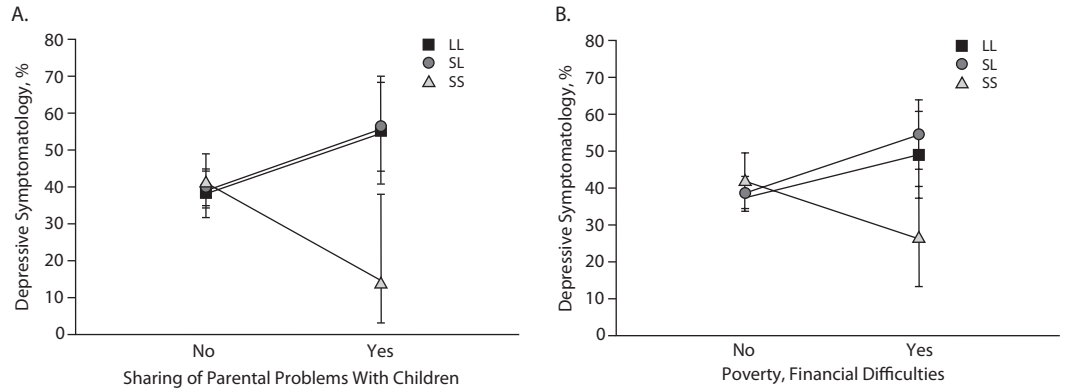
The distribution of *5-HTTLPR* did not deviate from Hardy-Weinberg equilibrium ($\chi^2 = 0.06$, $df = 2$, $P = .97$). Interaction effects between *5-HTTLPR* genotype and childhood events having a significant relationship with depressive symptomatology were examined, adjusting for age, gender, education, marital status, hypertension, and recent life events, with stratification by genotype.

The risk for depression in relation to too frequent sharing of parental problems with children was increased in LL subjects (OR = 1.93, 95% CI = 0.95 to 3.90) and in SL subjects (OR = 2.00, 95% CI = 1.15 to 3.48), with a nonsignificant tendency for protection in SS subjects (OR = 0.30, 95% CI = 0.08 to 1.19). A comparable pattern was observed in subjects who experienced poverty or financial difficulties. We observed a tendency for an increased risk for depression in LL subjects (OR = 1.51, 95% CI = 0.82 to 2.77), which was significant in SL subjects (OR = 2.54, 95% CI = 1.55 to 4.15). In the SS subjects, we found a nonsignificant tendency for reduced risk (OR = 0.64, 95% CI = 0.26 to 1.53).

Significant gene-event interactions were found in subjects with parents who excessively shared their problems (Wald $\chi^2 = 7.23$, $df = 2$, $P = .027$) and with poverty or financial difficulties (Wald $\chi^2 = 7.38$, $df = 2$, $P = .025$) (Figure 1).

As these results suggest a dominant effect of the L-carrying genotypes, we examined the effect of combining LL and LS subjects compared to SS subjects. The risk for depression with childhood poverty was significantly increased in LL/LS subjects (OR = 2.06, 95% CI = 1.42 to 3.00), with a nonsignificant tendency to be reduced in SS subjects (OR = 0.64, 95% CI = 0.26 to 1.53). The risk for depression in relation to too frequent sharing of parental problems with children was also increased in LL/LS subjects

Figure 1. Interaction Between Occurrence of Specific Childhood Events and Probability of Late-Life Depression



Abbreviations: L = long, S = short.

(OR = 1.94, 95% CI = 1.26 to 2.98), with a nonsignificant tendency to be reduced in SS subjects (OR = 0.30, 95% CI = 0.08 to 1.19).

Finally, subjects' lifetime risk for major depressive episodes (MDEs) was also ascertained from the MINI, adjusting only for age, education, and gender (life events and hypertension at the time of the episode being unknown). Significant risk factors were found to be, in ascending order, maternal affection (OR = 0.51, 95% CI = 0.33 to 0.79), sharing of parental problems with children (OR = 1.68, 95% CI = 1.11 to 2.54), maternal mental illness (OR = 1.69, 95% CI = 1.11 to 2.59), verbal abuse from parents (OR = 1.94, 95% CI = 1.07 to 3.55), poverty or financial difficulties (OR = 1.97, 95% CI = 1.37 to 2.83), home conflict (OR = 2.09, 95% CI = 1.43 to 3.05), and physical and/or sexual abuse (OR = 2.72, 95% CI = 1.04 to 7.08). Alcohol abuse by father, neglect, and abuse by schoolmates were only significant risk factors for cases of early-onset depression (occurring before age 50 years; data not shown).

DISCUSSION

Our study of an elderly cohort suggests that adverse childhood events may continue to constitute a significant risk factor for depression throughout the life span. Exposure to traumatic events in childhood was observed to double the risk of late-life depression and increase the risk of repeated episodes. On the other hand, protective factors were seen to diminish the risk of late-life depression and repeated episodes. A relationship between trauma and risk of chronicity has also been observed by Bernet and Stein,[5] who found increasing number of lifetime episodes to be also associated with severity of trauma, but numbers in our study were too small to break down number of depressive episodes by individual items.

Recent studies of the impact of life events on psychological functioning have underlined the necessity of examining the impact of individual stressors rather than summating events in aggregate measures due to the differential effect of specific events.[26] Our findings support this observation. Of the 25 negative factors studied, late-life depression was found to be significantly associated with only 8: verbal abuse from parents, mental cruelty, excessive punishment by parents, abuse by an adult outside the family, parental mental disorder, poverty, home conflict, and excessive sharing of parental problems with children. Physical and sexual abuse did not quite reach significance; however, only a small number of cases (n = 13) were reported. Maternal affection, impression of having had a happy childhood, and feeling that parents did their best constituted protective factors. These early life events were found to be pathogenic or protective even when potential proximal causes of depression (blood pressure, widowhood and separation, recent life events) were taken into account. No interactive effect was found with sex, although previous studies have reported gender differences in vulnerability to adverse life events occurring later in life.[27] Examining individual childhood events and lifetime risk for MDE, we found certain events to be related only to MDE occurring before age 50 years (neglect, paternal alcohol problems, and mistreatment at school by classmates) and others to be related to MDE onset both before and after age 50 years (verbal and physical abuse, maternal mental disorder, and poverty), suggesting some events to have less far-reaching effects than others.

No association was found between *5-HTTLPR* and late-life depression. This observation is in accordance with previous meta-analyses suggesting that these polymorphisms do not directly modulate vulnerability to depression.[9] Significant interaction was observed, however, between these polymorphisms and some childhood environmental factors. Interestingly, these gene-environment interactions appear to concern more general and long lasting environmental conditions, such as poverty, rather than specific aggressive acts of limited duration. This latter type of event may

interact, on the other hand, with genes coding for proteins involved in the development and plasticity of the central nervous system, such as brain-derived neurotrophic factor.[28] Most previous human genotype-by-environment studies report a susceptibility (codominant, dominant, or recessive) effect with the S-carrying genotypes.[9] On the contrary, in the present population, we found a susceptibility-dominant effect with the LL/LS genotypes. Surtees et al[12] reported a similar interaction for past-year prevalent depression and adverse experience in childhood in men—(LL homozygotes) OR = 1.69, 95% CI = 1.17 to 2.44; (LS heterozygotes) OR = 1.26, 95% CI = 0.91 to 1.75. This interaction did not quite reach significance, and the authors suggest this may be due to the fact that it may have occurred predominantly in older subjects, the wide age range of the sample (41–80 years) masking the true effect. Our results lend further support to the hypothesis of a different form of interaction in late-life as opposed to early-onset depression. The L allele has very recently been linked to increased cardiovascular reactivity to mental stress,[29] which may in turn lead to subcortical ischemic disease and volumetric changes, notably in the hippocampus. The authors noted, furthermore, that increased cardiovascular reactivity in adulthood was also observed to be associated with childhood poverty.

We conclude from this study that certain types of early childhood trauma continue to constitute risk factors for depression in old age, their effect outweighing more recent life events and other proximal causes of depression. *5-HTTLPR* genotype alone does not modulate the effect of highly pathogenic events involving individual victimization, but it may increase vulnerability to global environmental factors such as poverty and excessive sharing of parental problems. Strengths of this study were the large, representative general population cohort, which allowed us to take into account competing causes of depression; analysis of a wide range of individual childhood events; and clinical assessment of late-life depressive episodes. There were 2 principal shortcomings in this study: (1) We assumed that subjects taking antidepressant treatment were depressed, which may not have been the case since antidepressants may be prescribed for other neurologic conditions. This may have weakened the associations examined; however, we could not eliminate these subjects as they would at least in part constitute a successfully treated depressed group. (2) The use of a self-report measure of childhood events may also have weakened the associations examined in this study; prospective data from birth cohorts would have been preferable in terms of reducing recall bias. Further studies of this cohort examining possible biologic correlates of the impact of adverse childhood events, such as persistence of abnormal basal cortisol levels and elevated adrenocorticotropic hormone response, as observed in cohorts of abused children,[30] may provide further validation of self-reported adversity and support for the hypothesis that childhood abuse leads to permanent structural and functional changes of the nervous system.

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