

University of Groningen

Childhood trauma and social stress reactivity in psychosis

Veling, Wim; Counotte, Jacqueline; Pot-Kolder, Roos; Van Os, Jim; Van Der Gaag, Mark

Published in:
Journal of Cyber Therapy and Rehabilitation

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Veling, W., Counotte, J., Pot-Kolder, R., Van Os, J., & Van Der Gaag, M. (2016). Childhood trauma and social stress reactivity in psychosis: A virtual reality study. *Journal of Cyber Therapy and Rehabilitation*, 9(1), 19.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Childhood trauma, psychosis liability and social stress reactivity: a virtual reality study

W. Veling^{1,2,3*}, J. Counotte², R. Pot-Kolder^{2,4}, J. van Os^{3,5} and M. van der Gaag^{2,4}

¹Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

²Parnassia Psychiatric Institute, The Hague, The Netherlands

³Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, the Netherlands

⁴Department of Clinical Psychology and EMGO Institute of Health and Care Research, VU University, Amsterdam, The Netherlands

⁵Department of Psychosis Studies, King's College London, King's Health Partners, Institute of Psychiatry, London, UK

Background. Childhood trauma is associated with higher risk for mental disorders, including psychosis. Heightened sensitivity to social stress may be a mechanism. This virtual reality study tested the effect of childhood trauma on level of paranoid ideations and distress in response to social stress, in interaction with psychosis liability and level of social stress exposure.

Method. Seventy-five individuals with higher psychosis liability (55 with recent onset psychotic disorder and 20 at ultra-high risk for psychosis) and 95 individuals with lower psychosis liability (42 siblings and 53 controls) were exposed to a virtual café in five experiments with 0–3 social stressors (crowded, other ethnicity and hostility). Paranoid ideation was measured after each experiment. Subjective distress was self-rated before and after experiments. Multilevel random regression analyses were used to test main effects of childhood trauma and interaction effects.

Results. Childhood trauma was more prevalent in individuals with higher psychosis liability, and was associated with higher level of (subclinical) psychotic and affective symptoms. Individuals with a history of childhood trauma responded with more subjective distress to virtual social stress exposures. The effects of childhood trauma on paranoia and subjective distress were significantly stronger when the number of virtual environmental stressors increased. Higher psychosis liability increased the effect of childhood trauma on peak subjective distress and stress reactivity during experiments.

Conclusions. Childhood trauma is associated with heightened social stress sensitivity and may contribute to psychotic and affective dysregulation later in life, through a sensitized paranoid and stress response to social stressors.

Received 28 January 2016; Revised 18 July 2016; Accepted 2 August 2016; First published online 13 September 2016

Key words: Childhood trauma, paranoia, psychosis, stress sensitivity, virtual reality

Introduction

Childhood trauma can have negative long-term consequences for mental health later in life, including an increased risk for psychotic disorders (Varese *et al.* 2012). Traumatic experiences in early life may cause an enduring heightened sensitivity of the hypothalamic–pituitary–adrenal axis to stress (Heim & Nemeroff, 2001). As a result, physiological, emotional and behavioral responses to social stress exposures later in life may grow stronger (Collip *et al.* 2008; Elsey *et al.* 2015), which eventually can lead to a mental disorder (Heim & Nemeroff, 2001; Collip *et al.* 2008) in interaction with other factors that increase liability, such as genetic variants.

Social stress and heightened stress sensitivity have been implicated in the onset of psychosis (Myin-Germeys & van Os, 2007; Phillips *et al.* 2007). Research directly investigating the link between stress and psychosis has provided inconsistent results, but has been criticized for focusing on major life events rather than minor daily life stressors, and not taking into account subjective appraisal of stressful events (Phillips *et al.* 2007). Epidemiological studies established that environmental factors such as urban birth, population density, neighborhood ethnic density and social minority status mediate risk for psychosis (van Os *et al.* 2010). Exposure to social stress has been suggested as a common mechanism underlying these associations (Lederbogen *et al.* 2011; Selten *et al.* 2013). Experience sampling studies observed that patients with psychotic disorder, compared to controls, responded with more negative affect and more paranoia to minor events in daily life (Collip *et al.* 2011; Reininghaus *et al.* 2016). Moreover, patients with a history of childhood trauma had stronger affective and psychotic responses to daily life events

* Address for correspondence: Dr W. Veling, Department of Psychiatry, University of Groningen, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. (Email: w.veling@umcg.nl)

than patients without trauma (Glaser *et al.* 2006; Lardinois *et al.* 2011; Kramer *et al.* 2012). These findings implicate that stress sensitivity may be a mechanism linking childhood trauma, sensitivity to environmental social stress and psychosis liability. For a direct test of this hypothesis, individuals with different psychosis liability should ideally be randomly exposed to controlled social environments with different levels of exposure to social stressors. This is not possible in real life, as daily social environments are complex, highly dynamic and different for everyone. Furthermore, events are strongly dependent of individuals' behavior (Freeman *et al.* 2015). Controlled experiments are feasible using virtual reality (VR) (Fornells-Ambrojo *et al.* 2008; Freeman *et al.* 2010; Veling *et al.* 2014a). Virtual environments can elicit negative emotions and paranoid thoughts about virtual characters, in particular when environments induce anxiety (Fornells-Ambrojo *et al.* 2015) and when individuals have high levels of anxiety, depression, worry and interpersonal sensitivity (Freeman *et al.* 2008). We recently reported that paranoia and subjective distress increased in a dose-response fashion with the level of social stress in the virtual environment, and were positively associated with psychosis liability and pre-existing affective and psychotic symptoms (Veling *et al.* 2016). A recent study found that a history of childhood bullying was associated with more paranoid ideation in a neutral VR environment, both in people at ultra-high risk for psychotic disorder (UHR) and controls (Valmaggia *et al.* 2015b).

The aim of this VR study was to test the links between childhood trauma, heightened social stress sensitivity, (subclinical) psychotic and affective symptoms, and psychosis liability. The lifetime risk for psychotic disorder is 3% in the general population (van Os *et al.* 2009), ~10% for siblings of patients with a psychotic disorder (Gottesman 1991), 36% for UHR subjects (Fusar-Poli *et al.* 2013) and, by definition, 100% for patients with recent onset psychotic disorder. Phenotypically, UHR subjects and patients with a diagnosis of psychotic disorder all have (subclinical) psychotic symptoms, whereas most siblings and general population controls have not. Taking into account both lifetime risk and phenotype, we classified siblings and controls as having lower psychosis liability, and UHR subjects and patients with a psychotic disorder as having higher psychosis liability.

Higher and lower psychosis liability groups, both including individuals with and without history of childhood trauma, were exposed to various social stressors in virtual environments. We hypothesized that:

- (1) childhood trauma is more prevalent in individuals with higher psychosis liability, and is associated

with higher level of (subclinical) psychotic and affective symptoms;

- (2) individuals with a history of childhood trauma respond with more paranoia and subjective distress to virtual social stress exposure than those without childhood trauma; and
- (3) the effect of childhood trauma on paranoia and subjective distress in VR is stronger when level of social stress increases and if psychosis liability is higher.

Method

Participants

Four groups with different levels of liability to psychosis were included. Patients with psychotic disorder were eligible if the first diagnosis of any psychotic disorder was established within the last 5 years. All DSM-IV categories of psychotic disorder were included, except for substance-induced psychotic disorder and psychotic disorder due to a medical condition. In all patients, either the Comprehensive Assessment of Symptoms and History (Andreasen *et al.* 1992) or the Schedules for Clinical Assessment in Neuropsychiatry (Wing *et al.* 1990) were used to make a DSM-IV diagnosis. Patients were recruited from five psychiatric institutes in the Netherlands. Siblings of patients with a psychotic disorder were included if they endorsed the statement that they had never received the diagnosis of, or treatment for, any psychotic disorder. Patients at UHR for psychosis were identified among patients seeking help for non-psychotic psychiatric problems at outpatient departments of two psychiatric institutes in the Netherlands, using the Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria (Yung *et al.* 2005). Controls were eligible if they declared that they had a negative history of psychotic disorder and did not have a first degree family member diagnosed with a psychotic disorder. They were recruited in waiting rooms of dentists, vocational schools and among staff of a psychiatric institute. Based on lifetime psychosis risk and phenotype, patients with psychotic disorder and UHR patients were classified as having a higher liability to psychosis, siblings and controls as having a lower liability. For all groups, exclusion criteria were epilepsy, IQ <75 and not speaking Dutch. Written informed consent was obtained from all participants. The study was approved by the medical ethical committee of Leiden University Medical Center. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

VR set-up

The virtual environment was a café with an indoor and an outdoor part, built by CleVR with Vizard software. Participants could navigate in the virtual environment, using a Logitech F310 Gamepad. They wore a Sony HMZ-T1 head-mounted display with a HD resolution of 1280 × 720 per eye, with 51.6 diagonal field of view, a 3 DOF tracker for head rotation, and built-in headphones. Virtual humans (avatars) were sitting or standing at a table, chatting and had drinks. Café background noises were played during the experiments.

Environmental social stress experiments

The experiments are described in detail elsewhere (Veling *et al.* 2016). Participants were exposed to environmental social stress in five experiments of 4 min each, in a single session, with breaks of ~10 min between experiments. Three characteristics of the virtual environment were varied: (1) number of virtual café visitors (from here: avatars), (2) ethnic appearance of avatars, and (3) facial expression of avatars. Different levels of social stress were created by exposing participants to no, one, two or three stressors. In the no-stress condition, the café was quiet, with only six avatars, who had a neutral facial expression, and more than 80% of which had a Dutch appearance for Dutch participants and a non-Dutch (North African) appearance for non-Dutch participants. The café was crowded in the experiment with one stressor, increasing the number of avatars from six to 40. The experiments with two stressors involved either a crowded café with the majority of avatars having an ethnicity other than that of the participant, or a crowded café with avatars looking in an angry, hostile fashion at participants when they approached and also at other, random moments. In the experiment with three stressors, the café was filled with 40 hostile avatars of other than own ethnicity. Participants were instructed to explore the café and to find avatars wearing a number on their clothing. The order of the experiments was random, except that the fifth experiment always had at least two stressors.

Measures

Sociodemographic characteristics

Ethnicity was classified Dutch if the participant and both parents were born in the Netherlands, and non-Dutch in all other cases. Level of education was classified as no/primary education, vocational education ((V)MBO), higher secondary education (HAVO or VWO) and higher tertiary education (HBO or University).

Baseline (subclinical) symptoms

Paranoia was assessed with the Green Paranoid Thoughts Scale (GPTS; Green *et al.* 2008), social anxiety with the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998) and frequency scores of (subclinical) positive, negative and depressive symptoms with the Community Assessment of Psychic Experiences (CAPE; Konings *et al.* 2006).

Childhood trauma

Childhood trauma was assessed with the Childhood Trauma Questionnaire Short Form (CTQ-SF), a widely used, well validated retrospective self-report 25-item measure of abuse and neglect before the age of 18 years (Bernstein *et al.* 2003). Emotional abuse and neglect, physical abuse and neglect and sexual abuse were rated as present if the total scores of the respective subscales were classified as moderate or severe, according to published norm scores (Bernstein & Fink, 1998). A dichotomous variable of childhood trauma was created, in which childhood trauma was defined as a positive score on any of the subscales.

Subjective distress and state paranoia

Before each experiment, participants were asked to rate their momentary subjective distress (SUD) in units on an analog scale, with range 0–100 (SUD before). Immediately after each experiment, participants rated their maximum SUD during the experiment (peak SUD). Stress reactivity was calculated for each experiment by subtracting SUD before the experiment from the peak SUD during the experiment. Paranoid thoughts about avatars were measured after each experiment with the State Social Paranoia Scale (SSPS; Freeman *et al.* 2007). The SUD and SSPS scores of the two experiments with two stressors were averaged in order to get mean SUD and SSPS scores for the condition of two stressors. Hence, four SUD and SSPS scores of experiments remained, with no, one, two and three stressors respectively.

Statistical analyses

Sociodemographic and clinical characteristics were compared between participants with and without a history of childhood trauma, using independent sample *t* tests for continuous variables and χ^2 tests for categorical variables.

For the analyses of the effects of childhood trauma on paranoia and subjective distress in the five experiments, multilevel random intercept regression models were used, taking into account the repeated measure structure of the data (with experiments as level 1 and individual as level 2). *B* is the regression coefficient

of the predictor in the multilevel model. We analysed the data using the multilevel random intercept XTREG procedure in Stata v. 13 (StataCorp., USA). Regression models were fitted with continuous paranoia (SSPS) and subjective distress (SUD) scores as dependent variables and the dichotomous childhood trauma measure as independent variable. As a second step, number of stressors, psychosis liability, age and sex were added as covariates. Maximum-likelihood estimates were used to test random effects.

Next, interaction terms were added to the models. Two-way interactions were tested between childhood trauma on the one hand, and number of stressors and psychosis liability on the other. *B* coefficients of the main effects and the interaction terms were compared using the MARGINS DYDX procedure, estimating linear marginal effects at the different levels of virtual social stress and psychosis liability.

Results

Fifty-five patients with psychotic disorder, 20 patients at UHR for psychosis, 42 siblings and 53 controls were included (Table 1). Thirty-five percent of the total sample had a history of childhood trauma. Women had significantly higher rates of childhood trauma than men, ethnic minorities reported higher rates than Dutch participants, and level of education was lower in individuals with childhood trauma.

Individuals with childhood trauma had higher baseline levels of paranoid thoughts, social anxiety, positive, negative and depressive symptoms, compared to individuals without childhood trauma. These differences were statistically significant in the higher psychosis liability group, but not in the lower psychosis liability group. Childhood trauma was much more prevalent in the UHR group (80%) and psychosis group (49%) than in siblings (19%) and controls (17%). Emotional neglect was the most common type of trauma ($n=42$), sexual abuse had the lowest prevalence ($n=13$).

The multilevel regression analyses showed that in the total sample, childhood trauma was associated with higher paranoia in the virtual social stress experiments [Table 2; $B=2.8$, 95% confidence interval (CI) 0.5–5.1, $p=0.016$]. This association was reduced ($B=1.3$, $p=0.308$) after adjustment for number of stressors, psychosis liability, age and sex. Peak subjective distress during experiments was significantly higher in individuals with childhood trauma (adjusted $B=8.0$, 95% CI 0.2–15.7, $p=0.044$). Increase in subjective stress during virtual social stress exposure (stress reactivity) was predicted by childhood trauma (adjusted $B=4.2$, 95% CI 0.3–8.1, $p=0.033$). In the analyses stratified for psychosis liability, childhood trauma had significant effects on peak subjective distress and stress reactivity,

in the higher psychosis liability group, but not in individuals with lower psychosis liability.

Mean paranoia, peak subjective distress and stress reactivity scores during experiments of higher and lower psychosis liability groups with and without childhood trauma are shown in Fig. 1.

There was a positive interaction between childhood trauma and degree of environmental social stress on paranoia (overall adjusted B of the interaction term = 1.12, 95% CI 0.2–2.0, $p=0.013$). The interaction between childhood trauma and level of virtual social stress on peak subjective distress was also statistically significant (overall adjusted $B=1.9$, 95% CI 0.4–3.5, $p=0.012$), the overall interaction term with stress reactivity as outcome was not (adjusted $B=1.1$, 95% CI –0.7 to 2.9, $p=0.221$). Linear predictions at each level of social stress showed that the effects of childhood trauma on paranoia, peak distress and stress reactivity were stronger when social stress level increased (Table 3).

Overall interaction terms between childhood trauma and psychosis liability on paranoia, peak subjective distress and stress reactivity in VR were not statistically significant. The marginal effects at the separate levels of psychosis liability, however, showed that higher psychosis liability increased the effect of childhood trauma on peak subjective distress and on stress reactivity (Table 3).

Discussion

In this experimental VR study, we aimed to test heightened social stress reactivity as a pathway between childhood trauma, psychosis liability, paranoid ideation and distress. Childhood trauma was highly prevalent in patients with (UHR for) psychotic disorder and was associated with level of baseline (subclinical) psychotic and affective symptoms. Individuals with a history of childhood trauma reported more paranoid ideation and subjective distress after exposure to virtual social stress environments than individuals without childhood trauma. These associations were stronger in individuals with higher psychosis liability, but the effects of childhood trauma on subjective distress measures remained after adjustment for psychosis liability. The effects of childhood trauma on paranoia and subjective distress were significantly stronger when the number of virtual environmental stressors increased. Higher psychosis liability increased the effect of childhood trauma on peak subjective distress and stress reactivity during experiments.

Meaning of findings

These findings provide experimental evidence that heightened sensitivity to social stress is a mechanism

Table 1. Description and clinical characteristics of the study sample

	No childhood trauma			Childhood trauma		
	Lower psychosis liability ^a (n = 78)	Higher psychosis liability (n = 32)	Total (N = 110)	Lower psychosis liability (n = 17)	Higher psychosis liability (n = 43)	Total (N = 60)
Age, years	25.4 (4.5)	25.5 (4.9)	25.4 (4.6)	25.3 (5.4)	25.3 (4.6)	25.3 (4.8)
Female sex, n (%)	34 (43.6)	7 (21.9)	41 (37.3)	13 (76.5) ^b	19 (44.2) ^b	32 (53.3) ^b
Non-Dutch origin, n (%)	56 (71.8)	23 (71.9)	79 (71.8)	11 (64.7)	21 (48.8) ^b	32 (53.3) ^b
Level of education, n (%)						
No/primary	0 (0.0)	2 (6.3)	2 (1.8)	0 (0.0)	1 (2.3)	1 (1.7)
Vocational [(V)MBO]	18 (23.1)	8 (25.0)	26 (23.6)	6 (35.3)	25 (58.1)	31 (51.7)
Higher secondary (HAVO/VWO)	10 (12.8)	8 (25.0)	18 (16.4)	4 (23.5)	7 (16.3) ^b	11 (18.3) ^b
Higher tertiary (HBO/University)	49 (62.8)	14 (43.8)	63 (57.3)	7 (41.2)	10 (23.3)	17 (28.3)
Paranoid thoughts ^c	36.5 (7.6)	51.1 (26.3)	40.8 (16.9)	38.5 (9.3)	65.9 (31.3) ^b	58.2 (29.6) ^b
Social anxiety	15.4 (10.8)	24.9 (15.2)	18.2 (12.9)	19.3 (12.2)	36.1 (17.5) ^b	31.4 (17.8) ^b
Depressive symptoms	12.3 (2.4)	14.3 (3.0)	12.9 (2.7)	13.1 (2.8)	17.7 (4.9) ^b	16.4 (4.9) ^b
Positive symptoms	24.0 (3.8)	28.6 (7.4)	25.3 (5.5)	24.0 (5.1)	33.4 (8.5) ^b	30.8 (8.8) ^b
Negative symptoms	21.5 (4.2)	26.7 (6.8)	23.0 (5.6)	20.8 (4.2)	29.9 (7.1) ^b	27.3 (7.6) ^b

^a Lower psychosis liability includes controls and siblings, higher psychosis liability includes ultra-high risk and psychotic disorder.

^b $p < 0.05$, no childhood trauma compared to childhood trauma, within psychosis liability groups (lower, higher and total).

^c Paranoid thoughts assessed with Green Paranoid Thoughts Scale, social anxiety with Social Interaction Anxiety Scale, other symptoms with Community Assessment of Psychic Experiences.

Table 2. Effect of childhood trauma on paranoia and subjective distress in virtual social stress experiments

	No childhood trauma		Childhood trauma		Unadjusted			Adjusted		
	Mean ^a	s.d.	Mean ^a	s.d.	B ^b	95% CI	p	B ^c	95% CI	p
Total sample										
Paranoid thoughts about avatars	17.45	7.39	19.73	7.8	2.8	0.5 to 5.1	0.016	1.3	-1.2 to 3.8	0.308
Peak subjective distress	24.76	20.8	41.07	25.6	15.7	8.3 to 23.0	<0.0005	8.0	0.2 to 15.7	0.044
Stress reactivity ^d	7.85	8.22	11.68	9.8	5.2	1.5 to 8.9	0.006	4.2	0.3 to 8.1	0.033
Lower psychosis liability group ^e										
Paranoid thoughts about avatars	16.8	7.0	19.0	8.1	0.4	-2.8 to 3.5	0.827	1.04	-2.2 to 4.3	0.527
Peak subjective distress	23.5	18.4	35.0	26.1	2.5	-6.9 to 11.9	0.600	1.8	-7.7 to 11.3	0.712
Stress reactivity	7.2	8.0	9.5	8.5	2.8	-3.6 to 9.2	0.391	3.0	-2.9 to 9.0	0.315
Higher psychosis liability group										
Paranoid thoughts about avatars	16.8	6.2	20.9	8.1	2.1	-1.6 to 5.8	0.275	1.4	-2.2 to 5.0	0.452
Peak subjective distress	26.2	20.8	48.7	26.8	13.8	1.9 to 25.6	0.023	12.5	0.4 to 24.6	0.043
Stress reactivity	8.6	10.3	12.8	9.6	5.5	0.5 to 10.6	0.032	5.1	-0.1 to 10.3	0.055

CI, Confidence interval.

^a State Social Paranoia Scale score and Subjective Units of Distress averaged over experiments.

^b Random effects multilevel regression, B coefficient of childhood trauma.

^c Random effects multilevel regression, B coefficient of childhood trauma, adjusted model includes number of virtual stressors, age and sex. In total sample also adjusted for psychosis liability.

^d Peak subjective distress during experiments minus distress before experiments.

^e Lower psychosis liability includes controls and siblings, higher psychosis liability includes ultra-high risk and psychotic disorder.

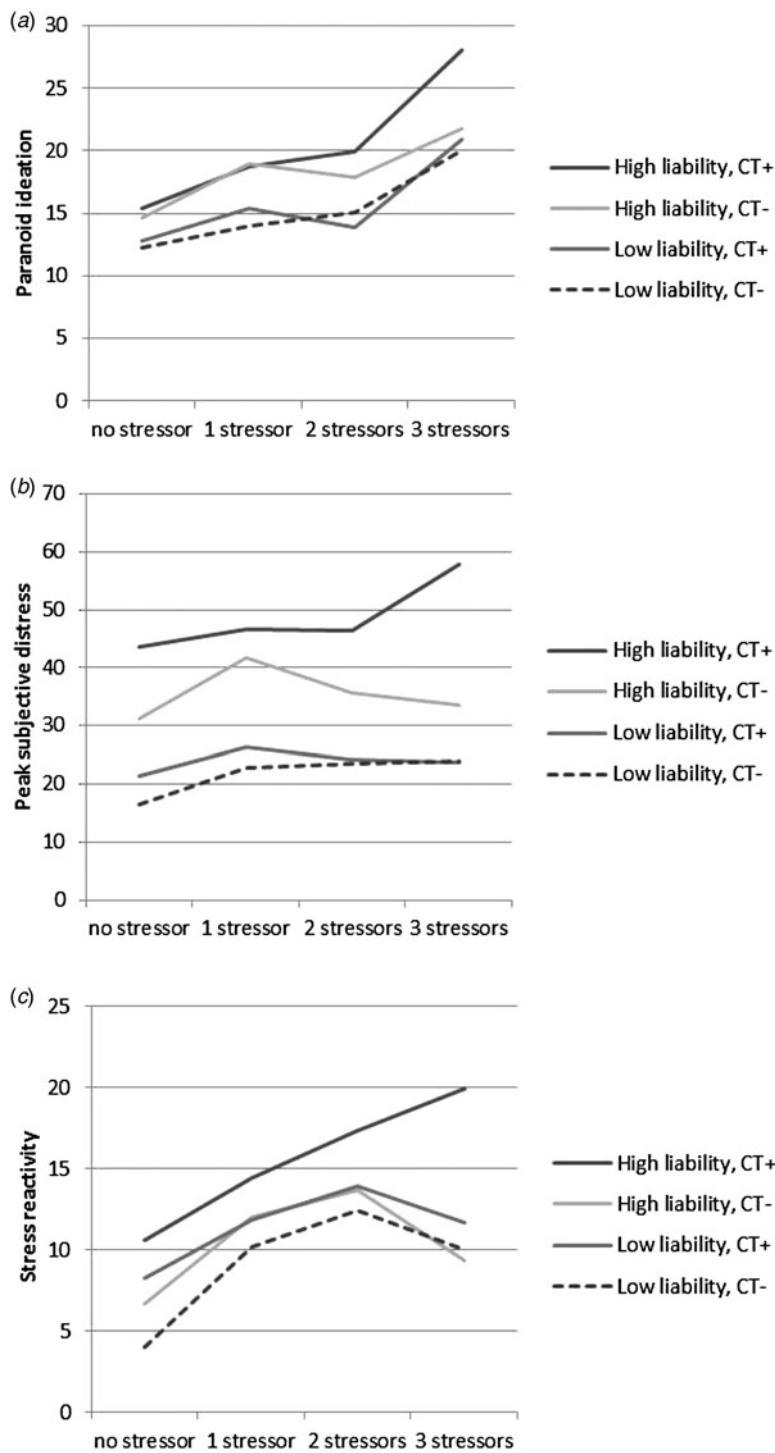


Fig. 1. (a) Paranoid ideations, (b) peak subjective distress and (c) stress reactivity in virtual experiments, by degree of environmental social stress, psychosis liability and childhood trauma. Stressor, level of exposure to virtual social stressors; High liability, subjects with psychosis or ultra-high risk for psychosis; Low liability, siblings and controls; CT, Childhood trauma; paranoid ideations measured with State Social Paranoia Scale; Peak subjective distress during experiments in units 0–100; Stress reactivity, peak distress during experiments minus distress before experiments.

Table 3. Interactions between childhood trauma and level of virtual social stress on paranoia and subjective distress

Interaction terms	Paranoia			Peak subjective distress			Stress reactivity ^a		
	B	95% CI	p value	B	95% CI	p value	B	95% CI	p value
Childhood trauma × number of virtual social stressors ^b									
No stress	-0.3	-3.1 to 2.5	0.816	5.1	-3.0 to 13.2	0.215	2.6	-2.1 to 7.3	0.273
1 stressor	0.8	-1.7 to 3.3	0.535	7.1	-0.7 to 14.9	0.076	3.7	-0.3 to 7.7	0.068
2 stressors	1.9	-0.6 to 4.4	0.137	9.0	1.2 to 16.8	0.024	4.8	0.8 to 8.8	0.019
3 stressors	3.0	0.2 to 5.9	0.036	10.9	2.8 to 19.0	0.008	5.9	1.2 to 10.7	0.015
Childhood trauma × psychosis liability ^c									
Lower psychosis liability ^d	0.4	-3.4 to 4.1	0.838	1.5	-10.1 to 13.1	0.800	2.9	-3.0 to 8.8	0.328
Higher psychosis liability	1.9	-1.3 to 5.1	0.236	12.8	2.7 to 22.8	0.013	5.2	0.1 to 10.2	0.045

CI, Confidence interval.

^a Peak subjective distress during experiments minus distress before experiments.

^b Multilevel random regression analysis, B coefficients of interaction terms, adjusted for age, sex and psychosis liability.

Estimated using Stata MARGINS DYDX procedure, at the four levels of virtual social stress.

^c Multilevel random regression analysis, B coefficients of interaction terms, adjusted for age, sex and number of stressors.

Estimated using Stata MARGINS DYDX procedure, at the two levels of psychosis liability.

^d Lower psychosis liability includes controls and siblings, higher psychosis liability includes ultra-high risk and psychotic disorder.

by which childhood trauma can increase the risk for psychotic and affective dysregulation later in life. Preclinical and clinical studies have shown that early life trauma induces persisting hypersensitivity of the biological stress system, resulting in enhanced endocrine, autonomic and behavioral responses to stress (Heim & Nemeroff, 2001). Whereas childhood trauma has been related consistently to increased risk for adult psychotic, depressive and other mental disorders (Hovens *et al.* 2010; Varese *et al.* 2012), it is less clear how symptoms of these disorders develop in daily life and if social stress sensitivity contributes to psychopathology. Studies using experience sampling methods (ESM) found that (subclinical) psychotic symptoms in patients and in the general population are associated with higher stress reactivity in daily life (Myin-Germeys & van Os, 2007; Collip *et al.* 2013; Reininghaus *et al.* 2016). Exposure to trauma during childhood was associated with increased levels of emotional and psychotic reactivity to stress in the general population (Kramer *et al.* 2012), as well as in patients with a psychotic disorder (Lardinois *et al.* 2011). Consistent with our results, a recent VR study reported an association between a history of bullying victimization and stronger paranoid response to a neutral social environment in people at UHR for psychosis (Valmaggia *et al.* 2015b).

Socio-developmental, neurobiological and cognitive models of psychosis suggest that gene variants, early

hazards to the brain and childhood adversity sensitize the dopamine system, which has been implicated in the development of psychosis (Collip *et al.* 2008; Howes & Murray, 2014). Exposure to subsequent stressors results in excessive dopamine release in the striatum, which in turn leads to aberrant assignment of salience to stimuli, the cognitive interpretation of which may produce negative affective and psychotic symptoms (Garety *et al.* 2007; Howes & Murray, 2014; Reininghaus *et al.* 2016). There is evidence that anxiety, depression and worry fuel paranoia, in particular in combination with perceptual anomalies (Freeman *et al.* 2008). Affective dysregulation may thus contribute to the development of psychosis (Myin-Germeys & van Os, 2007; Freeman *et al.* 2013). A qualitative VR study found that patients with persecutory delusions were able to evaluate interpersonal threat accurately when the environment did not raise their anxiety (Fornells-Ambrojo *et al.* 2015). This is consistent with our findings of a stronger effect of negative affect on paranoid thoughts about avatars and subjective distress when level of environmental stress increased (Veling *et al.* 2016). A personal history of childhood trauma may further enhance the tendency to negative or threatening cognitive interpretations and negative affect, given that early life adversity often gives rise to persistent negative schematic beliefs about the self and others (Garety *et al.* 2007). Experiences of social defeat, characterized by strong

negative beliefs about self and others, have been associated with higher levels of paranoia in a neutral VR environment (Valmaggia *et al.* 2015a). The results of our interaction analyses suggest that paranoia and distress are likely to be elevated in the event of co-occurrence of higher psychosis liability, a history of childhood trauma and a high level of environmental social stress.

These findings also indicate that social stressors do not need to be traumatic or a major life event in order to contribute to psychotic and affective dysregulation. Normal daily life situations, such as crowded environments, presence of people with ethnic appearance that is different from your own and people looking unfriendly at you, already triggered an enhanced paranoid and stress response in individuals with a history of childhood trauma. This tentatively suggests that heightened social stress sensitivity in vulnerable individuals may be a mechanism of epidemiological findings of urbanicity and low ethnic density as risk factors for psychosis (van Os *et al.* 2010).

Strengths and limitations

This study is among the first to use VR to investigate the effects of childhood trauma on social stress response and psychopathology (Valmaggia *et al.* 2015b). It is difficult to measure how individuals respond to complex social environments. Traditionally, studies have used questionnaires and interviews, but these are retrospective and indirect. In social stress research, the Trier Social Stress Test (TSST) is a well validated laboratory task (Kirschbaum *et al.* 1993), but this is a very specific experiment, involving negative evaluation of a job interview and an arithmetic task, which is quite remote to daily life situations. More recently, ESM has been developed for measuring daily life experiences in relation to psychopathology (Myin-Germeys *et al.* 2009). ESM is much more ecologically valid, but relies on brief subjective reports on events and daily stressors, which are thus highly individual and dependent on subjective appraisal of social situations, limiting the reliability and generalizability of findings (Lardinois *et al.* 2011). In addition, ESM cannot rule out the possibility that individuals with childhood trauma live in different, more stressful environments. In the present study, social stress exposures were strictly defined, the same for all participants, and could not be influenced by the individual's history or behavior. VR may be a complementary paradigm for the study of social context, daily life and psychopathology, as it combines the ecological validity of complex social daily life environments with controlled exposure. Although VR is not equal to real life experience, virtual environments elicit similar emotions, thoughts and

physiological responses, as shown in studies of anxiety disorders (Oprış *et al.* 2012), UHR (Valmaggia *et al.* 2007, 2015b) and psychosis (Fornells-Ambrojo *et al.* 2008; Veling *et al.* 2014b).

As the numbers of siblings and controls with a history of childhood trauma were low, and, conversely, only few UHR subjects did not report childhood trauma, it was not possible to test the effects of childhood trauma in separate psychosis liability groups. Instead, higher and lower psychosis liability categories were defined, based on lifetime psychosis risk and experience of (subclinical) psychotic symptoms. Future studies may include larger samples in order to investigate childhood trauma and social stress reactivity in more homogeneous psychosis liability categories.

The nature of the social stressors was chosen based on epidemiological studies and clinical experience. Environmental risk factors for psychosis include urbanicity, low ethnic density and social exclusion (van Os *et al.* 2010). High number of avatars in the virtual environment, low number of avatars with the same ethnicity and hostile facial expression of avatars may be argued to mimic these social experiences, but are of course an oversimplification. However, patients often report that they are more distressed and have more symptoms when they are in crowded situations and in unfamiliar or unfriendly company (Collip *et al.* 2011; Freeman *et al.* 2015). Childhood trauma was measured retrospectively, but the CTQ has been shown to be a valid measure of childhood trauma (Bernstein *et al.* 2003) and is used in many clinical and epidemiological studies. Most patients in the psychosis group used antipsychotic medication (64%) (Veling *et al.* 2016), which is likely to have influenced the results. Antipsychotics decrease dopamine transmission in the striatum, as a result of which salience of social stimuli is attenuated (Kapur *et al.* 2005). Paranoid and stress response to virtual social stressors is therefore likely to be reduced, which may have led to underestimation of the effects of childhood trauma in this group.

Conclusion and clinical implications

Childhood trauma is associated with heightened social stress sensitivity and may contribute to psychotic and affective dysregulation later in life, through a sensitized paranoid and stress response to social stressors. These findings underscore the importance of assessing and addressing childhood trauma and sensitivity to daily social stress in treatment of patients with psychotic disorders. Posttraumatic stress disorder should be treated (van den Berg *et al.* 2015) and stress management interventions may increase psychological resilience to social stress.

Acknowledgements

This work was supported by The Netherlands Organization for Health Research and Development (Veni laureate to W.V., grant no. 916.12.013), and by the European Community's Seventh Framework Program (grant no. HEALTH-F2-2009-241909, project EU-GEL; J.v.O.).

References

- Andreasen NC, Flaum M, Arndt S (1992). The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Archives of General Psychiatry* **49**, 615–623.
- Bernstein DP, Fink L (1998). *Childhood Trauma Questionnaire: A Retrospective Self-report Manual*. The Psychological Corporation: San Antonio, TX.
- Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse and Neglect* **27**, 169–190.
- Collip D, Geschwind N, Peeters F, Myin-Germeys I, van Os J, Wichers M (2013). Putting a hold on the downward spiral of paranoia in the social world: a randomized controlled trial of mindfulness-based cognitive therapy in individuals with a history of depression. *PLoS ONE* **8**, e66747.
- Collip D, Myin-Germeys I, Van Os J (2008). Does the concept of 'sensitization' provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin* **34**, 220–225.
- Collip D, Oorschot M, Thewissen V, Van Os J, Bentall R, Myin-Germeys I (2011). Social world interactions: how company connects to paranoia. *Psychological Medicine* **41**, 911–921.
- Elsej J, Coates A, Lacadie CM, McCrory EJ, Sinha R, Mayes LC, Potenza MN (2015). Childhood Trauma and Neural Responses to Personalized Stress, Favorite-Food and Neutral-Relaxing Cues in Adolescents. *Neuropsychopharmacology* **40**, 1580–1589.
- Fornells-Ambrojo M, Barker C, Swapp D, Slater M, Antley A, Freeman D (2008). Virtual reality and persecutory delusions: safety and feasibility. *Schizophrenia Research* **104**, 228–236.
- Fornells-Ambrojo M, Freeman D, Slater M, Swapp D, Antley A, Barker C (2015). How do people with persecutory delusions evaluate threat in a controlled social environment? A qualitative study using virtual reality. *Behavioural and Cognitive Psychotherapy* **43**, 89–107.
- Freeman D, Dunn G, Fowler D, Bebbington P, Kuipers E, Emsley R, Jolley S, Garety P (2013). Current paranoid thinking in patients with delusions: the presence of cognitive-affective biases. *Schizophrenia Bulletin* **39**, 1281–1287.
- Freeman D, Emsley R, Dunn G, Fowler D, Bebbington P, Kuipers E, Jolley S, Waller H, Hardy A, Garety P (2015). The stress of the street for patients with persecutory delusions: a test of the symptomatic and psychological effects of going outside into a busy urban area. *Schizophrenia Bulletin* **41**, 971–979.
- Freeman D, Gittins M, Pugh K, Antley A, Slater M, Dunn G (2008). What makes one person paranoid and another person anxious? The differential prediction of social anxiety and persecutory ideation in an experimental situation. *Psychological Medicine* **38**, 1121–1132.
- Freeman D, Pugh K, Green C, Valmaggia L, Dunn G, Garety P (2007). A measure of state persecutory ideation for experimental studies. *Journal of Nervous and Mental Disease* **195**, 781–784.
- Freeman D, Pugh K, Vorontsova N, Antley A, Slater M (2010). Testing the continuum of delusional beliefs: an experimental study using virtual reality. *Journal of Abnormal Psychology* **119**, 83–92.
- Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkötter J, McGuire P, Yung A (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry* **70**, 107–120.
- Garety Pa, Bebbington P, Fowler D, Freeman D, Kuipers E (2007). Implications for neurobiological research of cognitive models of psychosis: a theoretical paper. *Psychological Medicine* **37**, 1377–1391.
- Glaser JP, van Os J, Portegijs PJM, Myin-Germeys I (2006). Childhood trauma and emotional reactivity to daily life stress in adult frequent attenders of general practitioners. *Journal of Psychosomatic Research* **61**, 229–236.
- Gottesman II (1991). *Schizophrenia Genesis: The Origins of Madness*. New York: W. H. Freeman.
- Green CEL, Freeman D, Kuipers E, Bebbington P, Fowler D, Dunn G, Garety Pa (2008). Measuring ideas of persecution and social reference: the Green *et al.* Paranoid Thought Scales (GPTS). *Psychological Medicine* **38**, 101–111.
- Heim C, Nemeroff CB (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry* **49**, 1023–1039.
- Hovens JGFM, Wiersma JE, Giltay EJ, Van Oppen P, Spinhoven P, Penninx BWJH, Zitman FG (2010). Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders *v.* controls. *Acta Psychiatrica Scandinavica* **122**, 66–74.
- Howes OD, Murray RM (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet* **383**, 1677–1687.
- Kapur S, Mizrahi R, Li M (2005). From dopamine to salience to psychosis-linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research* **79**, 59–68.
- Kirschbaum C, Pirke KM, Hellhammer DH (1993). The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* **28**, 76–81.
- Konings M, Bak M, Hanssen M, van Os J, Krabbendam L (2006). Validity and reliability of the CAPE: a self-report

- instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatrica Scandinavica* **114**, 55–61.
- Kramer IMA, Simons CJP, Myin-Germeys I, Jacobs N, Derom C, Thiery E, van Os J, Wichers M** (2012). Evidence that genes for depression impact on the pathway from trauma to psychotic-like symptoms by occasioning emotional dysregulation. *Psychological Medicine* **42**, 283–294.
- Lardinois M, Lataster T, Mengelers R, Van Os J, Myin-Germeys I** (2011). Childhood trauma and increased stress sensitivity in psychosis. *Acta Psychiatrica Scandinavica* **123**, 28–35.
- Lederbogen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, Wüst S, Pruessner JC, Rietschel M, Deuschle M, Meyer-Lindenberg A** (2011). City living and urban upbringing affect neural social stress processing in humans. *Nature* **474**, 498–501.
- Mattick RP, Clarke JC** (1998). Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. *Behaviour Research and Therapy* **36**, 455–470.
- Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, van Os J** (2009). Experience sampling research in psychopathology: opening the black box of daily life. *Psychological Medicine* **39**, 1533–1547.
- Myin-Germeys I, van Os J** (2007). Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. *Clinical Psychology Review* **27**, 409–424.
- Oprış D, Pinteş S, García-Palacios A, Botella C, Szamoskőzi Ş, David D** (2012). Virtual reality exposure therapy in anxiety disorders: a quantitative meta-analysis. *Depression and Anxiety* **29**, 85–93.
- Phillips LJ, Francey SM, Edwards J, McMurray N** (2007). Stress and psychosis: towards the development of new models of investigation. *Clinical Psychology Review* **27**, 307–317.
- Reininghaus U, Kempton MJ, Valmaggia L, Craig TKJ, Garety P, Onyejiaka A, Gayer-Anderson C, So SH, Hubbard K, Beards S, Dazzan P, Pariante C, Mondelli V, Fisher HL, Mills JG, Viechtbauer W, McGuire P, van Os J, Murray RM, Wykes T, Myin-Germeys I, Morgan C** (2016). Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: an experience sampling study. *Schizophrenia Bulletin* **42**, 712–722.
- Selten J-P, van der Ven E, Rutten BPF, Cantor-Graae E** (2013). The social defeat hypothesis of schizophrenia: an update. *Schizophrenia Bulletin* **39**, 1180–1186.
- Valmaggia L, Freeman D, Green C, Garety P, Swapp D, Antley A, Prescott C, Fowler D, Kuipers E, Bebbington P, Slater M, Broome M, McGuire PK** (2007). Virtual reality and paranoid ideations in people with an ‘at-risk mental state’ for psychosis. *British Journal of Psychiatry* **1**, 63–68.
- Valmaggia LR, Day F, Garety P, Freeman D, Antley A, Slater M, Swapp D, Myin-Germeys I, McGuire P** (2015a). Social defeat predicts paranoid appraisals in people at high risk for psychosis. Elsevier B.V. *Schizophrenia Research* **168**, 16–22.
- Valmaggia LR, Day FL, Kroll J, Laing J, Byrne M, Fusar-Poli P, McGuire P** (2015b). Bullying victimisation and paranoid ideation in people at ultra high risk for psychosis. *Schizophrenia Research* **168**, 68–73.
- van den Berg DPG, de Bont PaJM, van der Vleugel BM, de Roos C, de Jongh A, Van Minnen A, van der Gaag M** (2015). Prolonged exposure *v.* eye movement desensitization and reprocessing *v.* waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. *JAMA Psychiatry* **72**, 259–267.
- van Os J, Kenis G, Rutten BPF** (2010). The environment and schizophrenia. *Nature* **468**, 203–212.
- van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L** (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.
- Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, Read J, Van Os J, Bentall RP** (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin* **38**, 661–671.
- Veling W, Brinkman W-P, Dorrestijn E, van der Gaag M** (2014a). Virtual reality experiments linking social environment and psychosis: a pilot study. *Cyberpsychology, Behavior and Social Networking* **17**, 191–195.
- Veling W, Moritz S, Van Der Gaag M** (2014b). Brave new worlds – review and update on virtual reality assessment and treatment in psychosis. *Schizophrenia Bulletin* **40**, 1194–1197.
- Veling W, Pot-Kolder R, Counotte J, van Os J, van der Gaag M** (2016). Environmental social stress, paranoia and psychosis liability: a virtual reality study. *Schizophrenia Bulletin*. Published online: 2 April 2016. doi:10.1093/schbul/sbw031.
- Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N** (1990). SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Archives of General Psychiatry* **47**, 589–593.
- Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell’Olio M, Francey SM, Cosgrave EM, Killackey E, Stanford C, Godfrey K, Buckley J** (2005). Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian and New Zealand Journal of Psychiatry* **39**, 964–971.