The primacy of context : a study of person-environment interaction in schizophrenia

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Contents

CHAPTER 1

Introduction

The phenomenology of schizophrenia

Schizophrenia is a major psychiatric disorder, with a worldwide prevalence of about 1% (Sartorius et al. 1986). It is a devastating disease, often disabling people in all major domains of life, such as work, marriage and social relations. The central symptoms of schizophrenia according to the DSM IV (APA 1994) are delusions, hallucinations, disorganized speech, catatonic behavioral signs and negative symptoms such as flat affect (absence of variation in emotional expression), avolition (disinterest in engaging in goal-directed work, recreational and social activities) and alogia (poverty of speech). Schizophrenia clearly is a very heterogeneous disorder associated with an extreme variety in clinical pictures.

Several researchers have suggested a division of the schizophrenia disorder into subtypes, to reduce the clinical heterogeneity (Robins & Guze 1970; Crow 1980; Andreasen 1985; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998). Subclassifications based on clinical picture, outcome, development, underlying pathology and factor analyses of the symptoms, have been suggested. Two main subsyndromes of schizophrenia have been identified. The positive syndrome, good-outcome, non-deficit, type I schizophrenia (Robins & Guze 1970; Crow 1980; Andreasen 1985; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998) is mainly characterized by the presence of positive symptoms, such as delusions and hallucinations; an acute onset; an episodic course, often with good-outcome; and good reactions to neuroleptic treatment. The main underlying pathology has been assumed to be a neurochemical abnormality (such as a hyperdopaminergic activity), and this sub-syndrome has been hypothesized to be most reactive to environmental risk factors (Robins & Guze 1970; Crow 1980; Andreasen 1985; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998). The negative syndrome, poor-outcome, deficit, type II schizophrenia (Robins & Guze 1970; Crow

1980; Andreasen 1985; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998), on the other hand, was mainly characterized by negative symptoms such as flat affect, avolition and alogia; intellectual and cognitive impairments; an insidious onset; a chronic and often deteriorating course; and poor response to neuroleptic treatment. Structural brain abnormalities seem to be the main underlying pathology, which are probably the result of deficits already present at birth (Robins & Guze 1970; Crow 1980; Andreasen 1985; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998). The use of factor analyses extended the division to three sub-syndromes of schizophrenia (Liddle 1987; Liddle et al. 1989; Peralta et al. 1992; Johnstone & Frith 1996): the psychomotor poverty syndrome (e.g. poverty of speech, affective non-response, unchanging facial expression), disorganisation syndrome (e.g. poverty of content of speech, derailment, inappropriate affect) and reality distortion syndrome (e.g. the presence of voices, delusions of persecution). The division into different sub-types has some clinical validity. For instance, the positive syndrome is more responsive to neuroleptic medication. In contrast, not much agreement has been reached concerning the underlying aetiology. Some authors argue that the different sub-types reflect independent diseases caused by separate underlying aetiologies (Robins & Guze 1970; Murray et al. 1992), while others suggest that they are expressions of different pathological processes, which are caused by the same fundamental underlying abnormality (Crow 1985; Liddle 1987). To date, the discussion whether we should look for a single gene (Crow 1995), a unitary pathogenesis such as neurocognitive deficits (Goldberg & Weinberger 1995), or multiple aetiological factors (Tsuang & Faraone 1995), has not been solved.

The diversity of symptoms, the diversity of outcomes and the uncertainty about aetiology, has led some researchers to conclude that *schizophrenia* is no recognizable entity (Bentall et al. 1988). They have suggested an alternative approach to study abnormal behavior, namely the study of specific symptoms (Costello 1993). The thorough study of isolated symptoms, their course, treatment and aetiology, might provide evidence for a new classification of disorders. Although this approach may seem appealing and straightforward, it still provides us with a number of difficulties. For one, symptoms are not simple entities. Let us take the example of 'delusions'. All persons concerned with schizophrenia feel they have a good sense of what is considered a

delusion and indeed, there is a remarkable interrater agreement among clinicians in detecting delusions in practice (Spitzer 1990). However, defining delusions in general terms is much harder. The definition used in the DSM IV classification is based on criteria originally formulated by Jaspers (Jaspers 1913) such as falsity of beliefs, absolute conviction and incorrigibility. However, the specificity and validity of these concepts have been criticised by numerous researchers (Moor & Tucker 1979; Garety 1985; Spitzer 1990; Walkup 1990; Harper 1992). *Falsity of beliefs* is applicable to all of us as we all have false beliefs from time to time (Moor & Tucker 1979), and the question of truth and falsity is in some cases either not applicable (e.g. in the case of religious beliefs) or applicable but hardly likely to be solved (e.g. in the case where the clinician cannot actually disprove the claims of the patient (Spitzer 1990)). Concerning *absolute conviction,* Garety (Garety 1985; Garety & Hemsley 1994) reported that both the fixity (i.e. the maintainance of a belief over time) and the intensity (i.e. the degree of conviction) of delusional beliefs vary over time. *Incorrigibility* is described in DSM IV (APA 1994) as 'firmly sustained in spite of what constitutes incontrovertible and obvious proof or evidence to the contrary.' However, it is unclear what constitutes incontrovertible proof as it would be difficult to provide formally incontrovertible proof against most assertions. Furthermore, most claims of deluded people are not routinely investigated or refuted by their clinicians, while they still will be called delusions (Moor & Tucker 1979; Harper 1992). All other aspects of the complete DSM IV definition of delusions have been similarly criticized. Apparently, even defining smaller entities such as single symptoms still seems hazardous.

Apart from the problems in definition, some researchers have doubted the existence of symptoms as discrete entities. Indeed, the concept of psychiatric symptoms has evolved from being defined dichotomously, either you had it or you did not, to being situated on continua ranging from normal to highly abnormal experiences (Strauss 1969). It has even been reported that these continua are not restricted to clinical populations, but apply to the general population, as such broadening the psychosis phenotype beyond the clinical concept of schizophrenia (Van Os et al. 2000). Furthermore, symptoms have been reported to be complex phenomena, which should be described according to a number of separate dimensions, which are independent and all with their own variability over time.

Again in the case of delusions, they can be described based on dimensions such as belief conviction, preoccupation, bizarreness, obtrusiveness, and subjective distress (Kendler et al. 1983; Garety & Hemsley 1994; Oulis et al. 1996).

The single symptom approach, although it has its own limitations, might provide more insight in the essence of the underlying symptoms and in the causal pathways leading to the development of specific psychopathology . Furthermore, it might provide support for the current classification systems in psychiatry such as DSM IV (APA 1994), although it is equally possible that completely new classification systems might come forward.

In conclusion, it seems that over 100 years after the first detailed description of the disorder (Kraepelin 1896; Bleuler 1911/1950), our understanding of the main characteristics of the disorder called 'schizophrenia' is still evolving. The clinical differentiation has been generally accepted, but no conformity has been reached concerning underlying aetiologies. At a more basic phenomenological level, the general knowledge about the basic symptoms could be deepened to come to a thorough understanding of what it implies to 'hear voices' or to 'think that the CIA is following you'.

The vulnerability-stress model of schizophrenia

The next section of the introduction concerns the fundamental issue of causes and aetiology of schizophrenia. The most prominent model to study possible causes of schizophrenia (and other psychiatric disorders) (Zuckerman 1999) has been the vulnerability-stress model (Zubin & Spring 1977; Zubin et al. 1983). It integrates underlying theoretical and empirical perspectives from diverse areas such as genetics, neurobiology, psychology and behavioral sciences. The vulnerability-stress model states that psychiatric symptoms will emerge whenever a threshold of stressors exceeds the individual's vulnerability level, the latter being a stable characteristic. The vulnerability-stress model is essentially interactional. It is aimed to show how subjects who have a certain level of vulnerability deal or fail to deal with stress, which results in the

occurrence of symptoms. Especially this interactional aspect remains difficult to investigate, as it is hard to find research methods that allow the study of how vulnerable subjects interact with the stresses of the real world. Therefore, most research to date has focussed on either the vulnerability indicator or the stressor, whereas their interplay is rarely examined.

Vulnerability for schizophrenia has been defined as the individual proneness to the initial development of the illness or for schizophrenic episodes to return (Zubin & Spring 1977). The individual vulnerability for schizophrenia is partly inborn and partly acquired (Zubin & Spring 1977). There is a considerable inborn, genetic contribution. First-degree relatives of patients with schizophrenia have a 10 % chance to become ill compared to only a 1% chance in the general population (Gottesman 1991). The acquired component includes intra-uterine influences such as maternal viral infections (Kirch 1993), maternal exposure to stress (Van Os & Selten 1998), and obstetric complications (Geddes & Lawrie 1995), as well as post-natal influences such as parental communication deviance (Miklowitz & Stackman 1992).

The detection of the underlying vulnerability is essential to identify persons at increased risk for schizophrenia, which might be important for prediction and ultimately prevention of the disorder. In order to detect the underlying vulnerability, most research searched for behavioral or structural abnormalities, so called vulnerability-markers, which might be considered expressions of the underlying genotype. In addition to being an indicator of genetic risk, vulnerability markers can also be causally related to the development of psychopathological symptoms. These vulnerability markers are thus important to reveal possible causal mechanisms underlying schizophrenia.

Vulnerability markers should meet some formal criteria (Green 1998). A vulnerability marker expresses itself as a structural abnormality or an abnormality in functioning, deviant from what is found in the normal population. The abnormality should be present before the onset of the illness, during psychotic episodes and during remission periods to ensure that it is not a consequence of experiencing or having experienced pathological symptoms. And the deviance should optimally be specific to a disorder, rather than being related to psychopathology in general. In order to identify vulnerability markers for schizophrenia, different research strategies have been used (Green 1998). One option is

the study of patients in remission, although it is difficult to determine whether the abnormal functioning is the cause or rather the consequence of the disorder. An alternative approach is the study of subjects who share part of their genetic constitution with their ill relative and, therefore, might share some of the underlying vulnerability for schizophrenia. Children from parents with schizophrenia are investigated when they are still at risk for developing the disorder (the so-called high-risk groups), in order to detect functional abnormalities that precede the onset of illness. The study of first-degree relatives, on the other hand, who most likely would not develop the disorder, provides information on functional abnormalities that are related to underlying vulnerability, separate from signs and symptoms of the disorder. Finally, it is also interesting to investigate subjects in the general population who are functioning normally, but report sub-clinical levels of psychotic psychopathology (schizotypal personality or psychosis-proneness). The study of these subjects provides insight into deviancies related to the *underlying vulnerability*, to the extent that these groups share a common genetic vulnerability to schizophrenia.

Several vulnerability markers for schizophrenia have been identified. One of the most thoroughly investigated markers is a deviant neurocognitive level of functioning. Impairments in working memory, attention and executive functions have been identified in patients suffering from schizophrenia, in their first-degree relatives, in high-risk populations and in subjects with schizotypal personality disorder (Green 1998; Toomey et al. 1998; Faraone et al. 1999; Krabbendam et al. in press). In addition, abnormalities in smooth-pursuit eye movements (Schwartz et al. 1995; Ross et al. 1998), alterations in event-related potentials (Karoumi et al. 2000; Kimble et al. 2000; Turetsky et al. 2000) and structural brain abnormalities (Cannon et al. 1998) have been reported as indicators of an underlying vulnerability for schizophrenia. Although all of these indicators are thoroughly investigated, they basically ignore the interactional aspect of the vulnerability-stress model. Although these studies indicate how groups with different vulnerability differ from each other, they do not provide information on how vulnerable subjects react to stress. Some of these markers do include the reaction to an external stimulus or "stressor", but it is not clear how these stressors are related to real life

stressors. "The concept of vulnerability needs the concept of the stressor. Vulnerability means vulnerability to a specific stressor" (Katschnig 1991).

The second element of the vulnerability-stress model is the stressor related to the onset and relapses of schizophrenia. Global environmental factors such as living in an urban region (Marcelis et al. 1999) have been linked to an increased risk for schizophrenia. The presence of life events (Lukoff et al. 1984; Bebbington et al. 1993; Norman & Malla 1993) and of critical relatives (Brown et al. 1972; Lukoff et al. 1984; Butzlaff & Hooley 1998) has been associated with higher levels of symptomatology and increased relapse rates. Minor hassles have been identified as important predictors of psychological symptoms in general (Kanner et al. 1981; Monroe 1983), of subjective distress (Norman & Malla 1991), and of relapse rates in schizophrenia (Malla et al. 1990). However, all these stressors have been examined without acknowledging their specific effects on vulnerable persons, as such again ignoring the interactional aspect of the vulnerability-stress models.

The vulnerability-stress model has been developed to move ahead from the standstill all major research areas in schizophrenia research had come to at the time. And indeed, a mass of new research and new findings indulged following this model. However, the vulnerability-stress model did not evolve from a strictly heuristic model, post hoc describing relevant factors, towards a predictive model, predicting the course and relapses in patients suffering from schizophrenia. The study of the interactional aspect of the vulnerability-stress model might enrich the knowledge of underlying mechanisms, which might be another step toward true prediction.

The Experience Sampling Method

When studying schizophrenia, one needs to consider the most appropriate way to study psychopathology. Most information to date has come from clinical observation and (semi-) structured interviews such as the Psychotic Symptom Rating Scales (Haddock et al. 1999), the Brief Psychiatric Rating Scale (Overall & Gorham 1962; Ventura et al. 1993) and the Life Chart (Susser et al. 2000). However, the question might rise whether

these tools are sufficient to fully apprehend the essence of psychiatric symptoms. First, most psychiatric symptoms are internal mental phenomena, which limits the applicability of clinical observations. By consequence, we have to rely on self-report and introspection to gain information (Stone et al. 2000). Clinical interviews are based on these methods, but their structure (they are mostly retrospective) makes them vulnerable to bias. First, there is the problem of recall bias (Tourangeau 2000). Recall is limited by forgetting, but the pattern of forgetting is not random, e.g. more salient events would be more easily recalled than less salient ones and current mood would make mood-congruent memories more accessible (Stone & Shiffman 1992; Kihlstrom et al. 2000). Furthermore, subjects might construct their recall based on their self-perception of their typical behavior, rather than on their actual behavior (Stone et al. 1998). Another bias concerns what is called 'effort-after-meaning'. The fact that you already know how situations have evolved might influence your memory of the situation (Stone et al. 1998). Second, psychiatric symptoms are embedded in the context of daily life. They occur during daily activities, while patients are interacting with the persons and the world around them (deVries 1992; Delespaul 1995). Psychiatric symptoms are, therefore, possibly very closely related to the way patients feel, the activities they are involved in and so on. It is also imaginable that symptoms are triggered by experiences in the environment, or that the environment protects subjects from psychopathological symptoms. So far, little is known about the subjective experience of psychopathological symptoms in daily life. Clinical interviews are not particularly suited to investigate these interactions, as some of these interaction patterns are probably not apparent for the subjects themselves. Clinical observation could be used to study the context but this would be very intrusive and not ethical as it would involve following patients around in their daily environment. And there still is the problem of psychopathological symptoms as internal phenomena.

Therefore, there is a need for methods in psychiatry that 1) diminish the time between occurrence and assessment of symptoms, 2) study patients prospectively and longitudinally to explore interaction patterns, and 3) open up daily life in a non-intrusive way. These methods would further deepen our understanding of psychopathological symptoms and would enable the study of the interaction between stressors and vulnerable persons.

Such a method exists and is called the Experience Sampling Method (ESM). ESM is a family of methods and has been developed to systematically and validly assess experiences and behaviors as they occur in daily life, as well as the context in which they occur (Csikszentmihalyi et al. 1977; Csikszentmihalyi & Larson 1987; deVries 1992). It is a structured diary technique, mostly used for prospective studies and studies that investigate variability in relation to context (e.g. with multiple assessments). In the presented studies, subjects receive a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emits a signal (beep) at unpredictable moments between 7.30 a.m. and 10.30 p.m. After every "beep", reports of thoughts, current context (activity, persons present, location), appraisals of the current situation, and mood are collected, as such providing a wealth of information.

ESM has been successfully applied in psychiatric populations such as schizophrenia (Delespaul 1995), depression (Barge-Schaapveld et al. 1999), bulimia (Larson & Asmussen 1992), and panic disorder (Dijkman-Caes & devries 1991) and the feasibility, validity, and reliability of ESM in these populations has been demonstrated (deVries 1992).

Outline and aims of the study

The introduction discussed problems both at the level of phenomenology and at the level of aetiology of schizophrenia. The research presented in this doctoral dissertation used the Experience Sampling Method as thread to tackle some of the problems mentioned in the introduction. Chapter 2 and 3 will focus on the phenomenological level, while chapter 4, 5 and 6 will focus on the vulnerability-stress model in schizophrenia.

Emotional experiences in schizophrenia

In *chapter 2,* flat affect, a central and well-described negative symptom of schizophrenia, will be studied in the context of daily life. Flat affect, defined as a restriction in the range and intensity of emotional *expression*, has been extensively described in schizophrenia.

The subjective *experience* of emotions has much less been investigated. Some laboratory studies reported the presence of both positive and negative emotions in relation to simple laboratory conditions such as looking at videotapes. The study described in *chapter 2* will study the *experience* of emotions in the complex natural situations of daily life, both in schizophrenia patients with blunted and non-blunted expression of emotions.

The context of delusions in daily life

Delusions are one of the primary positive symptoms in schizophrenia. Global characteristics and psychosocial risk factors related to delusions have been identified. The study described in *chapter 3* will extend these findings to the level of everyday functioning. The aims of the study are 1) to identify characteristic features of delusional moments in daily life and the specific contextual conditions under which they occur, 2) to investigate variability in the presence of delusions of hours and days, and 3) to identify aspects of daily experience that may precipitate delusional experiences.

Emotional stress-reactivity as a marker for psychosis

As lined out in the second part of the introduction, a vulnerability-stress model for schizophrenia is essentially interactional. It involves a person with an underlying vulnerability for schizophrenia and it involves the occurrence of stress. The study presented in *chapter 4* will use ESM as an interactive approach to address the following questions: (1) how do the affects of a person vulnerable to psychosis shift when he or she encounters a stressor in his or her natural environment and (2) in what way does the emotional reaction to real life stressors vary with differing degrees of vulnerability? Three groups will be studied on the basis of differences in vulnerability for schizophrenia: patients, their first-degree relatives and non-affected controls.

The relation between cognitive impairments and stress-sensitivity in schizophrenia

Cognitive impairments have been widely recognized as underlying vulnerability substrate for schizophrenia, related to functional outcome. Altered stress-sensitivity has also been reported in patients with schizophrenia and their first-degree relatives. To date, it has not been studied whether both mechanisms are part of one underlying vulnerability or

whether they constitute independent or even mutually exclusive mechanisms. The study presented in *chapter 5* will study the possible association between altered stress-sensitivity and cognitive impairments in patients suffering from schizophrenia.

Emotional stress-reactivity in schizophrenia and affective disorders

Vulnerability-stress models have been postulated in the study of aetiology and course of all major psychiatric disorders. Major stressors seem to precede the onset and relapse of depression, bipolar disorder and psychotic disorder, although quantitative differences have been reported. The study described in *chapter 6* aims to (1) further refine the concept of stress in relation to mental health by studying the effect on mood of even smaller disturbances in the realm of daily life and (2) to explore the differences in emotional reactivity to daily life stress between the following psychiatric disorders: non-affective psychosis, bipolar disorder, and major depression.

In *chapter 7,* the summary of all studies will be given; the results will be discussed and both the theoretical and clinical implications will be addressed.

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CHAPTER 2

Schizophrenia patients are more emotionally active than is assumed based on their behavior[1]

Abstract

Flat affect is a core symptom of schizophrenia. To date, researchers have focused primarily on emotional expression. Only recently has the emotional experience of patients with schizophrenia been studied in laboratory settings. The goal of this study is to assess emotional experience in the complex world of daily life. A structured time-sampling technique, the Experience Sampling Method, was used to collect data. Schizophrenia subjects (n=58) were compared to 65 nonpatient controls. Patients were divided into blunted and nonblunted subgroups on the basis of Brief Psychiatric Rating Scale (BPRS) behavioral ratings of flat affect. Schizophrenia subjects experienced more intense and more variable negative emotions than controls. For the positive emotions, we found less intensity and less variability in the schizophrenia subjects. No difference in patterns of affect was found between the blunted and the nonblunted schizophrenia subgroups. Our findings suggest that patients with schizophrenia are more emotionally active than has been assumed based on behavioral observations.

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[1] Inez Myin-Germeys, Philippe A.E.G. Delespaul and Marten W. deVries (2000). Schizophrenia patients are more emotionally active than is assumed based on their behavior. *Schizophrenia Bulletin*, 26, 847-854.

Introduction

Flat affect has traditionally been considered a core feature of schizophrenia. At the turn of the century, Kraepelin (1919/1971) identified emotional dullness as one of the symptoms contributing to dementia praecox. Bleuler (1911/1950) considered emotional dullness a fundamental symptom of schizophrenia. Flat affect has also triggered the interest of many clinicians working with patients with schizophrenia. Emotional activity is at the heart of every interpersonal interaction and is therefore of central importance for all therapies and rehabilitation strategies.

In the last decades, research has focused primarily on emotional *expression* in patients with schizophrenia, corresponding to the *DSM* definition of flat affect as "a restriction in the range and intensity of emotional expression" (*DSM-IV,* American Psychiatric Association 1994). Rating scales such as the BPRS (Overall & Gorham 1962), the Scale for Assessment of Negative Symptoms (Andreasen 1982), and the Emotional Blunting Scale (Abrams & Taylor 1978) assess behavioral correlates such as facial expression, expressive gestures, and vocal inflections during the interview (Andreasen 1982, 1987; Johnstone 1989; Silk & Tandon 1991; Ventura et al. 1993). Research has demonstrated that behavioral encoding (the expression of emotions) is seriously disturbed in schizophrenia (Berenbaum & Oltmanns 1992; Knight & Valner 1993; Kring et al. 1993; Kring et al. 1994; Kring & Neale 1996).

Much less interest has been shown in the subjective *experience* of emotions in patients with schizophrenia. The study of subjective experiences requires a specific methodology including introspection and self-reports. Such research strategies are more difficult to implement and are often considered unreliable, particularly in patients with schizophrenia (Andreasen 1982; Silk & Tandon 1991). However, there is some evidence that patients experience the full range of intense emotions (Berenbaum & Oltmanns 1992; Kring et al. 1993; Kring et al. 1994; Kring & Neale 1996). Bouricius (1989) described her son, who has schizophrenia and had been assessed by several psychiatrists as emotionally blunted. The son wrote extensive diaries describing the emotions that were raging inside him. The richness of the emotional life reflected in the diaries thus contrasted sharply with his blunted emotional expression. Self-report questionnaires have been used in laboratories to study change in inner experiences under simple experimental conditions, such as

looking at videotapes or drinking good- or bad-tasting beverages. These studies confirmed that patients with schizophrenia do experience as intense and diverse emotions as normal controls (Berenbaum & Oltmanns 1992; Kring et al. 1993; Kring et al. 1994; Kring & Neale 1996). The question remains, however, whether patients with schizophrenia experience the full range of emotions in the complex natural situations of daily life.

The Experience Sampling Method (ESM) was developed to systematically and validly assess experiences and behaviors as they occur in daily life, as well as changes in response to environmental challenges (Csikszentmihalyi & Larson 1987; Devries 1992). ESM has been used to study various aspects of daily experience in chronic schizophrenia, including the quality of life, the experience of hallucinations, and daily patterns of time use (Delespaul & Devries 1987; Devries & Delespaul 1989; Delespaul 1995), and the validity and reliability of ESM in this context has been documented (Delespaul 1995).

In the present study, we used ESM to assess the emotional experiences of patients with schizophrenia in daily life. We compared both the intensity and the variability of positive and negative mood states of patients versus normal control subjects. We also compared subgroups of patients with schizophrenia with either blunted or nonblunted emotional expression on these ESM measures of emotional experience.

Methods

Subjects

Participants included 58 schizophrenia spectrum disorder patients and 65 control subjects. Patients were recruited through the clinical and ambulatory mental health facilities in Maastricht, the Netherlands. They were referred with a diagnosis of schizophrenia according to DSM-III-R criteria (APA 1987) by their treating psychiatrist. The diagnoses of 44 subjects were later cross-checked using the Operational Criteria Checklist (Mcguffin et al. 1991). This confirmed the clinical diagnoses: primarily schizophrenia (n = 39) with small groups of atypical psychosis (n = 2), delusional disorder (n = 1) and schizoaffective disorder (n = 2), according to the DSM-III-R criteria. The sample included highly symptomatic paranoid and

catatonic patients. Of the 70 patients with schizophrenia recruited, 12 were unable to comply with the demanding research protocol (see below). Dropout was unrelated to illness severity. The final sample included 36 men and 22 women, with a mean age of 36 years (Standard Deviation (*SD*) = 9). Most patients were stabilized on antipsychotic medication (in haloperidol equivalents: mean (*M*) = 11.7 mg/day, *SD* = 14.7, range 0 - 60 mg/day); 2 patients were not medicated. Half of the sample were outpatients, 20 percent lived in transitional care facilities, and 30 percent were inpatients. Of the 49 patients for whom data were available, 31 percent had finished elementary school only, 52 percent had finished secondary school, and 18 percent had attended higher education.

The control subjects (39 men, 26 women) were recruited from primary care practices and from the university student population. The former were healthy and symptom-free, according to the Diagnostic Interview Schedule (Burke 1986) and the Symptom Checklist (Arrindell & Ettema 1981), the latter according to the Differential Personality Questionnaire (Tellegen 1982). The mean age was 30 years (*SD* = 14). Twelve percent had finished elementary school only, 20 percent had completed secondary school, and 68 percent had attended higher education. The control sample was significantly more highly educated than the schizophrenia sample (Mann-Whitney, $z = -4.8$, $p < 0.0001$).

ESM

ESM is a random time sampling self-assessment technique. Subjects received a digital wristwatch and a set of ESM assessment forms. Ten times a day on six consecutive days, the watch emitted a beep at unpredictable moments between 7:30 a.m. and 10:30 p.m. After every beep, reports of thoughts, current context (activity, location, company), moods, and severity of symptoms were collected. The self-assessments were rated on 7-point Likert scales, ranging from 1 "not at all" to 7 "very". Open-ended descriptions of thoughts and context were later coded by the research staff.

The ESM procedure was explained during an initial briefing session. Researchers assessed that all subjects were able to understand the 7-point Likert scale format. Subjects were instructed to write down their reports immediately after the beep, thus minimizing memory distortions, and to record the time at which they completed the form. Furthermore, we repeatedly phoned the subjects to assess whether they were

complying with the briefing instructions. All reports completed more than 15 minutes after the signal were excluded from the analysis. Delespaul (1995) has shown that reports completed after this interval were less reliable and consequently less valid. Twelve subjects with fewer than 20 valid reports were excluded from the analyses (described as dropouts above). The schizophrenia subjects included in this study produced an average of 42 valid reports ($SD = 9$). An identical number was obtained from the control subjects ($M = 42$, $SD = 8$). Only valid reports were included in the analyses.

Assessment of Emotional Experience

The ESM assessment forms contained 10 Likert-type items about mood states. Positive and negative emotions were analyzed separately. Happy, cheerful, relaxed, and pleased formed the positive mood scale (Pos; Cronbach's alpha = 0.79). The negative mood scale (Neg) was composed of feeling angry/irritated, lonely, anxious, insecure, down, and guilty (Cronbach's alpha = 0.92). *Emotional intensity* (INT) was measured by computing the positive and negative scale totals for each moment and averaging these over all reports for each subject (see appendix, equation [1]). Emotional variability was measured in two ways. *Profile divergence* (P-VAR) was computed by calculating the average score on every mood scale separately for each subject. Absolute deviation scores from individual means were calculated and averaged into a positive and negative scale score for each moment and each subject. These were averaged over the reports of each subject (see appendix, equation [2]). P-VAR indicates how much the beep scores differed from the mean emotional profile of that subject. *Variability over time* (T-VAR) was obtained by calculating the difference of all mood items on two consecutive beeps. We then calculated the mean of the absolute difference scores on the positive and negative mood scales and averaged these for every subject (see appendix, equation [3]). Rapid mood changes from one moment to the next result in a high T-VAR.

BPRS

Within a week after the ESM period, a trained research assistant obtained BPRS (Overall & Gorham 1962) ratings for 51 of the 58 patients with schizophrenia via a semistructured interview (range 1 "not present" to 7 " very seriously present"). Flat

affect was scored based on the behavior shown by the patient during this interview (Ventura et al. 1993). A cutoff score of 3 was used to differentiate a blunted (n = 30, M = 3.9, SD = 0.9) from a nonblunted subgroup (n = 21, M = 1.4, SD = 0.5). High scores reflect observations of a restricted range in emotional expression of face, voice or gestures.

Analysis

We first compared ESM mood ratings of patients with schizophrenia to those of control subjects. Second, we compared subgroups of blunted and nonblunted patients with schizophrenia on these measures. Analyses were performed for all three dimensions (INT, P-VAR, and T-VAR) and for positive and negative emotions separately. Two-tailed t tests for independent samples were used, with alpha = 0.05 (SPSS 1990).

Results

The frequency distributions of the positive and negative mood scale are presented for the schizophrenia and control subjects in figures 1A and 1B. Both samples used the same range of response categories with similar frequency distributions, which indicates that the schizophrenia subjects were not responding at random to the Likert scales.

figure 1 A. *Frequency distribution of the 7-point-Likert scale of the combined positive mood items.*

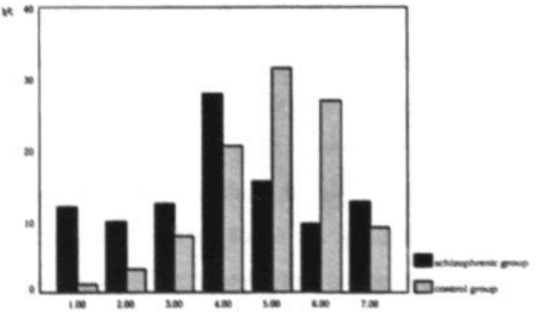
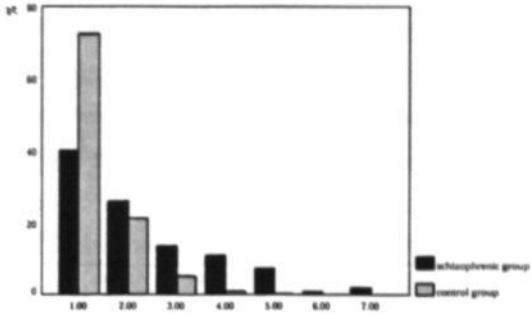


figure 1 B. *Frequency distribution of the 7-point-Likert scale of the combined negative mood items.*



Patients with schizophrenia compared to normal controls

The results of the comparison between patients with schizophrenia and controls are displayed in table 1. The mean intensity of positive emotional experiences was significantly lower for patients with schizophrenia than for control subjects; t (84) = -4.9, $p < 0.001$. On the negative mood scale, in contrast, the patients with schizophrenia showed significantly more emotional intensity than the control subjects; t (69) = 5.9, $p < 0.001$.

The profile divergence in emotional experience for the positive scale was lower for patients with schizophrenia than for control subjects; t (87) = -3.3, $p < 0.001$. On the negative scale, patients with schizophrenia were more variable than the control subjects; t (120) = 2.73, $p < 0.05$.

Finally, the emotional variability over time was studied. Patients with schizophrenia did not differ from controls in variability in positive moods; t (96) = 1.7, *ns*. For negative moods, however, patients with schizophrenia scored significantly higher than the control subjects; t (82) = 3.9, $p < 0.001$.

table 1. *Scores for the schizophrenia and control groups on measures of positive and negative moods*[1]

	Mean Score (SD)					
	Intensity		Profile Divergence		Variability over time	
Group	Pos	Neg	Pos	Neg	Pos	Neg
Schizophrenia	4.14 (1.22)	2.34 (1.12)	0.75 (0.14)	0.59 (0.26)	1.17 (0.66)	0.84 (0.68)
Control	5.01 (0.65)	1.42 (0.39)	0.91 (0.35)	0.45 (0.32)	1.00 (0.43)	0.46 (0.34)

[1] Neg = negative mood; Pos = positive mood; SD = standard deviation.

Blunted versus nonblunted patients with schizophrenia

Table 2 presents the results for the blunted and nonblunted schizophrenia subgroups. No significant difference was found between the two subgroups on any of the three measures of emotional experience. Blunted and nonblunted schizophrenia subjects did not differ significantly in the intensity of positive or negative mood; t (49) = 1.1, *ns* and t (49) = -1.3, *ns*. Results were also nonsignificant for profile divergence (pos: t (47) = 1.15, *ns*; neg: t (47) = -0.8, *ns*.) and for variability over time (pos: t (49) = 0.9, *ns*; neg: t (27) = -0.4, *ns*).

table 2. *Scores for the blunted and nonblunted schizophrenia subgroups on measures of positive and negative moods*[1]

	Mean Score (SD)					
	Intensity		Profile Divergence		Variability over time	
Group	Pos	Neg	Pos	Neg	Pos	Neg
Blunted	4.03 (1.30)	2.10 (1.10)	0.73 (0.16)	0.60 (0.25)	1.10 (0.72)	0.84 (0.78)
Nonblunted	4.42 (1.10)	2.50 (1.20)	0.76 (0.14)	0.56 (0.28)	1.27 (0.61)	0.70 (0.44)

[1] Neg = negative mood; Pos = positive mood; SD = standard deviation.

Discussion

In order to study affective experience in schizophrenia, we assessed positive and negative emotions in the context of daily life. In comparing schizophrenia subjects with nonpatient controls, we found no evidence for lessened experience of negative emotions, nor was the variability of positive emotions over time diminished for the schizophrenia subjects. The results did indicate that the intensity and deviations from their personal profile of positive emotional experiences were reduced for schizophrenia subjects. Schizophrenia subjects with blunted versus nonblunted BPRS ratings reported the same dynamics of emotional experiences during the day, suggesting that emotional expression as assessed during an interview is unrelated to emotional experience in daily life. The finding that schizophrenia patients are more emotionally active and responsive than is usually assumed using behavioral observations may be of considerable importance for practitioners involved in the rehabilitation process.

These findings replicate the results of Blanchard et al. (1998), who reported less positive affect and significantly greater negative affect in patients with schizophrenia, compared with controls. The results of laboratory studies also support a greater intensity of negative feelings in schizophrenia subjects (Berenbaum & Oltmanns 1992; Kring et al. 1993; Kring & Neale 1996), but in contrast to our results, do not support lower intensities of positive moods. An explanation for these differences could lie in the absence of social context in the laboratory studies. In the naturalistic context of the current study, it is possible that patients with schizophrenia were indeed capable of experiencing the same positive moods as normal controls but engaged less often in situations that are likely to elicit positive experiences. For example, Barge-Schaapveld and colleagues (1997) described activity-related ratings of "feeling happy". The highest positive emotions were reported during hobbies, sports, and social activities, whereas watching television and doing nothing were associated with the lowest rated happiness. Neither the pattern of activity-related positive emotions nor the overall intensity differed between patients with schizophrenia and normal controls with the exception of social activities; these were accompanied by less intense positive moods in patients with schizophrenia. Delespaul (1995) reported that, compared to normal control subjects, patients with schizophrenia described

themselves as "doing nothing" five times more often. This difference in time use could account for the lower intensity of positive mood states in individuals with schizophrenia. Blanchard et al. (1998) also reported a correlation between poor social functioning and low-trait positive affect.

Other nonintrinsic influences -for example, specific family interaction patterns- may also have had an impact. Expressed emotion (EE) research has shown that patients with schizophrenia are highly sensitive to criticism and emotional overinvolvement by family members (high EE). Not only is living with a high-EE family member related to a poor illness course (Brown et al. 1972; Vaughn & Leff 1976), but patients with schizophrenia living in high EE environments also perceive these family members as more critical (compared with patients living in low EE environments; (Tompson et al. 1995)). Family members of patients with schizophrenia are also more critical and hostile than family members of patients with organic diseases (Bressi 1996) and show higher levels of communication deviance, defined as unclear, amorphous, disruptive, or fragmented communication (Miklowitz 1994). These environmental characteristics could have contributed to lower positive emotions in this group.

No evidence for a reduction in the intensity or variability of negative emotions was found. The intensity and deviation from personal profile of positive emotional experiences, although significantly decreased, could hardly be called flat. The schizophrenia subjects scored an average of 4 on the 7-point Likert scales, indicating that, to some extent, they were able to experience positive emotions. This lower intensity or diminished capacity to enjoy is described by several authors (Kayton & Koh 1975; Krupa & Thornton 1986).

When comparing the blunted and nonblunted schizophrenia subgroups, we found no differences in self-reports of emotional experience. Apparently, the level of emotional expression observed in the clinical interview did not necessarily correspond with the underlying emotional experiences assessed with ESM in daily life. In other words, flattened behavioral expression does not necessarily reflect flattened inner experience (Berenbaum & Oltmanns 1992; Kring et al. 1993; Kring & Neale 1996). This apparent gap between expression and emotion in patients with schizophrenia presents an intriguing challenge for researchers to clarify the nature, function, and

cause of this disparity and a challenge for clinicians to find ways of integrating these underlying emotions in therapy.

Some methodological considerations should be noted. Since ESM samples subjects frequently in normal daily life circumstances, missing data are inevitable. Delespaul (1995) has shown that most missing data occur at moments when it is impossible to hear the signal (noisy environments or during sleep).

One research assistant conducted all of the BPRS interviews in this study, so interrater reliability could not be assessed. However, the research assistant was trained and supervised following the guidelines set out by Ventura et al. (1993); moreover, in another study where the same assistant was one of two raters for each BPRS interview, interrater reliability on the item "flat affect" was high ($\kappa = 0.85$).

Finally, most patients with schizophrenia in this study were medicated. Blanchard & Neale (1992) argued that medication induces a state very similar to flattened emotional expression. However, little is known about the influence of medication on emotional experience.

In conclusion, patients with schizophrenia showed more intense and variable negative emotional experiences than controls. In contrast, positive emotions were less intense and the overall variability was reduced. Behavioral blunting of affect was unrelated to self-reported emotional experience. The finding that patients with schizophrenia are more emotionally active and responsive than is assumed using behavioral and external observations may be of central importance for practitioners involved in the rehabilitation process. Adequate assessments of the patient's positive experience can help clinicians to recognize effective coping and to stimulate patients to engage in emotionally rewarding activities and social contexts more often. This would allow customizing of intervention strategies to the patient's individual needs and strengths.

Appendix

These are the formulas for the three emotional experience measures for the positive emotions [p] (mean of 'happy', 'cheerful', 'relaxed' and 'pleased'). The formulas can be applied by analogy to the definitions of negative emotions [n] (mean of 'angry/irritated', 'lonely', 'anxious', 'insecure', 'down' and 'guilty').

Emotional intensity: $$INT_{i/p} = X_{i.[p]} \qquad [1]$$

Profile divergence $$P\text{-}VAR_{i/p} = \frac{\sum_{j=1}^{n_i} \frac{\sum_{h=1}^{k_p} |X_{ijh} - X_{i.h}|}{k_p}}{n_i} \qquad [2]$$

Variability over time: $$T\text{-}VAR_{i/p} = \frac{\sum_{j=1}^{n_i} |X_{i\,j\,[p]} - X_{i\,(j-1)\,[p]}|}{n_i} \qquad [3]$$

X_{ijh}

i = subjectnumber [1 - m] (with m=58 for schizophrenic subjects and m=65 for normal controls)
j = beepnumber [1 - n_i] (number of valid beeps for subject i)
h = moodscale [1 - k_i] (with k_p = 4 for positive and k_n = 6 negative emotions)

$X_{i.[p]}$

i = subjectnumber
. = mean over all beeps
[p] = mean of all positive moodscales; [n] = mean of all negative moodscales

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CHAPTER 3

The context of delusional experiences in the daily life of patients with schizophrenia [1]

Abstract

Global characteristics and psychosocial risk factors related to delusions have been identified. The present study extends these findings to the level of everyday functioning, identifying characteristics of delusional moments (DMs) and contextual risk and protective factors for delusional exacerbations in daily life. Data were collected using the Experience Sampling Method (ESM), a time-sampling technique. Forty-eight chronic patients diagnosed with schizophrenia rated the intensity of pathological symptoms and mood states and described their thoughts and the environmental context during consecutive moments in daily life. Delusions were defined on the basis of self-rated suspicion, preoccupation, feeling controlled, and coded thought pathology. Daily context included current activity, persons present, and location. Characteristics of DMs and non-delusional moments (nDMs) were compared, and a multilevel logistic regression model was used to identify contexts that might trigger or prevent DMs. On average, patients experienced delusions less than one-third of the time. DMs were characterised by higher negative affect and lower positive affect. The presence of family or acquaintances decreased the risk of subsequently experiencing a DM, whereas withdrawal from activities increased this risk. Data support the validity of ESM for investigating delusions in schizophrenia. Daily life contexts appear to alter the probability that delusions will occur. Knowledge about such contexts may therefore be useful in helping patients develop better coping strategies and in creating therapeutic interventions that can lessen emotional distress.

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[1] Inez Myin-Germeys, Nancy A. Nicolson and Philippe A.E.G. Delespaul (2001). The context of delusional experiences in the daily life of patients with schizophrenia. *Psychological Medicine*, 31:489-498.

Introduction

Delusions are complex phenomena that occur in a variety of psychiatric disorders. Together with hallucinations, they are considered the most important positive symptom in schizophrenia (DSM-IV: APA 1994). In order to design successful interventions, more need to be known about the characteristics of delusions, their variability over time, and possible triggering factors.

Research over the last decades has led to the conclusion that delusions represent points along a continuum from normal to highly abnormal patterns of thoughts. In addition, delusional belief systems can be characterized according to a number of separate dimensions (Strauss 1969). One dimension that is acknowledged to be of central importance is belief conviction, the extent to which an individual is convinced of the objective reality of the thought (Kendler et al. 1983; Garety & Hemsley 1994; Oulis et al. 1996). Other dimensions include bizarreness (Kendler et al. 1983; Garety & Hemsley 1994; Oulis et al. 1996), subjective distress (Garety & Hemsley 1994; Oulis et al. 1996), obtrusiveness and preoccupation (Kendler et al. 1983; Garety & Hemsley 1994), and concern (Garety & Hemsley 1994). Dimensions of delusions appear to be largely independent of each other and to vary in intensity over time. Garety and Hemsley (1994), for example, showed that the degree of belief conviction and preoccupation could vary considerably over a period of weeks.

Variability over time in delusional dimensions has been described in relation to the effects of therapeutic interventions (Garety & Hemsley 1994). Other studies have sought to identify precipitating factors that contribute to delusional relapse. These include fear of losing control (Melges & Freeman 1975), insecurity, restriction of freedom, social and sensory isolation, and an intolerable injury to self-esteem (Roberts 1992). To our knowledge, no research has been done on factors in the daily environment that might influence the occurrence of delusions. More empirical research is necessary to clarify "the cross-sectional and longitudinal vicissitudes and contexts of delusions" (Strauss 1991). Knowledge of risk and protective factors in daily life could lead to new clinical strategies to diminish the impact of delusions on the quality of life in schizophrenia.

The current study was designed to investigate delusions at the microscopic level of everyday functioning. What are the most characteristic features of delusional moments in daily life and under which specific contextual conditions do delusions occur? Additional aims of the study were to investigate variability in the presence of delusions over hours and days and to identify aspects of daily experience that may precipitate delusional moments. We used the Experience Sampling Method (ESM), which entails the collection of self-report data about thoughts, mood, and the context of experiences in the natural flow of daily life (Csikszentmihalyi & Larson 1987; Devries 1992). Previous applications of ESM in schizophrenia (Delespaul 1995) and other psychiatric disorders (Devries 1992) have demonstrated the feasibility, validity, and reliability of the method in these populations. Schizophrenic symptoms such as hallucinations (Delespaul 1995; Delespaul et al. 1998) and flat affect (Myin-Germeys et al. 2000) have previously been investigated with this method.

Methods

Subjects

Sixty-four patients diagnosed with schizophrenia were recruited through clinical and ambulatory mental health facilities in Maastricht, The Netherlands. Of these, 16 patients were unable to comply fully with the research protocol (see ESM, below). The final study sample thus included 48 chronic patients, suffering from a variety of symptoms. Sociodemographic and clinical characteristics of the patient sample are summarized in table 1. The diagnosis of schizophrenic spectrum disorder was made according to *DSM-III-R* criteria (APA 1987) by the treating psychiatrist. For 38 patients, we obtained additional diagnostic information with the Operational Criteria Checklist (Mcguffin et al. 1991); the OPCRIT diagnostic categories (DSM-III-R) were as follows: schizophrenia (n = 34), atypical psychosis (n = 2), delusional disorder (n = 1) and schizo-affective disorder (n = 1).

table 1. *Patient characteristics*

	Sociodemographic variables
Gender	28 male, 20 female
Age (years)	*M* = 35 years, *SD* = 7 (range 21-54)
Marital Status	17% Married or living together 15% Divorced 68% Single
Living situation	17% Living alone 36% Living with partner or family 47% Living in sheltered home
Work situation	13% Significant household tasks 4% School or regular job 56% Unemployed 27% Sheltered work
Education (highest level attended)	27.5% Elementary school 50% Secondary school 22.5% Higher education
	Clinical variables
BPRS scores[1]: delusional thought content hallucinations flat affect	*M* = 3.3, *SD* = 2.1 (range 1 - 7) *M* = 3, *SD* = 2.2 (range 1 - 7) *M* = 3, *SD* = 1.5 (range 1 - 6)
Duration of illness	*M* = 13 years, *SD* = 8 (range 1 - 36)
Neuroleptic treatment dosage (haloperidol equivalents)	*M* = 11.17 mg/day, *SD* = 15.08 (range 0-60)

[1] BPRS scores were available for 42 subjects

BPRS

Within a week after the ESM period, a trained research assistant assessed 42 of the 48 patients with the Brief Psychiatric Rating Scale (BPRS), a semi-structured interview (Ventura et al. 1993). The 24 BPRS items are scored on scales ranging from 1 "not present" to 7 "very strongly present". The items "unusual thought content", "hallucinations" and "flat affect" were used in the current analysis. In a related study in which each BPRS interview was scored by two raters (including the current rater),

interrater reliability for these three items was high (kappas of 0.75, 0.79, and 0.85, respectively).

ESM

The Experience Sampling Method is a random time-sampling, self-assessment technique. Subjects received a digital wristwatch and ESM assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal at unpredictable moments between 7.30 a.m. and 10.30 p.m. After every "beep", reports of thoughts, moods, current context (activity, persons present, location), and severity of symptoms were collected.

The ESM procedure was explained during an initial briefing session; at the end, subjects completed a practice form to confirm that they understood how to fill in each item. Subjects were instructed to complete their reports immediately after the beep, thus minimizing memory distortions, and to record the time at which they completed the form. During the actual sampling period, research staff contacted subjects frequently by phone to assess whether they were complying with the instructions. All reports completed more than 15 minutes after the signal were excluded from the analysis. Delespaul (Delespaul 1995) has shown a drop in the reliability of reports completed after this interval. Of the 16 subjects excluded from the analysis (see Subjects, above), 12 subjects had fewer than 20 valid reports and 4 subjects had fewer than 20 reports with the items concerning delusions filled in. The remaining 48 schizophrenia subjects each completed an average of 42 valid reports ($SD = 9$).

Open-ended descriptions of thoughts and contexts were coded by the research staff, and the original coding categories were further collapsed prior to statistical analysis. The subset of ESM measures used in the current analysis are summarized in table 2.

table 2. Description of the ESM measures used

Delusions (dependent variable)	
Preoccupation (R)	'I'm preoccupied by my thoughts'
Suspicion (R)	'My thoughts are suspicious'
Feeling controlled (R)	'My thoughts are being influenced'
Thought pathology (C)	'What am I thinking about at this moment?' (categories: not delusional, delusional)
Thoughts	
Valence (R)	'My thoughts are *pleasant / normal / clear*'
Content (C)	'What am I thinking about at this moment?' (categories: situations, psychological wellbeing, physical wellbeing, other, nothing)
Nature (C)	'What am I thinking about at this moment?' (categories: neutral, evaluation, introspection, planning)
Mood	
Negative states (R)	'I feel anxious / angry / lonely / insecure / unwell' and dislike of activities ('I would rather do something else')
Positive mood (R)	'I feel cheerful / relaxed'
Symptoms	
Auditory hallucinations (R)	'I hear voices'
Visual hallucinations (R)	'I am seeing things that are not real'
Context [1]	
Current activity (C)	'What am I doing at this moment?' (categories: *doing nothing, working (including study and volunteer work) and leisure activities*)
Change in activity	Changes between 2 contingent reports (categories: *no change, change to doing nothing, starting to work, starting a leisure activity*)
Persons currently present (C)	'Whom am I with at the moment?' (categories: *nobody present, family and acquaintances, strangers*)
Change in company	Changes between 2 contingent reports (categories: *no change, transition to being alone, transition to being with family or acquaintances, transition to being with strangers*)
Current location (C)	'Where am I?' (categories: *at home, network (including familiar places such as family's house and work) and public place (grocery store, transportation, on the street)*)
Change in location	Changes between 2 contingent reports (categories: *no change, change to home, transition to network, transition to public place*)

(R) Subject ratings on 7 point Likert-scales (from 1 'not at all' to 7 'very').
(C) Subjects' responses to open questions, coded by research staff.
[1] Context variables were dummy coded for the multilevel analysis. For current activity, doing nothing was chosen as the reference group and two dummy variables were created, namely working (coded 1 when working and 0 in all other cases) and leisure activity (coded 1 during leisure activity and 0 in all other cases). The βs for these dummy variables indicate whether there is an increase or decrease as opposed to the reference group. The same principle was used for all other context variables (the reference group is underlined)
Inter-rater agreement (kappas) for activity (0.91), location (0.94), and persons (0.96) (Van Eck 1996).

Definition of delusional moments

Assessing delusions on the basis of self-report can only be done indirectly, as not all psychotic symptoms are recognized as such by chronic schizophrenia patients. Although patients can, for example, distinguish between hearing real voices and verbal hallucinations (Romme et al. 1992; Delespaul 1995), poor insight into delusions (Debowska et al. 1998; Schwartz 1998) makes it impossible for patients to report their presence or absence at specific moments in time. Self-report instruments for evaluating delusional thoughts do exist, such as the Personal Questionnaire (Brett Jones et al. 1987; Chadwick & Lowe 1990; Garety & Hemsley 1994), but these are not appropriate for repeated administration during daily activities in a large subject sample.

To circumvent these problems, three items intended to assess aspects of mental state that have been directly associated with delusions in schizophrenia (Junginger et al. 1992; DSM-IV: APA 1994) were added to the ESM booklet. These were "preoccupation", "suspicion", and "feeling controlled", rated on 7-point Likert scales. A cut-off point for each self-rated variable was set at one SD above the mean of all patient ratings, with individual ratings above these points considered delusional. The use of conservative cut-off points was intended to reduce false positives and to limit the analysis to relatively severe delusions. A fourth measure of DM was based on descriptions subjects provided of their current thoughts. Responses were coded according to degree of evident thought pathology. Prior to statistical analysis, this variable was dichotomized so that unambiguously abnormal thoughts were considered delusional. Interrater reliability for thought pathology, as established in a separate study with three raters, is high ($\kappa = 0.91$).

A delusional moment (DM) was identified if any one of the following four criteria were met: suspicion rating ≥ 5 ($M = 2.1$, $SD = 1.8$); preoccupation rating ≥ 6 ($M = 2.7$, $SD = 2.1$); feeling controlled rating ≥ 6 ($M = 2.6$, $SD = 2.1$); and, thought pathology, thoughts coded as delusional.

The following are examples of reported thoughts and how they were coded: "I'm thinking about the war factories that have to be built in the underdeveloped regions of outer space" (thought pathology, delusional; content, situation; nature, planning);"You know it was a conspiracy to get you to the beautician" (thought pathology, delusional; content, situation; nature, neutral); "I'm thinking about my financial situation" (thought

pathology, non-delusional; content, situation; nature, neutral);"I should start doing something else, because all the knitting is not doing me good" (thought pathology, non-delusional; content, psychological well-being; nature, introspection).

Statistical procedures

Unilevel analyses

All unilevel analyses were performed with the Statistical Package for the Social Sciences (SPSS 1990). Tests were two-tailed, with significance level set at $\alpha = 0.05$, unless otherwise stated.

Three analyses were performed to assess the validity of the ESM definition of DM. Firstly, kappas were calculated per subject to measure agreement among the four dichotomized criterion variables for defining DMs. Kappas that could not be calculated because of a lack of variance in one of the variables were set to 1 if there was a perfect match or to 0 in all other cases. A one-sample *t* test was conducted to test whether the kappas were significantly different from zero. Secondly, the correlations between the frequency of DMs in each subject and the separate BPRS symptom ratings for unusual thought content, hallucinations and flat affect were examined. If ESM-defined DMs are specifically related to delusions and not just to schizophrenic psychopathology, one would expect that *r* (% DMs, BPRS unusual thought content) > *r* (% DMs, BPRS hallucinations) > *r* (% DMs, BPRS flat affect). Finally, we used an independent sample *t* test to compare the frequency of DMs in patients with the same measure in a group of 42 healthy control subjects recruited from the community with the expectation that patients would have more frequent DMs than controls.

To assess whether specific mood states, contexts, or thought characteristics were associated with DMs, the mean score for each subject on each ESM variable was first calculated separately for DMs and for nDMs. Subject mean scores under each of the two conditions were then compared with a paired *t* test.

Multilevel analysis: Contextual influences on DMs

Multilevel or hierarchical linear modelling techniques (Goldstein 1987) are ideally suited for the analysis of ESM data (Schwartz & Stone 1998; Affleck et al. 1999), in which

repeated ESM observations (beeps) are nested within subjects. The statistical program MIXOR (Hedeker & Gibbons 1996) for multilevel logistic regression was used to identify triggering or protective factors in the daily environment for DM, a dichotomous outcome variable. To extend the univariate analysis of concurrent relationships, context variables on previous moments (t-1) were added in a multilevel model predicting the presence or absence of delusions at the target moments (t). All context variables were dummy coded (see footnote to table 2). Sex, a subject-level variable, was dummy coded '0' for male and '1' for female. The βs are the fixed regression coefficients of the predictors.

The expectation of DM is related to its determinants by the regression equation:

$$\begin{aligned}\text{Log (odds E (DM)} = \beta_0 &+ \beta_1 \text{ (persons present at 't-1')} + \beta_2 \text{ (change in company)} \\ &+ \beta_3 \text{ (activity at 't-1')} + \beta_4 \text{ (change in activity)} \\ &+ \beta_5 \text{ (location at 't-1')} + \beta_6 \text{ (change in location)} \\ &+ \beta_7 \text{ sex} + r\end{aligned}$$

The residual vector r can be decomposed in two terms, namely r_2 representing the variability in DM per person that is not explained by the predictors and r_1 representing the residual variability in DM. A forward stepwise procedure was used; the predictors were selected on theoretical grounds, using both the significance of the individual weight parameter (using two-tailed significance tests) and the significant improvement of the overall fit of the model (using a likelihood ratio test (Snijders & Bosker 1999) p. 88).

By design, this model applies to the subset of DMs (at time t) that are preceded (at time 't - 1') by nDM. Observations at 't - 1' in which DMs were present or data were missing (i.e. items not completed or when t = first beep of the day) were therefore excluded from the model, resulting in a reduction of sample size from 2091 to 581 observations.

Results

The validity of the ESM definition of delusions

The majority of patients (41 of 48) experienced DMs at some time during the ESM sampling period. With the percentages split according to each of the four variables used to define DMs, 27 subjects reported suspicion (frequency: M = 19.1%, SD = 24), 31

subjects reported preoccupation (frequency: $M = 21.8\%$, $SD = 23$), 29 subjects reported feeling controlled (frequency: $M = 22.4\%$, $SD = 22.9$) and 27 subjects displayed thought pathology (frequency: $M = 27.6\%$, $SD = 26.46$). The kappas of association among the criteria for DM are shown in table 3. All kappas are in the "fair" to "moderate" range (Landis & Koch 1977), which provides evidence that the four criterion measures represent the common construct delusion.

On average, subjects reported DMs 32% of the time ($SD = 29.8$, range 0 – 100%). Subjects with DM frequency 0% ($n = 7$) or 100% ($n = 1$) were excluded from further analyses. As predicted, the ESM measure "% of time with DMs" was most highly correlated with the BPRS item "unusual thought content" ($r = 0.56$, $p < 0.001$); DM correlations with BPRS items "hallucinations" and "flat affect" were smaller ($r = .36$, $p < 0.02$, and $r = 0.18$, ns, respectively). In addition, the patient group had much more frequent DMs ($M = 32\%$, $SD = 29.8$) than the healthy control group ($M = 0.15\%$, $SD = 0.24$; $t(88) = -6.92$, $p < 0.0001$), who rarely reported any DM.

table 3. *Level of agreement (corrected kappas) among the four criteria used to define DM*[1]

	Suspicion	Preoccupation	Feeling controlled	Thought Pathology
Suspicion	-			
Preoccupation	0.37 (0.43) ****	-		
Feeling controlled	0.37 (0.43) ****	0.28 (0.44) ****	-	
Thought pathology	0.46 (0.41) ****	0.35 (0.41) ****	0.28 (0.44) ****	-
DM	0.51 (0.38) ****	0.25 (0.41) ****	0.51 (0.39) ****	0.35 (0.44) ****

[1]All variables were scored either 1 or 0, based on the cut-off scores. Mean kappas (SD) over subjects are shown.
*** $p < 0.0001$

Characteristics and contexts of DMs

Table 4 presents characteristics of delusional thoughts as compared to non-delusional thoughts. Subjects rated thoughts during DMs as significantly less pleasant than during nDMs; ratings of thoughts as "common" or "clear" were similar, however. While more

time was spent thinking about situations during nDMs, thoughts concerning psychological well-being were more common during DMs. Thoughts during DMs tended to be more often introspective ($p < 0.07$), whereas thoughts during nDMs were more often neutral. Other differences were not statistically significant.

table 4. *Comparison of thought characteristics during DM versus nDM*[1]

	Descriptors[2]			Content[3]				Nature[3]			
	Pleasant	Common	Clear	Situations	Psychological Well-being	Physical well-being	Nothing	Neutral	Evaluation	Introspection	Planning
DM	3.6 (1.8)	4.2 (1.6)	4.9 (1.5)	0.26 (0.27)	0.25 (0.28)	0.08 (0.23)	0.05 (0.12)	0.45 (0.33)	0.23 (0.28)	0.13 (0.22)	0.10 (0.19)
nDM	4.3 (1.2)	4.5 (1.2)	5.3 (1.3)	0.40 (0.20)	0.14 (0.14)	0.05 (0.06)	0.04 (0.13)	0.54 (0.24)	0.27 (0.20)	0.06 (0.08)	0.10 (0.12)
$p <$	.05	ns	ns	.05	.05	ns	ns	.05	ns	ns	ns

[1] Notes. Significance levels are for 2-tailed paired *t* tests ($n = 41$).
[2] Mean ratings (*SD*).
[3] Estimated mean frequency (*SD*) for each category of thought.

With respect to concurrent emotional states and symptoms (see table 5), DMs were accompanied by significant elevations in negative feelings, including anxiety, anger, loneliness, uncertainty, feeling unwell, and dislike of the current activity. In contrast, positive states (cheerful and relaxed) were significantly lower during DMs. Patients reported more intense auditory hallucinations (but no difference in visual hallucinations) during DMs. Daily contexts (current activity, persons currently present, current location) were, however, surprisingly similar for DMs and nDMs (see table 6).

table 5. *Comparison of mood states and symptoms during DM versus nDM*[1]

	Negative mood[2]						Positive Mood[2]		Hallucinations[2]	
	An-xious	Angry	Lonely	Inse-cure	Feeling unwell	Dislike activity	Cheer-ful	Re-laxed	Audi-tory	Visual
DM	2.4 (1.4)	2.5 (1.4)	2.6 (1.5)	3.1 (1.5)	2.5 (1.4)	3.3 (1.8)	3.7 (1.4)	3.9 (1.4)	1.8 (1.3)	1.5 (0.8)
nDM	2.0 (1.2)	1.8 (1.0)	2.2 (1.4)	2.4 (1.3)	2.1 (1.1)	2.6 (1.2)	4.2 (1.2)	4.2 (1.2)	1.5 (0.9)	1.4 (0.8)
$p \leq$	.05	.001	.05	.001	.05	.05	.05	.05	.05	ns

[1] Notes. Significance levels are for 2-tailed paired *t* tests ($n = 41$).
[2] Mean ratings (*SD*).

table 6. *Comparison of contexts during DM versus nDM*[1]

	Current activity[2]			Persons currently present[2]			Current location[2]		
	Doing Nothing	Working	Leisure Activities	Alone	With acquain-tances	With stran-gers	At home	Network	Public Place
DM	0.17 (0.25)	0.23 (0.25)	0.59 (0.31)	0.36 (0.3)	0.56 (0.32)	0.05 (0.16)	0.62 (0.37)	0.24 (0.3)	0.12 (0.22)
nDM	0.16 (0.2)	0.30 (0.18)	0.56 (0.20)	0.44 (0.24)	0.49 (0.26)	0.04 (0.07)	0.68 (0.25)	0.18 (0.19)	0.12 (0.12)
$p <$	ns	ns	ns	ns	ns	ns	ns	ns	ns

[1] Notes. Significance levels are for 2-tailed paired *t* tests ($n = 41$).
[2] Mean proportion of time (*SD*) spent in this context.

Contextual triggers of DM

We performed a multilevel logistic regression analysis to clarify the contribution of daily context variables as predictors of DMs. Table 7 presents the estimates obtained. The

variables *activity at 't-1'*, *location at 't-1'*, *change in company* and *change in location* had no significant main effects.

Persons present at 't-1' (roughly 90 min earlier) and *changes in activity* between moments 't - 1' and 't' had the largest effects on the probability of DM occurrence. Being with an acquaintance significantly decreased the risk of experiencing DMs. On the other hand, withdrawing from activities (i.e. changing from work or leisure at 't - 1' to doing nothing at 't') significantly increased the risk of a DM.

table 7. *Multilevel model estimates for the occurrence of delusions* [1]

Variable	B	SE B	Z [2]
Intercept	-1.866	0.480	-3.890 ***
	Beep level		
Persons present at 't-1' [3]			
Acquaintances	-0.715	0.342	- 2.093 *
Strangers	0.924	0.523	1.765
Change in activity [3]			
Transition to doing nothing	1.127	0.455	2.475 *
Transition to work	-0.927	0.900	- 1.031
Transition to leisure activity	0.374	0.443	0.844
	Subject level		
Sex (Male = 1; Female = 0)	0.621	0.772	0.804

[1] Notes. The analysis is based on 581 ESM reports from 36 subjects. Four subjects had no consecutive nDM and DM observations and were therefore excluded from the analysis. The following variables had non-significant effects and were therefore not entered in the forward stepwise procedure: change in company, current activity, location, change in location.

[2] Z-values are calculated by dividing the estimated regression coefficient (B) by its standard error (SE B).

* $p < 0.05$, *** $p < 0.001$.

[3] Variable fulfilled = 1; otherwise = 0.

Discussion

Limitations

Confirmatory OPCRIT diagnoses were not available for 10 subjects. However, these patients, who were recruited through the same facilities and therefore diagnosed by the same psychiatrists as the other 38 subjects, did not differ from the OPCRIT-confirmed group on the BPRS item delusional thought (OPCRIT group: $M = 3.1$, $SD = 2.2$; remaining group: $M = 4.3$, $SD = 1.8$; $t(40) = 1.40$, *ns*) or on sociodemographic variables such as marital situation or working situation. Furthermore, the two groups did not differ on mean percentage of time with DMs (OPCRIT group: $M = 30\%$, $SD = 30$; remaining group: $M = 40\%$, $SD = 28$; $t(46) = -1$, *ns*).

Due to the complexity of ESM, a number of patients were unable to comply adequately with the research protocol and were later excluded from the analysis. The mean percentage of time with a DM did not differ, however, in excluded versus included subjects (36% versus 32%; $t(62) = -0.46$, *ns*), which suggests that the included sample was representative of all patients who entered the study.

ESM definition of delusions

The validity of the ESM definition of delusions is crucial to the interpretation of the results. The three ESM self-report items used to define DMs are conceptually related to two of the identified dimensions of delusions in schizophrenia (Strauss 1969), namely delusional content and preoccupation, which lends face validity to the ESM operationalization. Furthermore, the fourth criterion (thought pathology, as evaluated by an independent coder) showed significant associations with each of the three self-report criteria. This strengthens the case for assuming that all four variables represent the same underlying construct and reduces the possibility that associations among the self-report variables are due to shared method variance alone. The positive correlation between frequency of DMs and BPRS scores and the virtual absence of DMs in a group of healthy controls lend additional support to the validity of the ESM definition of delusions.

Characteristics and contexts of delusional experiences

Previous studies have shown that certain dimensions of delusions vary over periods of weeks or months (Brett Jones et al. 1987; Garety & Hemsley 1994) and that the frequency of delusions can be modified by therapeutic intervention (Chadwick et al. 1994). Our data confirm that patients diagnosed with chronic schizophrenia are not involved in delusional thinking all day long. The majority of patients had many moments on which delusions were either totally absent or only weakly present.

In the literature on Cognitive Behavior Therapy (CBT) for psychosis (Fowler et al. 1995), emotional disturbance is recognized as a central aspect of psychosis; unhappiness and worry have been found to be associated with delusional beliefs (Garety & Hemsley 1994). The current study replicates these findings in daily life. Negative affect might be related to the introspective, self-oriented nature of thoughts during DMs (Garety & Hemsley 1994). In an ESM study of healthy individuals, for example, self-referential ideas were accompanied by increased negative affect and decreased motivation (Csikszentmihalyi & Figurski 1982). It is not yet clear, however, whether negative feelings cause self-referential ideas and delusional beliefs, or vice versa (Fowler et al. 1995).

The main goal of contemporary interventions is the reduction of distress and disability associated with symptoms and their attributions (Tarrier 1992; Sensky et al. 2000), for example using Socratic questioning (Rutter & Friedberg 1999) or reinforcement strategies (Corrigan & Storzbach 1993). Finding ways to limit the time spent in delusional thinking might be another valuable therapeutic approach. To this end, factors related to the onset of DMs in daily life need to be identified.

Contextual triggers of delusional experiences

The multilevel analysis indicated that aspects of the daily life context were significant predictors of delusion onset within approximately 90 minutes. More specifically, the presence of acquaintances and family members appeared to be a protective factor. The same has been reported in some expressed emotion (EE) studies. Although EE research has mainly focussed on the increased risk of psychotic relapse when high EE family members are present (Brown et al. 1972; Vaughn & Leff 1976), some studies have also

shown that warmth in low EE family members can have a protective function (Bebbington & Kuipers 1994; Ivanovic et al. 1994). Unfortunately, in the current study no information was available about the high/low EE nature of the relationships with the persons present; however, the fact that patients rated the company of those present as moderately pleasant ($M = 5.5$, $SD = 1.3$ on a 7-point scale) lends some support to the protective function of positively evaluated social contacts. Similarly, Jorgensen & Aagaard (1988) found that frequent social contacts predicted good outcome in patients suffering from delusions. The social interaction with family members might serve as a normalizing force as it continually confronts patients with reality.

The other contextual variable with a significant effect in the multilevel model was transition from involvement in an activity to doing nothing, which increased the risk of experiencing a DM at the next moment. Inactivity has long been acknowledged as a factor contributing to poor outcome in schizophrenia (Wing & Brown 1970; Curson et al. 1992). Indeed, an implicit rationale for vocational therapy is to avoid the danger of inactivity (Lehman 1995). To date, changes in activity have not been studied as a precipitating factor, but they have been recognized as important in attempts to reduce or control psychotic symptoms once present. Breier & Strauss (1983), for example, showed that some schizophrenia patients can control the intensity of their psychotic symptoms by either increasing or reducing their involvement in activities. Falloon and Talbot (1981) have described the importance of increasing activity in reducing auditory hallucinations. Although we were unable to find any significant relationship between increasing activities and a reduced probability of delusional experiences in daily life, we did find a positive relation between a reduction in activities and the presence of DMs. Apparently, a withdrawal from activities is a risk factor in daily life for delusional relapse. One should keep in mind, however, that the causal direction of temporal associations in ESM data cannot be firmly established.

Beyond its usefulness in research, the ESM could prove to be a useful tool in clinical practice, especially in the framework of CBT (Fowler et al. 1995; Kuipers et al. 1997; Haddock et al. 1998). The general approach in CBT for psychotic disorder is based on working towards a collaborative understanding of the development of symptoms and the reduction of distress and disability. An important part of the therapy includes the

examination of the antecedents of the emergence of the psychotic disorder, which will aid in developing a normalizing rationale. Our results suggest that ESM data may be helpful in assessing such antecedents, as well as the degree of distress and disability associated with symptoms in daily life. Guided discovery followed by graded homework tasks are also important elements in CBT for delusions (Sensky et al. 2000). This process could be aided by ESM, providing the therapist with a means to discuss the occurrence of delusional thinking in the context of the patient's actual daily experience.

Finally, ESM could prove useful in the context of clinical trials evaluating the effects of behavioral or pharmaceutical treatments on the frequency and severity of delusions, among other symptoms of schizophrenia.

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CHAPTER 4

Emotional reactivity to daily life stress in psychosis[1]

Abstract

The vulnerability-stress model of psychotic disorders in essence describes an interaction between personal vulnerability and environmental stressors. The present study investigated this interaction and studied emotional reactivity to daily life stress as a vulnerability marker for psychotic illness. Patients with psychotic illness (n = 42), first-degree relatives (n = 47) and control subjects (n = 49) were studied with the Experience Sampling Method (ESM is a structured diary technique assessing thoughts, current context and mood in daily life) to assess 1) appraised subjective stress of daily events and smaller disturbances in daily life and 2) emotional reactivity conceptualised as changes in both negative affect and positive affect. Multilevel regression analyses showed that an increase in subjective stress was associated with an increase in negative affect and a decrease in positive affect in all groups. However, the groups differed quantitatively in their pattern of reaction to stress. Psychotic patients reacted with more intense emotions to subjective appraisals of stress in daily life than controls. The decrease in positive affect in the relatives was similar to that of the patients, whilst the increase in negative affect in this group was intermediary to that of patients and controls. Higher levels of familial risk for psychosis were associated with higher levels of emotional reactivity to daily life stress in a dose-response fashion. Subtle alterations in the way persons interact with their environment may constitute part of the vulnerability for psychotic illness.

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[1] Inez Myin-Germeys, Jim J. van Os, Joseph E. Schwartz[1], Arthur A. Stone[1], and Philippe A. Delespaul (in press). Emotional reactivity to daily life stress in psychosis. *Archives of General Psychiatry*.

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Introduction

The vulnerability-stress model (Zubin & Spring 1977; Nuechterlein & Dawson 1984; Katschnig 1991) has been widely accepted as a heuristically useful framework for the study of the aetiology and clinical course of schizophrenia and other psychotic disorders. According to this model, psychiatric symptoms emerge whenever a threshold of stressors exceeds the individual's vulnerability level, the latter being a stable characteristic (Zubin et al. 1983). The stress-vulnerability concept is essentially interactional, and as such remains difficult to investigate. Most research to date using this model has focussed on either the indicator of vulnerability or the stressor, whereas their interplay has rarely been examined (Tarrier et al. 1979). For example, cognitive deficits (Faraone et al. 2000), abnormalities in smooth-pursuit eye movements (Ross et al. 1998), alterations of event-related potentials (Turetsky et al. 2000), and cerebral structural abnormalities (Cannon et al. 1998) are more prevalent in the first degree relatives of patients with schizophrenia, which suggests that they are indicators of vulnerability. Similarly, onset and relapse of schizophrenia and other psychotic disorders are associated with minor daily hassles (Malla et al. 1990), life events (Lukoff et al. 1984; Bebbington et al. 1993), exposure to the stresses of urban life (Marcelis et al. 1999), or a hostile family environment (Lukoff et al. 1984), but these have been mostly examined without acknowledging their specific effects on vulnerable persons, and without acknowledging that reaction to stress is a continuous process with important intra-individual variation over time.

In the current study, we used an intensive field method (Delespaul 1995; Myin-Germeys et al. 2000; Myin-Germeys et al. 2001) to examine subjective experience in the flow of daily life in order to address the following questions: i) how does the affect of persons vulnerable to schizophrenia shift when they encounter a stressor in his or her natural environment and ii) in what way does the emotional reaction to a real life stressor vary with differing degrees of vulnerability? Three groups were included on the basis of differences in vulnerability for schizophrenia: patients (most vulnerable), first-degree relatives (intermediate vulnerability) and controls (least vulnerable).

Methods

Subjects

The sample consisted of 50 psychotic subjects, 50 first-degree relatives of individuals with a psychotic illness and 50 control subjects. All patients were under current treatment. Selection criteria, assessed by a research physician or research psychologist, were a lifetime occurrence of psychotic symptoms according to the RDC for at least 2 weeks in clear consciousness for the patient group, no lifetime history of psychotic symptoms for the relatives group, and neither a family nor a personal history of psychosis, or current use of psychotropic medication for the control group. Inclusion criteria were 1) age 18 to 55 years, 2) sufficient command of the Dutch language to understand instructions and informed consent, and 3) normal physical examination. Exclusion criteria were 1) endocrine, cardiovascular, or brain disease, 2) use of alcohol in excess of five standard units per day, 3) weekly use of illicit drugs, and 4) history of head-injury with loss of consciousness. A fifth exclusion criterion for patients included being in need of in-patient care, intensive case management home care or case management crisis intervention. Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects. Patients were recruited through the in-patient and out-patient mental health facilities in Maastricht, The Netherlands and through patient associations in the Southern part of the Netherlands. Relatives were recruited through participating patients and relatives' groups in the same area. Control subjects were recruited from the general population in the local area through a random mailing procedure.

The diagnostic procedure included extensive screening with diagnostic interviews that included the Life Chart (Susser et al. 2000), the Brief Psychiatric Rating Scale (Ventura et al. 1993), and the Positive and Negative Syndrome Scale (Kay et al. 1987), to map psychiatric symptomatology. Interview data and clinical record data were used to complete the Operational Criteria Checklist for Psychotic Illness (OCCPI) yielding DSM-III-R diagnoses through the OPCRIT computer programme (Mcguffin et al. 1991).

Procedure

The Experience Sampling Method is a within-day self-assessment technique. Previous applications of ESM in schizophrenia (Delespaul 1995; Myin-Germeys et al. 2000; Myin-Germeys et al. 2001) have demonstrated the feasibility, validity, and reliability of the method in this population. Subjects were studied in their normal daily living environment. They received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal (beep) at unpredictable moments between 7.30 a.m. and 10.30 p.m. After every "beep", subjects were asked to stop their activity and fill out the ESM self-assessment forms previously handed to them, collecting reports of thoughts, current context (activity, persons present, location), appraisals of the current situation, and mood were collected. All self-assessments were rated on 7-point Likert scales.

The ESM procedure was explained to the subjects during an initial briefing session and a practice form was completed to confirm that subjects were able to understand the 7-point Likert scale format. Subjects were instructed to complete their reports immediately after the beep, thus minimising memory distortions and to record the time at which they completed the form. During the actual sampling period, research staff repeatedly called the subjects to assess whether they were complying with the instructions. In order to know whether the subjects had completed the form within 15 minutes of the beep, the time at which subjects indicated they completed the report was compared to the actual time of the beep. All reports completed more than 15 minutes after the signal were excluded from the analysis. Previous work (Delespaul 1995) has shown that reports completed after this interval are less reliable and consequently less valid. Subjects with less than 20 valid reports were excluded from the analysis.

Measures

Mood states were assessed with 10 mood adjectives rated on 7-point Likert scales (1 *not at all* to 7 *very*). Factor analyses (principal component analysis with Harris-Kaiser rotation) on the raw within-subject scores identified 2 factors with eigenvalues greater than 1 explaining 41% of the total variance. Two factor-based scales with equal weights for each item were created. The mood adjectives *down, guilty, insecure, lonely and*

anxious formed the NA scale (Negative Affect), (Cronbach's $\alpha = 0.79$). The mood adjectives *happy, cheerful, relaxed* and *satisfied* formed the PA scale (Positive Affect), (Cronbach's $\alpha = 0.89$). The item *angry* had low loadings on both factors and was excluded to enhance differentiation between the two factors.

Stress was conceptualised as the subjective appraised stressfulness of distinctive events and minor disturbances that continually happen in the natural flow of daily life. Four different stress measures were computed. For event-related stress, subjects were asked to report the most important event that happened between the current and the previous report. This event was subsequently rated on a 7-point bipolar scale (-3 = *very unpleasant*, 0 = *neutral*, 3 = *very pleasant*). Responses were recoded to allow high scores to reflect stress (-3 = *very pleasant*, 0 = *neutral*, 3 = *very unpleasant*). For activity-related stress, subjects judged their current activity on 3 self-report items (scored on 7 point Likert scales, 1 = *not at all* and 7 = *very*). The mean of the scales '*I am not skilled to do this activity*', '*I would rather do something else*' and '*This activity requires effort*' formed the *activity-related stress* scale ($\alpha = .52$). For thought-related stress, subjects judged their thoughts at the moment of the beep on the 7-point Likert scale '*My current thought is unpleasant*'. For social stress, subjects were asked to evaluate the social context when other persons were present on two 7-point Likert scales '*I don't like the company*' and '*I would rather be alone*' ($\alpha = .59$). The mean constituted the *social stress* scale.

Statistical analyses

ESM data have a hierarchical structure; multiple observations (level 1) are nested within subjects (level 2). Initial pairwise group comparisons were performed on the subject averages for the independent and dependent variables, using one-way analysis of variance with the Tukey multiple comparison procedure. Correlations between the independent variables and the dependent variables were calculated per subject and subsequently analysed as an individual-level variable, corrected with a Fisher Z transformation. One-sample two-tailed t tests with $\alpha = 0.05$ were conducted to test whether the mean across people of these individual-level correlation coefficients significantly deviated from zero.

To estimate the effect of the independent variables (stress) on the dependent variables (mood), a multilevel linear random regression model (Goldstein 1987) was used.

Multilevel or hierarchical linear modelling techniques are a variant of the more often used unilevel linear regression analyses and are ideally suited for the analysis of ESM data, consisting of multiple observations within one person, ie at 2 levels (ESM-beep level and subject level) (Schwartz & Stone 1998). Since – in ESM - observations from the same subject are more similar than observations from different subjects, the residuals are not independent. Conventional regression techniques do not take into account the variance components at the two different levels. Furthermore, the variance explained by autocorrelation (observations from 1 subject which are closer to each other in time will be more similar than those further apart) was taken into account by including the autoregression factor in the model.

Data was analysed with the SAS PROC MIXED module (SAS Technical Report P-229, 1992).The β is the fixed regression coefficient of the predictor in the multilevel model and can be interpreted identically to the estimate in a unilevel linear regression analysis.

Multilevel linear regression analyses were conducted with standardized NA and PA as the dependent variables (standardized NA= NA/Standard Deviation (*SD*) of NA in the whole sample). Thus, the effect of the independent variable (stress measures) was expressed in units *SD* of the dependent variable (NA and PA). According to Cohen (1988), .8 *SD* can be considered as a large effect size, and .2 *SD* as a small effect size. A group variable was constructed to reflect different levels of vulnerability for psychosis. Group was analysed as a 3-level categorical variable with value labels 0 = controls, 1 = relatives and 2 = patients. Group and the different stress measures as well as their interactions (stress x group) were the independent variables. To assess the main effects of group on mood and to test whether the effect of stress on mood was modified by group, *F* tests were conducted analysing whether the differences in intercepts and slopes were significant between the three categories of the group variable. The controls were treated as the reference group in these analyses. Analyses were conducted separately for each stress measure, followed by an analysis with all stress measures entered jointly into the model so as to assess the relative independence of their effects.

Results

Subjects

Of the 150 subjects who entered the study, 1 control subject was excluded because of technical problems with the signaling device (see ESM). Two relatives stopped their collaboration after one day of sampling because of objections on the part of their ill relative. Two patients did not return the diary booklets. One family member and 6 patients were unable to comply with the research protocol (they had fewer than 20 valid reports and were therefore excluded from the analyses, see ESM). The final study sample thus consisted of 138 subjects (table 1).

Stress and mood measures

Relatives and controls did not differ significantly on any of the 4 stress measures (table 2), while patients scored significantly higher only on the *event-related stress* measure and the *social stress measure* compared to the controls and the relatives and controls respectively. All four stress measures were significantly correlated within subjects but the correlations were low: the highest mean correlation of .28 between the *activity-related stress scale* and the *social stress scale* (95% CI: .23 - .34) and the lowest mean correlation was .13 between the *event-related stress scale* and the *social stress scale* (95% CI: .09 - .18).

The patient group reported significantly more NA and less PA than both the relatives and the control group, who did not differ from each other (table 2). The two dependent variables were significantly, but moderately, negatively correlated (mean r = -.47, 95% CI: -.62 - -.33).

table 1. *Sociodemographic and clinical characteristics of the research sample*

	Psychotic Subjects ($n = 42$)	First-Degree Family Members ($n = 47$	Control Subjects ($n = 49$)
	Sociodemographic variables		
Age	31.9 (7.7); (range 20-48)	36.5 (10.7); (range 19-55)	35.2 (8.9); (range 21-50)
Sex (M- F)	22 - 20	25 - 22	24 - 25
Education			
Elementary school	24%	20%	8%
Secondary school	67%	40%	63%
Higher education	9%	40%	29%
Marital Status			
Married or living together	21%	68%	82%
Divorced	5%	6%	2%
Never married	74%	26%	16%
Work Situation			
Working	24%	90%	98%
Unemployed		4%	2%
Incapable to work	66%	4%	
Protected work	10%	2%	
	Clinical variables		
OPCRIT DSM III R diagnosis (lifetime) Schizophrenia	39	0	0
Schizo-affective disorder	2	0	0
Atypical psychosis	1	0	0
Major depression	0	6	0
Total BPRS score	38 (9.8); range (24-73)	28.5 (5.3); (range 24-51)	25.7 (2.3); (range 24-36)
Age of first psychotic episode	22.5 (5.8); (range 14-41)	NA	NA
Usual symptom severity last 5 years (Lifechart)			
Severe	36%	NA	NA
Mild to moderate	57%		
Recovered	7%		
Medication status (psychotropics)			
Typical antipsychotics	50%	2%	0%
Atypical antipsychotics	45%	0%	0%
Antidepressants	19%	4%	0%
Benzodiazepines	24%	8%	0%
Lithium	5%	2%	0%
Anticholinergics	14%	0%	0%
No medication	5%	83%	100%

table 2. *Means (standard deviation)* [1] *and F-test statistics of the number of valid reports and the independent and dependent variables for patients, relatives and controls*

	M (SD)			F	p	Tukey-HSD test
	Patients (n = 42)	Relatives (n = 47)	Controls (n = 49)	df=2, 135		
Valid reports	45 (10)	49 (6)	51 (5)	8.03	0.001	1< 2, 3[3]
Stress-related Variables						
1. Event	-1.2 (.9)	-1.3 (.8)	-1.7 (.7)	4.59	0.01	1> 3
2. Activity	2.5 (.7)	2.3 (.6)	2.4 (.6)	0.87	0.42	
3. Thought	3.8 (.9)	3.6 (.7)	3.7 (.8)	1.02	0.36	
4. Social	2.2 (.8)	1.8 (.6)	1.8 (.6)	4.54	0.01	1> 2, 3
Mood states[2]						
1. NA	1.7 (.7)	1.3 (.6)	1.2 (.3)	13.49	0.0001	1> 2, 3
2. PA	4.4 (1)	5.2 (1.1)	5.5 (.8)	16.32	0.0001	1< 2, 3

[1] For each subject, a mean was calculated over all reports, and these means were aggregated over the group to obtain the group mean (*SD*)
[2] NA = Negative Affect (not standardized); PA = Positive Affect (not standardized)
[3] 1 patients; 2 relatives; 3 controls

Predictors of Mood states

The multilevel random regression analyses (table 3, 4) showed that the 4 stress measures were all significantly associated with mood. In addition, group was also significantly associated with both PA and NA. In agreement with the unilevel analysis in table 2, the relatives did not differ significantly from the controls in prediction of mood while the patients scored significantly higher on NA and lower on PA than the controls in the multilevel model (results not shown).

Significant interaction effects were found between group and all 4 stress measures for both NA and PA, indicating that the level of underlying vulnerability modified the emotional reaction towards the different stressors. For example, the effect of *activity-related stress* on PA was -.22 for the patient group, meaning that 1 unit change in *activity-related stress* resulted in a decrease in PA of .22 *SD*. The difference between the extremes of the scales (between 1 and 7 of the 7-point Likert scale), therefore, was (6 x .22) 1.32 *SD*. In the same model, one unit change in *activity-related stress* resulted in a

-.21 *SD* decrease in PA for the relatives group and a -.12 *SD* decrease for the control group. This has been depicted in figure 1 where the predicted values of PA for each group have been calculated according to the formula: PA = intercept + slope for each of the 7 levels of *activity-related stress*. The two vulnerable groups (patients and relatives) reported a similar decrease in PA associated with stress (nearly parallel lines), both significantly larger compared to the decrease reported by the controls. For NA, the relatives showed a significantly greater increase in relation to stress than the controls, except for the *social stress scale*. The patients reported an even larger increase in NA compared to the controls. Thus, the effects of stress on NA varied in a dose-response fashion with group; the higher the degree of vulnerability, the bigger the increase in NA in response to stress.

figure 1. *Effect of activity-related stress on PA in the three groups, derived from the statistical model (see text)*

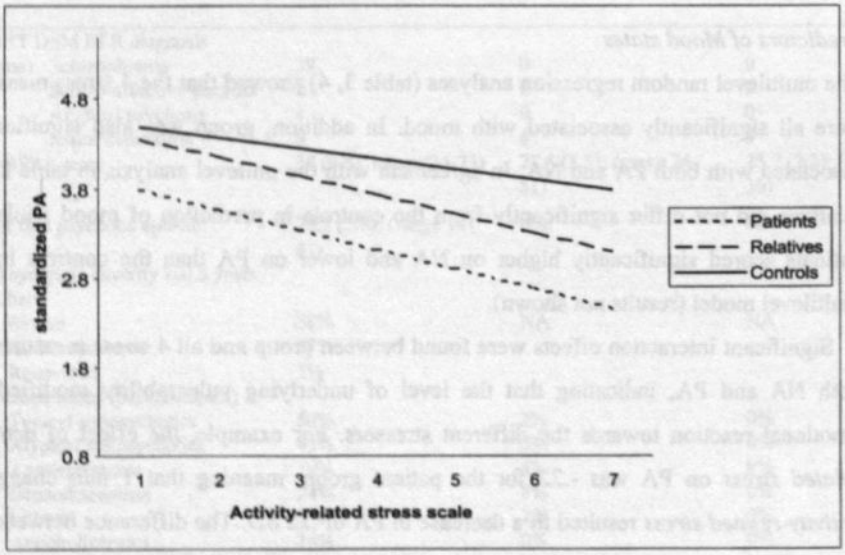

table 3. *Multilevel model estimates for PA*

	N	Effect of stress on mood [1] (slope for the entire group (a))	Effect of group on mood [1] (intercept stratified by group (b))				Effect of stress on mood, stratified by group [2] (slope stratified by group (c))					
			Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	F [3] (df=2, 135)	Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	F [3] (df=2,x) [4]	p [5] (2 vs 1)	p [5] (3 vs 1)
Event-related stress	6110	-.09 (.01) ***	4.19 (.10)	3.98 (.10)	3.37 (.11)	16.11 ***	-.06 (.01)	-.11 (.01)	-.11 (.01)	8.6 **	***	***
Activity-related stress	6491	-.18 (.01) ***	4.76 (.10)	4.52 (.10)	3.91 (.10)	19.32 ***	-.12 (.01)	-.21 (.01)	-.22 (.0)	19.3 ***	***	***
Thought-related stress	6504	-.11 (.00) ***	4.79 (.10)	4.54 (.10)	3.93 (.11)	19.00 ***	-.08(.01)	-.15 (.01)	-.15 (.01)	37.78 ***	***	***
Social stress [6]	4130	-.20 (.01) ***	4.73 (.10)	4.51 (.10)	3.93 (.11)	16.32 ***	-.14 (.02)	-.25 (.02)	-.21 (.03)	8.82 ***	***	**

N= number of beeps, n = number of subjects

[1] Based on the bivariate model: mood = B0 + B1 stress + B2 group + residuals. a = B1, b = B0 + B2 for each group.

[2] Based on the previous model including the interaction term B3 stress*group. c = (B1 + B3) * stress for each group.

[3] F test for main effect of group and the stress*group interaction term

[4] x = 5967 for event-related stress, x = 6348 for activity-related stress, x = 6361 for thought-related stress, and x = 3988 for social stress.

[5] Indicates whether the differences in slope between relatives and controls (2 vs 1) or patients and controls (3 vs 1), is significant. The controls were treated as the reference group.

[6] The smaller N for social stress reflects the fact that social stress was only reported when subjects were in the presence of other people.

** p<.01; *** p<.0001

table 4. *Multilevel model estimates for NA*

	N	Effect of stress on mood [1] (slope for the entire group (a))	Effect of group on mood [1] (intercept stratified by group (b))				Effect of stress on mood, stratified by group [2] (slope stratified by group (c))					
			Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	F [3] (df=2, 135)	Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	F [3] (df=2,x) [4]	p [5] (2 vs 1)	p [5] (3 vs 1)
Event-Related stress	6110	.06 (.01) ***	1.76 (.11)	1.98 (.11)	2.56 (.12)	12.94 ***	.02 (.01)	.06 (.01)	.11 (.01)	24.60 ***	***	***
Activity-Related stress	6491	.11 (.01) ***	1.40 (.11)	1.64 (.11)	2.23 (.12)	14.91 ***	.05 (.01)	.09 (.01)	.22 (.01)	43.15 ***	**	***
Thought-Related stress	6504	.05 (.00) ***	1.46 (.11)	1.71 (.11)	2.30 (.12)	14.26 ***	.01 (.01)	.05 (.01)	.12 (.01)	46.96 ***	***	***
Social stress [6]	4130	.10 (.01) ***	1.46 (.10)	1.70 (.10)	2.17 (.11)	12.17 ***	.06 (.02)	.10 (.02)	.14 (.02)	3.35 *	*	**

N= number of beeps, n = number of subjects

[1] Based on the bivariate model: mood = B0 + B1 stress + B2 group + residuals. a = B1, b = B0 + B2 for each group.

[2] Based on the previous model including the interaction term B3 stress*group. c = (B1 + B3) * stress for each group.

[3] F test for the main effect of group and the stress*group interaction term

[4] x = 5967 for event-related stress, x = 6348 for activity-related stress, x = 6361 for thought-related stress, and x = 3988 for social stress.

[5] Indicates whether the differences in slope between relatives and controls (2 vs 1) or patients and controls (3 vs 1) is significant. The controls were treated as the reference group.

[6] The smaller N for social stress reflects the fact that social stress was only reported when subjects were in the presence of other people.

* p<.05; ** p<.01; *** p<.0001

table 5. *Multilevel multivariate model estimates for PA and NA*

	PA (n = 3645) [1,2]					NA (n = 3647) [1,2]				
	Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	p (2 vs 1) [3]	p (3 vs 1) [3]	Controls (n = 49)	Relatives (n = 47)	Patients (n = 42)	p (2 vs 1) [3]	p (3 vs 1) [3]
Effect of event-related stress, stratified by group	-.04 (.01)	-.07 (.01)	-.07 (.01)	*	*	.01 (.01)	.04 (.01)	.09 (.01)	*	***
Effect of activity-related stress, stratified by group	-.08 (.01)	-.11 (.02)	-.14 (.02)		**	.04 (.02)	.07 (.02)	.14 (.02)		***
Effect of thought-related stress, stratified by group	-.06 (.01)	-.10 (.01)	-.12 (.01)	***	***	0 (.01)	.03 (.01)	.10 (.01)	*	***
Effect of social stress, stratified by group	-.11 (.02)	-.17 (.02)	-.12 (.02)	*		.04 (.02)	.06 (.02)	.05 (.02)		

N= number of beeps, n = number of subjects
[1] Based on the multivariate model: mood = B0 + B1 event-related stress + B2 activity-related stress + B3 thought-related stress + B4 social stress + B5 group + B6 event-related stress * group + B7 activity-related stress * group + B8 thought related stress * group + B9 social stress * group + residuals.
[2] F tests were conducted to test for stress*group interaction. For PA: F (df=2, 3496) = 3.77, p < .05 for *event-related stress*; F (df=2, 3496) = 3.87, p < .02 for *activity-related stress*; F (df=2, 3496) = 11.77, p < .0001 for *thought-related stress*; and F (df=2, 3496) = 2.83, p = .06 for *social stress*. For NA: F (df=2, 3498) = 12.81, p < .0001 for *event-related stress*; F (df=2, 3498) = 6.79, p < .001 for *activity-related stress*; F (df=2, 3498) = 25.54, p < .0001 for *thought-related stress*; F (df=2, 3498) = 0.25, ns for *social stress*.
[3] Indicates whether the differences in slope between relatives and controls (2 vs 1) or patients and controls (3 vs 1), is significant.
* p<.05; ** p<.01, *** p<.001

The multivariate regression analyses with all stress measures entered together in the model showed that all measures remained significant predictors of mood. In order to determine which stress measure differentiated best between the three groups in its effect on mood, the interaction effects were added to the model (table 5). *Thought-related stress* and *Event-related stress* differentiated best between the three groups.

In a final analysis, sex was included as a possible confounder in the multivariate multilevel regression model. No significant effect of sex (0 = female, 1 = male) was found for either NA (B = .002 (.088), p = .98) or PA (B = -.21 (.15), p = .15) and the estimated effects of the stress measures differed only by a very small amount.

Discussion

The results show an overall association between the subjective appraisals of events and small disturbances in the natural flow of daily life and concurrent mood. The effect sizes were small but not negligible, especially since we assessed frequently occurring exposures in daily life, the cumulative effects of which may be considerable. These results extend the results reported in several studies investigating the effects of daily events on mood (Bolger et al. 1989; Marco & Suls 1993; Stone et al. 1993; Affleck et al. 1994; Van Eck et al. 1998): increase in perceived stress was related to an increase in NA and a decrease in PA.

Although the 4 stress measures were all independent predictors of mood (in most analyses), we would not argue, for reasons of parsimony, for separate vulnerabilities related to specific stressors. As the 4 stress measures are weakly but significantly correlated, there may be a generalized sensitivity to stress, which can be expressed in different ways.

Can stress reactivity, as defined in the present study, be considered a marker of vulnerability for psychosis (Green 1998)? Psychotic patients deviated in emotional stress reactivity from the general population controls. The increased stress reactivity was not likely due solely to present psychopathology as none of the patients was in a florid psychotic state during the ESM period (as evidenced by the low scores on the BPRS) and all were in remission, defined as not in need of intensive in-patient or out-patient care. Nor was it solely due to past psychopathology as the healthy relatives group reported similar stress reactivity patterns to the patient group. For NA, the degree of stress reactivity paralleled the level of familial vulnerability, relatives showing values that were intermediate to those of patients and controls. For PA, an equal decrease was found for

patients and relatives. PA may be a less sensitive outcome to gauge subtle differences between patients and relatives. Taken together, the results suggest that stress reactivity may be considered as a behavioral expression of familial risk, and thus possibly qualify as a vulnerability marker for psychotic illness.

However, the differences might also be understood in terms of environmental and social circumstances differentially serving as risk or protective factors in the three subject groups. It has been reported that a lack of social support is associated with more emotional reactivity towards daily stressors (Delongis et al. 1988; Affleck et al. 1994). As social incompetence and social withdrawal are main characteristics of schizophrenia, it seems self-evident that psychotic patients also lack social support. The same might hold for the relatives group, as it has been reported that relatives of patients with schizophrenia are characterised by some schizophrenia-like or schizotypal traits (Kendler et al. 1995) such as social anhedonia (an indifference to other people) (Katsanis et al. 1990), social dysfunction (Kendler et al. 1995), and interpersonal problems (e.g. lack of close friends) (Bergman et al. 2000). Another explanation is that differences in stress appraisal and coping might mediate the effects of stress on mood (Lazarus & Folkman 1984). Appraised stress is essentially subjective and may not necessarily correspond to the objective situation. As psychotic patients tend to be more sensitive to environmental stress (Lukoff et al. 1984; Norman & Malla 1991), they would more easily report higher levels of appraised stress, given an objective situation. However, the present study used appraised stress as the primary independent measure and the patients did not report much higher levels of appraised stress. Apparently, the patients were living a 'normally stressful' life adjusted to their impairment. Coping, on the other hand, may have little effect on mood in within-day assessments (Marco et al. 1999) suggesting that coping efforts have no immediate impact on mood and therefore not on stress reactivity. Finally, living with an ill family member might strongly influence stress levels and mood in relatives. In the present study, however, only a few family members were living with their ill relative ($n = 11$) and no significant differences were found between relatives and controls on any dependent or independent variable.

If stress reactivity is, in addition to being an indicator of familial risk, also causally related to the development of the symptoms of schizophrenia, some clinical implications

would become apparent. Stress reactivity implies an emotional reaction toward daily life stress and as such leaves two options for intervention, either reducing the stressfulness of the environment or altering the personal reactivity. The first option has successfully been applied for instance in family intervention studies where reducing the stress in the social environment of patients (Leff 1994) decreased the risk of relapse. Altering the personal stress reactivity, on the other hand, may be more difficult. Stress reduction techniques such as physical exercise and meditation decreased symptom severity in chronic schizophrenia (Lukoff et al. 1986), and emotional management therapy, including relaxation and distraction techniques, improved emotional well-being in chronic schizophrenia but not in early psychosis (Hodel et al. 1998). Cognitive-behavioral therapy for psychosis, aimed at reducing emotional distress caused by psychotic symptomatology (Fowler et al. 1995), could possibly be extended to emotional reactivity during non-psychotic periods to prevent relapse.

The present results should be viewed in light of several potential methodological issues. First, they are based on subjective reports. Although subjective reports may not be highly reliable (e.g. do all subjects interpret or answer the questions identically?), they can be valid. On the other hand, the validity of objective approaches should not be taken for granted (Strauss 1994). Second, all results have been interpreted in terms of emotional reactivity towards subjective stress. The cross-sectional analyses of the data, however, make it impossible to establish a causal relationship. Therefore, the reverse might be true. A worse mood might influence the subjective appraisal of the environment. Additional experimental work is necessary to clarify this issue. However, either explanation has clinical relevance. Third, the results have been interpreted as supporting the hypothesis that stress reactivity is a vulnerability marker for psychosis. However, as no psychiatric control group was included, it is possible that stress reactivity is a vulnerability marker for psychiatric disorders in general (Van Os et al. 1998). Stress has been hypothesized to play a role in the aetiology of many psychiatric disorders (Hammen 1995). Further research, including samples of patients diagnosed with other disorders, might shed light on this issue. Fourth, patients showed significantly higher levels of the dependent variables NA and PA. Mood levels per se could not be considered a vulnerability marker, as relatives reported the same levels of NA and PA as the controls. Higher levels of NA

give rise to more variability which in turn enhances the detection of stress reactivity. However, this does not explain the increase in stress reactivity in relatives compared to controls. Last, the increased stress reactivity in the relatives group might be mainly caused by the 6 relatives with a lifetime diagnosis of major depression or by the 11 relatives who lived with a patient. However, post-hoc analyses showed that parameter estimates differed only slightly and remained highly significant when these subjects were excluded from the analyses.

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CHAPTER 5

Are cognitive impairments associated with stress-sensitivity? An Experience Sampling Study[1]

Abstract

Patients with a diagnosis of schizophrenia display cognitive impairments and altered stress-sensitivity. However, little is known about the relationship between these two endophenotypes. Neuropsychological tests were administered to 42 patients to assess cognitive functioning, and the Experience Sampling Method (ESM – a structured diary technique assessing current context and mood in daily life) was used to assess 1) appraised subjective stress related to daily events and activities and 2) emotional reactivity to these daily life stressors. Multilevel random regression analyses showed that in some instances, cognitive functioning did not alter emotional reactivity to stress. In other instances, an inverse relationship was found, indicating that a better performance on neuropsychological tests was related to increased emotional stress reactivity. The results indicate that daily-life emotional stress-reactivity may not be a consequence of cognitive impairments and that the two mechanisms may act through different pathways that are possibly related to the extremes of clinical outcome that have been observed in schizophrenia: an episodic, reactive, good outcome form and a more chronic form characterised by high levels of negative symptoms and cognitive impairments.

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Introduction

The focus in schizophrenia research has been extended from overt symptoms to more subtle impairments that might constitute the underlying vulnerability for the disorder. There has been a longstanding interest in cognitive impairments as the possible substrate of schizophrenia vulnerability (Kraepelin 1971; Harvey et al. 1996; Cosway et al. 2000; Weickert et al. 2000). Schizophrenia has been called a neurocognitive disorder (Green 1998), the true phenotype of which may be "an impairment in the smooth coordination of mental processes" or "cognitive dysmetria" (Andreasen et al. 1998; Andreasen et al. 1999). Neuropsychological impairments are not merely neutral indicators of an underlying vulnerability, but appear to causally contribute to course and outcome. For example, cognitive impairments are associated with prognostically unfavourable negative symptoms (Liddle 1987; Van Os et al. 1996) and several studies have found evidence that cognitive impairments independently predict functional outcome (Green 1996; Harvey et al. 1998).

The precise mechanisms by which the statistical association between cognitive impairment and functional outcome is mediated remain unknown. It is attractive to speculate, however, that part of the association between neuropsychological vulnerability and functional outcome can be interpreted in terms of another dominant paradigm in schizophrenia research: that of the stress-vulnerability model. It has been reported that patients suffering from schizophrenia are sensitive to life events (Bebbington et al. 1993; Norman & Malla 1993), daily hassles (Malla et al. 1990; Myin-Germeys et al. submitted), and critical environments (Lukoff et al. 1984; Butzlaff & Hooley 1998), and patients report more subjective stress than controls when confronted with the same objective situation (Lukoff et al. 1984). The most parsimonious explanation linking neuropsychological and stress sensitivity findings is to conceive of schizophrenia as the clinical manifestation of an impairment in higher brain functions that are necessary for the successful adaptation to the stresses of adult life. Thus, altered stress-sensitivity would lie on the causal pathway between cognitive impairments and the psychosis outcome. If this were true, one would expect the level of neuropsychological impairments to impact on reactivity to daily life stress in samples of patients with

schizophrenia. Alternatively, however, neuropsychological impairments and stress sensitivity may constitute independent or even mutually exclusive mechanisms associated with different clinical manifestations along the lines first proposed by Robins and Guze (Robins & Guze 1970). Thus, stress sensitivity may be associated with a more episodic type of illness and a predominance of positive symptoms, whereas neuropsychological impairments may be associated with a more chronic illness course associated with high levels of negative symptoms.

In the present study, we wished to investigate the possible association, in patients with a diagnosis of schizophrenia, between cognitive impairments and emotional stress-sensitivity, based on the Experience Sampling Method.

Methods

Subjects

The sample consisted of 50 subjects with psychosis. Selection criteria were a lifetime prevalence of psychotic symptoms according to the RDC for at least 2 weeks in clear consciousness. Inclusion criteria were 1) age 18 to 55 years, 2) sufficient command of the Dutch language, and 3) normal physical examination. Exclusion criteria were 1) endocrine, cardiovascular, or brain disease, 2) use of alcohol in excess of five standard units per day, 3) weekly use of illicit drugs, 4) history of head-injury with loss of consciousness, 5) in need of in-patient care, intensive case management home care or case management crisis intervention. Written informed consent conform the local ethics committee guidelines was obtained from all subjects. Patients were recruited through the in-patient and out-patient mental health facilities in Maastricht, The Netherlands and through patient associations in the southern part of the Netherlands.

All subjects were extensively screened before entering the study. Structured interviews were conducted by a research assistant and a research psychologist. The Brief Psychiatric Rating Scale (Ventura et al. 1993)(kappa = 0.77), and the Positive and Negative Syndrome Scale (Kay et al. 1987) (kappa = 0.70), were used to map psychiatric symptomatology. Interview data and clinical record data were used to complete the

Operational Criteria Checklist for Psychotic Illness, which was fed to the OPCRIT computer programme yielding DSM-III-R diagnoses (Mcguffin et al. 1991). Thirty-nine patients were diagnosed with schizophrenia, 2 patients with schizo-affective disorder and 1 patient with atypical psychosis.

Neuropsychological assessments

The neuropsychological assessment was directed at the following cognitive domains: episodic memory, semantic fluency, attentional span and speed of complex information processing. The Auditory Verbal Learning Task (AVLT; (Brand & Jolles 1985; Lezak 1995)) was used to evaluate learning and retrieval of information in episodic memory. In five consecutive trials, a list of 15 words has to be memorized and reproduced. The parameter used was the total number of words recalled over the five trials. The backward Digit span from the Wechsler Adult Intelligence Scale-Revised (Wechsler 1981) was used as a measure of attentional span ((Lezak 1995), p. 357-368). The relevant variable was the number of sequences that the subject could repeat correctly. As measures of speed of information processing were used the Stroop Color-Word Test (SCWT; (Stroop 1935)) and the Concept Shifting Test (CST; (Houx et al. 1991)) which is a modified version of the Trailmaking Test (Reitan 1958). For both tests, the parameter used was the interference score, which is the difference between performance on the complex task and performance on the simple task. For the SCWT, this means the time needed for the condition in which the subject has to name the print color and ignore the word minus the time needed for reading the color names. For the CST, the interference score is the time needed for the condition in which the subject has to switch between numbers and letters minus the number only condition. Word fluency was used to evaluate strategy-driven retrieval from semantic memory. Subjects had to generate as many animal names as possible in one minute (Lezak 1995).

ESM

Emotional reactivity to stressors in daily life was measured with the Experience Sampling Method, a within-day self-assessment technique. Previous applications of ESM in schizophrenia (Delespaul 1995; deVries 1992; Myin-Germeys et al. 2000; Myin-

Germeys et al. 2001) have demonstrated the feasibility, validity, and reliability of the method in this population. Subjects received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal (beep) at unpredictable moments between 7.30 a.m. and 10.30 p.m. After every "beep", reports of thoughts, current context (activity, persons present, location), appraisals of the current situation, and mood were collected. All self-assessments were rated on 7-point Likert scales.

The ESM procedure was explained to the subjects during an initial briefing session and a practice form was completed to confirm that subjects were able to understand the 7 - point Likert scale format. Subjects were instructed to complete their reports immediately after the beep, thus minimising memory distortions and to record the time at which they completed the form. During the actual sampling period, research staff repeatedly called the subjects to assess whether they were complying with the instructions. Based on times subjects indicated they completed the report, all reports completed more than 15 minutes after the signal were excluded from the analysis. Previous research (Delespaul 1995) has shown that reports completed after this interval are less reliable and consequently less valid. Subjects with less than 20 valid beeps were excluded from the analyses.

Emotional stress reactivity assessment

Previously, emotional stress reactivity was conceptualised as mood reactivity to daily events and minor disturbances in daily life (see (Myin-Germeys et al. submitted)). Both the mood measures and the stress measures are derived from the experience sampling reports as described below.

Assessment of mood

Mood states reported after each beep were assessed with 10 ESM items rated on 7-point Likert scales (1 *not at all* to 7 *very*). Factor analyses (principal component analysis with Harris-Kaiser rotation) on the raw within-subject scores identified 2 factors with eigenvalues greater than 1 explaining 41% of the total variance. Two factor-based scales with equal weights for each item were created. The items *down, guilty, insecure, lonely*

and anxious formed the NA scale (Negative Affect), (Cronbach's $\alpha = 0.79$). The items *happy, cheerful, relaxed* and *satisfied* formed the PA scale (Positive Affect), (Cronbach's $\alpha = 0.89$). The item *angry* had low loadings on both factors and was excluded to enhance differentiation between the two factors.

Assessment of stress

Stress was conceptualised as subjective appraised stressfulness of distinctive events as well as of minor disturbances that continually happen in the natural flow of daily life. These were:

1. Event-related stress: after each beep subjects were asked to report the most important event that happened between the current and the previous report. This event was subsequently rated on a 7-point bipolar Likert scale (-3 = *very unpleasant*, 0 = *neutral*, 3 = *very pleasant*). Responses were recoded to allow high scores to reflect stress (-3 = *very pleasant*, 0 = *neutral*, 3 = *very unpleasant*). Response on this item is called *event-related stress*.
2. Activity-related stress: after each beep, subjects judged their current activity on 3 self-report items (scored on 7 point Likert scales, 1 = *not at all* and 7 = *very*). The mean of the scales '*I am not skilled to do this activity*', '*I would rather do something else*' and '*This activity requires effort*' forms the *activity-related stress* scale (α = .54).

PANSS

At the end of the ESM period, all subjects were assessed with the Positive and Negative Syndrome Scale (Kay et al. 1987). This scale includes 7 positive symptom items and 7 negative symptom items, all scored on a 7-point scale (1 = *not present* and 7 = *extremely*). The sum of the 7 positive items constitutes the *positive symptom scale* and the sum of the 7 negative items constitutes the *negative symptom scale*.

Statistics

To estimate the effect of cognitive impairments on emotional reactivity to daily life stress, a multilevel linear regression model (Goldstein 1987) was used. Multilevel or

hierarchical linear modelling techniques are a variant of the more often used unilevel linear analyses and are ideally suited for the analysis of ESM data, consisting of multiple observations within one person, i.e. at 2 levels (ESM-beep level and subject level) (Schwartz & Stone 1998). The βs are the fixed regression coefficients of the predictors in the multilevel model and can be interpreted identically to the estimate in the unilevel linear regression analyses. Data was analysed with the SAS PROC MIXED module (SAS Technical Report P-229, 1992).

Multilevel linear regression analyses were conducted with NA and PA as the dependent variables. The scores on the neuropsychological tests, the two stress measures as well as their interactions (stress by neuropsychological score) were the independent variables, leading to the following model: mood = $\beta 0 + \beta 1$ stress $+\beta 2$ neuropsychological score + $\beta 3$ stress * neuropsychological score + residual. Analyses were conducted separately for each measure of stress combined with each neuropsychological measure. Expression of the neuropsychological test results was made directionally similar for these analyses, in that higher scores indicated poorer performance. The interaction term was of most interest in the present study as the main question concerned whether neuropsychological functioning modified the emotional reactivity to daily life stress. Therefore, stratified analyses were conducted whenever there was evidence of significant interaction effects. To this end, the sample was divided in three groups according to their tertile group level of functioning on the neuropsychological test: the worst performance group (± 33% subjects with lowest score on the test), the middle performance group (± 33% subjects with middle score on the test) and the best performance group (± 33% subjects with highest score on the test). For each of the neuropsychological tests, emotional reactivity to daily life stress was analysed in the three groups separately according to the following model: mood = $\beta 0 + \beta 1$ stress + residual.

Finally, the positive and negative symptom scale were included in the multilevel model assessing the relation between stress and neurocognitive functioning, as possible confounder of the associations between stress and neurocognitive functioning on the one hand, and mood on the other.

Results

Subjects and descriptive statistics

Of the 50 subjects who entered the study, two patients did not return the diary booklets and 6 subjects completed fewer than 20 valid reports and were therefore excluded from the analysis (see ESM). The final study sample thus consisted of 42 subjects. They completed an average of 45 valid reports (*SD* = 10).

Sociodemographic and clinical characteristics of the patient sample are described in table 1 and the mean scores on the independent and the dependent variables are shown in table 2.

table 1. *Demographic and clinical characteristics of 42 psychotic patients*

Characteristics	N	Mean (SD)	Range
Age (years)		31.9 (7.7)	20-48
Gender			
Male	22		
Female	20		
Marital Status			
Married or living together	9		
Divorced	2		
Never married	31		
Work situation			
Working	10		
Incapable to work	28		
Protected work	4		
Education			
Elementary school	10		
Secondary school	28		
Higher education	4		
Total BPRS score		38 (9.8)	24-73
Age of first psychotic episode		22.5 (5.8)	14-41
OPCRIT DSM R diagnosis (lifetime)			
Schizophrenia	39		
Schizo-affective disorder	2		
Atypical psychosis	1		

table 2. *Means (standard deviations) and correlations of the neuropsychological measures, the stress measures, the mood measures and the PANSS measures*

			Correlation-coefficients[1]				
	Mean (SD)	Range	1	2	3	4	5
Neuropsych. Measures							
1) Word learning	48.6 (8.2)	29 - 64	1				
2) Word fluency	21.7 (7)	8 - 37	.31 ***	1			
3) SCWT interference	51.1 (19.1)	23.0 – 96.0	.18 ***	.32 ***	1		
4) CST interference	12.7 (10.4)	0.4 – 56.2	.26 ***	.06 *	.41 ***	1	
5) Digit span	5.8 (1.6)	3 - 11	.29 ***	.09 ***	.07 **	.31 ***	1
Stress measures[2,3]							
1) Event-related stress	-1.2 (.9)	-3 - 3	1				
2) Activity-related stress	2.5 (.7)	1 - 7	.17 ***	1			
			t(41) = 3.75				
Mood measures[2]							
1) Positive Affect	4.4 (1)	1 - 7	1				
2) Negative Affect	1.7 (.7)	1 - 7	-.43 ***	1			
			t(41) = -8.14				
PANSS							
1) Positive Sympt. scale	11.3 (4.8)	7 - 25	1				
2) Negative Sympt. scale	11.3 (6)	7 - 34	-.17 ***	1			

[1] Pearson correlation coefficients were calculated.
[2] For each subject, the correlation between the 2 stress measures and the correlation between the 2 mood levels was calculated over all reports (max 60). Subsequently, these correlations were considered as an individual-level variable and corrected with a Fisher Z transformation. One-sample two-tailed t-tests (α = 0.05) were conducted to test whether the mean of these individual-level correlation coefficients significantly deviated from zero.
[3] For Event-related stress, skewness = .86 and kurtosis = -.15, for Activity-related stress, skewness = .88 and kurtosis = .63

Predictors of Mood states

The multilevel random regression analyses showed a significant main effect of the two stress measures ($\beta 1$) and neither a large nor a significant effect of neuropsychological functioning ($\beta 2$) on mood (results not shown). Significant interaction effects ($\beta 3$) (table 3) were found with Word learning, CST interference score, Word fluency and Digit span backward, indicating that the level of neuropsychological functioning on these tests modified the moment-to-moment emotional reaction towards the different stressors. No

significant interaction effects were found between SCWT interference score and the stress measures.

table3. *Multilevel model estimates for PA and NA*[1]

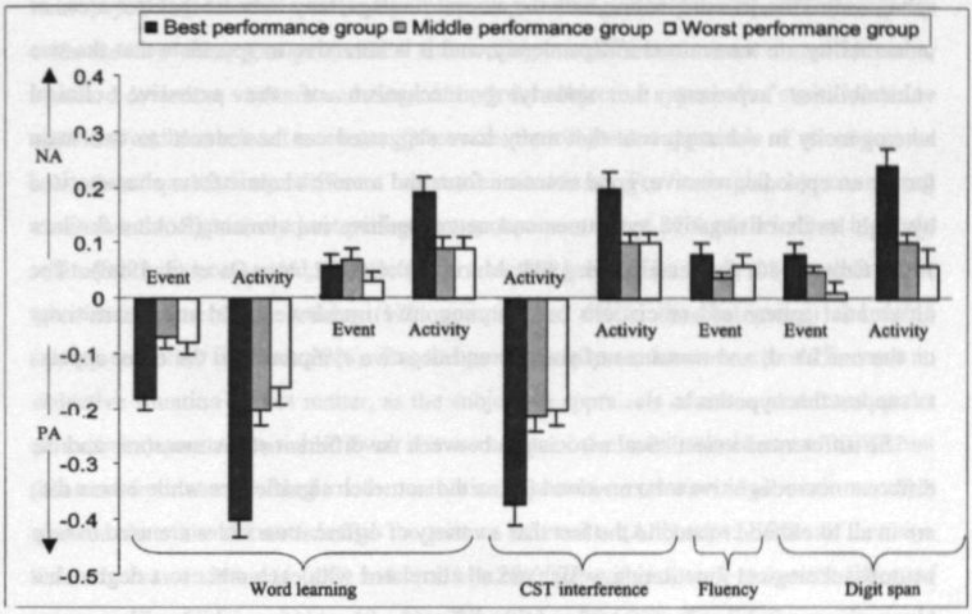
	PA				NA			
	B (SE) (Event* neurops.)	F (1, 1676)	B (SE) (Activity* neurops.)	F (1, 1782)	B (SE) (Event* neurops.)	F (1, 1676)	B (SE) (Activity* neurops.)	F (1, 1782)
Word learning	.007 (.002)	16.81 ***	.014 (.002)	32.41 ***	-.002 (.001)	4.35 *	-.01 (.002)	28.26 ***
SCWT interference	.001 (.001)	0.55	.001 (.001)	0.87	0 (0)	2.13	.001(.001)	0.58
CST interference	-.001(.002)	0.71	.01 (.002)	16.78 ***	0 (.001)	0.01	-.008 (.002)	16.48 ***
Word fluency	.003 (.002)	2.24	.004 (.003)	1.61	-.004 (.001)	9.75 **	.001 (.002)	0.13
Digit span	-.002 (.008)	0.07	-.003 (.012)	0.05	-.013 (.006)	4.70 *	-.025 (.009)	6.93 **

[1] The number of beeps used in the regression analyses were 1720 for the analyses with event-related stress and 1826 for the analyses with the activity-related stress
* p<.05, ** p<.01; *** p<.0001

Stratified analyses were conducted to further clarify the differential associations between stress and mood as a function of the level of neuropsychological functioning (figure 1). Overall, the group with the best performance on neuropsychological tests showed a stronger emotional reaction to stress, with a larger decrease in PA and a larger increase in NA, than both the middle and the worst group.

When the PANSS positive and negative symptom scale were entered in the multivariate analysis, the pattern of interactions between the stress measures and the neuropsychological assessments did not differ. There was no significant main effect of the negative symptom scale on mood while NA slightly increased with increase in the positive symptom scale ($B = .05$; $p < .05$) and PA slightly decreased ($B = -.07$, $p < .05$).

figure 1. *The effect of stress on mood (SE), calculated separately in the three performance groups on the neuropsychological tests*[1]



[1] Only the models for which a significant interaction effect was found, were analysed stratified per group

Discussion

Neurocognition and stress sensitivity

The present study showed that, in some instances, cognitive functioning did not alter the moment-to-moment emotional sensitivity to stress. In other instances, an inverse relationship was found, indicating that a better performance on the neuropsychological tests was related to more daily life stress sensitivity. The present results therefore suggest that moment-to-moment stress sensitivity may not be a consequence of cognitive

impairments and that both mechanisms may act on different pathways that may even be mutually exclusive to a degree. There is evidence that both cognitive impairments and altered stress-sensitivity are also present in the first-degree relatives of patients, albeit to a lesser degree (Faraone et al. 2000; Krabbendam et al. in press; Myin-Germeys et al. submitted). This, in combination with the current findings, may indicate that two areas of vulnerability are transmitted independently, and it is attractive to speculate that the two vulnerabilities represent the underlying mechanism of the extensive clinical heterogeneity in schizophrenia that many have suggested can be reduced to two main forms: an episodic, reactive, good outcome form and a more chronic form characterised by high levels of negative symptoms and neurocognitive impairment (Robins & Guze 1970; Crow 1980; Carpenter et al. 1988; Murray et al. 1992; Van Os et al. 1998). The differential pattern of associations between cognitive impairment and stress-sensitivity on the one hand, and measures of positive and negative symptoms on the other appears to support this hypothesis.

The differences in statistical association between the different stress measures and the different neurocognitive tests on mood (some did not reach significance while others did) are in all likelihood related to the fact that a variety of different variables are used to map neuropsychological functioning, which are all correlated with each other to a degree, but also represent independent domains, with different sources of variability. Thus, some neurocognitive tests were more sensitive to tap differences in mood reactivity to certain stressful situations.

Alternative explanations for the reported results can be postulated. Stress-sensitivity is measured by means of self-report and, therefore, requires the capacity of introspection. First, neuropsychological deficits might impair the capacity to self-reflect on inner mood states. However, this seems unlikely given that no main effects on mood were found for neuropsychological functioning. It has also been reported that cognitive impairments are related to negative symptoms such as flat affect, which might reduce the emotional responsiveness (Hawkins et al. 1997). However, there is evidence that flat affect is more a dysfunction in the realm of *expression* of emotions, rather than *experience* of emotions (Kring & Neale 1996; Myin-Germeys et al. 2000). Previous ESM research (Myin-Germeys et al. 2000) showed that patients, who were blunted affectively, reported the

same intensity and fluctuation in positive and negative emotions as the non-blunted patients. Second, a certain level of cognitive functioning might be necessary in order to experience the environment, *in casu* stress, and report it. This hypothesis, however, again seems unlikely as subjective appraisals of stress were not associated with the neuropsychological test results. By comparing the cognitively best performing group with the two other groups (middle and worst), no differences were found in mean, standard deviation, variance and range of both the subjective appraisal of stress related to activities and that related to events. Of course, the subjective appraisals of stress may be related to qualitatively different objective situations. For example, by comparing activities, the cognitively best performing group spent about 25% of their time in work-related activities compared to only 6% in the other group. The latter, on the other hand, spent more time doing nothing (12% compared to 6% in the best group) and doing leisure activities (30% vs 22%). For the present analyses, however, the differences in objective situation do not matter, as the subjective appraisals of stress were used as the primary independent variable. Even if it were argued that work-related stress is different in nature from stress related to other activities, a post-hoc exclusion of all work-moments showed that this did not change the pattern of results (All beeps: Effect of *activity-related stress* on NA=.16 (.02) and on PA=-.28 (.02); without work-moments: Effect of *activity-related stress* on NA=.17 (.02) and on PA=-.29 (.02)). Finally, the results could be explained by differences in coping. Lukoff and colleagues (Lukoff et al. 1984) put forward the hypothesis that cognitive impairments play an intermediate role between environmental stress and genetic vulnerability, possibly by impairing the coping skills of a patient. The present results do not agree with that hypothesis, at least not as far as coping with events in the flow of daily life is concerned. Patients who are impaired neuropsychologically may display poorer cognitive coping strategies, but poorer coping strategies per se may not lead to increased emotional reactivity and therefore greater stress-sensitivity. The advantage of the ESM method is that it confers ecological validity to measures of environmental stress.

Clinical implications

Although our results are a long way from offering direct therapeutical insights, there are, if stress sensitivity truly is a distinct area of vulnerability, some potentially important clinical implications, as the results suggest that specific therapies may be more useful for specific patients. For example, some patients may benefit more from cognitive remediation therapies while others would be more helped by focussing on coping techniques in dealing with the stresses of daily life. In other words, it may possibly be useful to tailor treatments according to the dominant underlying mechanism of vulnerability.

Methodological issues

The present results should be viewed in light of several methodological issues. First, they are based on subjective reports. Although subjective reports are considered less reliable (e.g. do all subjects interpret or answer the questions identically?), they can be valid whereas the validity of objective approaches should not be taken for granted (Strauss 1994). Second, stress sensitivity has been defined in terms of emotional reactivity towards subjective stress. The cross-sectional analyses of the data, however, make it impossible to establish a causal relationship. Therefore, the reverse might be true. A worse mood might influence the subjective appraisal of the environment. Additional experimental work is necessary to clarify this issue. Third, due to the complexity of ESM, 8 patients were unable to comply adequately with the research protocol and were later excluded from the analysis. The mean level of *activity*- and *event-related stress*, of NA and PA, of positive and negative symptoms, and of the neuropsychological test scores did not differ, however, in excluded versus included subjects, which suggests that the included sample was representative of all patients who entered the study.

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CHAPTER 6

Emotional reactivity to daily life stress in psychosis and affective disorder: An Experience Sampling Study[1]

Abstract

Vulnerability-stress models have been put forward to explain aetiology and course in all major psychiatric disorders, but no comparative work has been carried out at the level of emotional reactivity to stressful events in daily life. The aim of the present study is to investigate emotional reactivity to small disturbances in daily life in patients with non-affective psychosis, bipolar disorder, and major depression. 42 patients with non-affective psychosis (NAP), 38 with bipolar disorder (BD), 46 with major depression (MDD), and 49 healthy controls were studied with the Experience Sampling Method to assess 1) appraised subjective stress of small disturbances in daily life and 2) emotional reactivity, reflected in changes in positive (PA) and negative affect (NA). Multilevel regression analyses showed an increase in NA in the MDD, a decrease in PA in the BD and both an increase in NA and a decrease in PA in the NAP in association with the subjective appraisals of stress, compared to the control subjects. Individuals with NAP, MDD and BD display important differences in stress-reactivity. Type of mood disorder may exert a pathoplastic effect on emotional reactivity in individuals with MDD and BD. Individuals with non-affective psychosis may be most vulnerable to the effects of daily life stress.

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[1] Inez Myin-Germeys, Frenk Peeters, Rob Havermans, Nancy A. Nicolson, Philippe A.E.G. Delespaul, Marten W. DeVries, J. van Os. Emotional reactivity to daily life stress in psychosis and affective disorder: An Experience Sampling Study. Submitted.

Introduction

Vulnerability-stress models, according to which psychiatric symptoms emerge whenever cumulative stressors exceed the individual's vulnerability threshold, have been postulated to play a role in aetiology and course of all major psychiatric disorders (Zubin & Spring 1977; Zuckerman 1999). Stressors such as life events and high Expressed Emotion (EE) environments have been found to precede the onset and recurrence of depression (Hooley et al. 1986; Kessler 1997), bipolar disorder (Miklowitz et al. 1988; Ramana & Bebbington 1995), and psychotic disorders (Bebbington et al. 1993; Norman & Malla 1993). Quantitative differences between these groups have also been reported, with the largest effects of both high EE (Vaughn & Leff 1976; Butzlaff & Hooley 1998) and life events (Dohrenwend et al. 1995; Paykel 1978) in depression. Rather than the reactions to the extreme exposures that life events often represent, sensitivity to minor life events or daily hassles has been postulated to more closely resemble the underlying vulnerability for psychopathology, especially schizophrenia (Malla et al. 1990). The present study aims 1) to further refine the concept of stress in relation to mental health by studying the effect on mood of even smaller disturbances in the realm of daily life and 2) to explore differences in emotional reactivity to daily life stress between the following psychiatric disorders: non-affective psychosis, bipolar disorder, and major depression.

Methods

Subjects

The sample consisted of 50 patients with a diagnosis of non-affective psychosis (NAP) (DSM III-R diagnoses: 46 schizophrenia, 3 schizo-affective disorder, 1 atypical psychosis), 38 patients with bipolar disorder (BD), 47 patients with major depressive disorder (MDD), and 50 healthy control subjects. Inclusion criteria for NAP were a lifetime prevalence of psychotic symptoms according to the RDC for at least 2 weeks in clear consciousness, for MDD a score of $\geq$ 18 on the 17-item Hamilton Depression Rating Scale (HDRS), for BD a history of bipolar disorder currently in remission for at

least two months and being under regular treatment including the prescription of prophylactic drugs for at least 4 months, and for the control group no personal history of psychiatric disorder, hospital admission or current use of psychotropic medication.

Furthermore, inclusion criteria for all subjects were 1) age 18 to 55 (65 for BD and MDD) and 2) sufficient command of the Dutch language. Exclusion criteria were 1) current substance abuse (alcohol in excess of 5 standard units per day or weekly use of illicit drugs), 2) the presence of psychotic symptoms for MDD and 3) being in need of in-patient care, intensive case management home care, or crisis intervention for NAP.

NAP patients were recruited through the in-patient and out-patient mental health facilities in Maastricht, and through patient associations in the southern part of the Netherlands (Myin-Germeys et al. submitted). BD patients were out-patients at the out-patient clinics of the local Psychiatric hospital and the local Community Mental Health Centre (Havermans et al. submitted). MDD patients were recruited among individuals seeking treatment at the same out-patient clinics (Peeters et al. submitted). Control subjects were recruited from the general population in the Maastricht area through a random mailing procedure.

Interview data, including the Brief Psychiatric Rating Scale (Ventura et al. 1993) and the Positive and Negative Syndrome Scale (Kay et al. 1987), and clinical record data were used to complete the Operational Criteria Checklist for Psychotic Illness (OCCPI), yielding DSM-III-R diagnoses through the OPCRIT computer programme for the NAP and the controls (Mcguffin et al. 1991). The primary diagnosis of MDD and BD was assessed with the Structured Clinical Interview for axis I for DSM-IV (First & Gibbon 1996) by a research psychiatrist (F.P. or R.H.).

Written informed consent, conforming to the local ethics committee guidelines, was obtained from all subjects.

Experience Sampling Method

The Experience Sampling Method (ESM) is a repeated self-assessment technique. Previous applications of ESM in schizophrenia (Delespaul 1995; Myin-Germeys et al. 2000; Myin-Germeys et al. 2001), depression (Barge-Schaapveld et al. 1999), bipolar disorder (Havermans et al. submitted), and panic disorder (Dijkman-Caes & deVries

1991) have demonstrated the feasibility, validity, and reliability of the method in psychiatric populations (deVries 1992). Subjects were studied in their normal daily life environment. They received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. Ten times a day on six consecutive days, the watch emitted a signal (beep) at unpredictable moments between 7.30 a.m. and 10.30 p.m. After every "beep", subjects were asked to stop their activity and fill out the ESM self-assessment forms previously handed to them, collecting reports of thoughts, current context (activity, persons present, location), appraisals of the current situation, and mood. All self-assessments were rated on 7-point Likert scales.

The ESM procedure was explained to the subjects during an initial briefing session and a practice form was completed to confirm that subjects understood the scale format. Subjects were instructed to complete their reports immediately after the beep, thus minimising memory distortions, and to record the time at which they completed the form. During the actual sampling period, research staff repeatedly phoned the subjects to assess whether they were complying with the instructions. Based on the times at which subjects indicated they completed the report, all reports completed more than 15 minutes after the signal were excluded from the analysis. Previous work (Delespaul 1995) has shown that reports completed after this interval are less reliable and consequently less valid. Subjects with fewer than 20 valid reports were excluded from the analysis.

Measures

Assessment of mood

Mood states were assessed with 8 ESM items rated on 7-point Likert scales (1 *not at all* to 7 *very*). Factor analyses (principal component analysis with Harris-Kaiser rotation) on the raw within-subject scores identified 2 factors with eigenvalues greater than 1, together explaining 54% of the total variance. Two factor-based scales with equal weights for each item were created. The mood adjectives *down, guilty, lonely, and anxious* formed the NA scale (Negative Affect), (Cronbach's $\alpha = .85$ over the subject mean). The mood adjectives *happy, cheerful,* and *satisfied* formed the PA scale (Positive Affect), (Cronbach's $\alpha = .97$ over the subject mean). The item *angry* had low loadings on both factors and was excluded to enhance differentiation between the two factors.

Assessment of stress

Stress was conceptualised as the subjective appraisal of minor disturbances that continually happen in the natural flow of daily life. Items were selected based on their reflection of dissatisfaction with the current situation in two fields: activity and social situation.

1) Activity-related stress: subjects judged their current activity on 3 self-report items (scored on 7 point Likert scales, 1 = *not at all* and 7 = *very*). The mean of the items '*I am not skilled to do this activity*', '*I would rather do something else*' (for SSD and controls) or '*I enjoy my activity*' reverse coded to allow high scores to reflect stress (for BD and MDD) and '*This activity requires effort*' formed the *activity-related stress* scale ($\alpha = .75$ over the subject mean).
2) Social stress: subjects were asked to evaluate the social context when other persons were present on a 7-point Likert scale. The item '*I would rather be alone*' constituted the *social stress*.

Statistics

Descriptive pairwise group comparisons were performed on the subject averages for the independent and dependent variables, using one-way analysis of variance with the Tukey multiple comparison procedure. Correlations between the independent variables and the dependent variables were calculated per subject and subsequently analysed as an individual-level variable, corrected with a Fisher Z transformation. A one-sample two-tailed *t*-test with $\alpha = 0.05$ was conducted to test whether the mean of these individual-level correlation coefficients significantly deviated from zero.

To estimate the effect of the independent variables (stress) on the dependent variables (mood), a multilevel linear regression model was used (Goldstein 1987). Data was analysed with the SAS PROC MIXED module (SAS Technical Report P-229, 1992). Multilevel or hierarchical linear modelling techniques are a variant of the more often used unilevel linear regression analyses and are ideally suited for the analysis of ESM data, in which repeated ESM observations (beep level) are nested within persons (subject level) (Schwartz & Stone 1998). Since observations from the same subject are more similar than observations from different subjects, the residuals are not independent; multilevel

regression techniques take this into account. Since observations from a subject that are closer to each other in time will be more similar than those further apart, the autocorrelation was modelled. The βs are the fixed regression coefficients of the predictors in the multilevel model and can be interpreted in the same way as the estimates in a unilevel linear regression analysis.

Multilevel linear regression analyses were conducted with standardized NA and PA as the dependent variables (standardized NA = NA/Standard Deviation (*SD*) of NA in the whole sample). Thus, the effect of the independent variable (stress measures) was expressed in units *SD* of the dependent variable (NA and PA). According to Cohen (Cohen 1988), .8 *SD* can be considered as a large effect size, and .2 *SD* as a small effect size. A 4-level categorical group variable was constructed with value labels 0=controls, 1=NAP, 2=BD and 3=MDD. Group and the different stress measures were included as covariates as well as their interactions (stress x group). In addition to estimated intercepts and slopes for the 4 group categories, *F* tests were conducted to assess whether the differences in intercepts and slopes were significant between the four group categories, with a Bonferroni correction for multiple comparisons. To control for possible differences between the four groups in levels of the dependent variables NA and PA, the mean scores per person on NA and PA were added to the analyses as possible confounders of the statistical effect of the group by stress interaction on mood.

Results

Subjects and descriptive statistics

Of the 186 subjects who entered the study, one control subject was excluded because of technical problems with the signalling device (see ESM). Two NAP did not return the diary booklets. Six NAP, one BD, and one MDD patient were unable to comply with the research protocol (they had fewer than 20 valid reports and were therefore excluded from the analyses, see ESM). The final study sample thus consisted of 175 subjects (table 1).

table 1. *Sociodemographic and clinical characteristics of the research sample*

	NAP	BD	MDD	C
Sociodemographic variables				
Age	31.9 (7.7); (range 20-48)	46.2 (9.6); (range 27-65)	40.3 (11.1); (range 20-58)	35.2 (8.9); (range 21-50)
Sex				
Male	22	19	20	24
Female	20	19	26	25
Education (highest level achieved)				
Elementary school	24 %	29 %	41 %	8 %
Secondary school	67 %	37 %	46 %	63 %
Higher education	9 %	34 %	13 %	29 %
Marital Status				
Married or living together	21 %	53 %	67 %	82 %
Divorced	5 %	26 %	15 %	2 %
Never married	74 %	18 %	7 %	16 %
Widowed		3 %	11 %	
Work Situation				
Employed	24 %	53 %	55 %	98 %
Unemployed	0%	5 %	4 %	2 %
Pensioner	0%	3 %	0%	0%
Uncapable to work/ sick leave	66 %	36 %	41 %	0%
Sheltered work	10 %	3 %	0%	0%
Clinical variables				
Total BPRS score	38 (9.8)			25.7 (2.3)
HDRS		3.1 (2.6)	23.9 (3.9)	

The two stress measures were weakly but significantly correlated (r = .20, 95% CI: .15 - .26). NA and PA showed a moderate negative intercorrelation (r = -.33, 95% CI: -.38 - -.28). BD subjects experienced significantly more *activity-related stress* than all other groups (table 2). MDD subjects also reported more *activity-related stress* than control subjects who were not different from the NAP group. With respect to *social stress,* all groups reported equal amounts of experienced stress except for the MDD group, who scored significantly higher than the control subjects.

table 2. *Means (standard deviation)[1] and F-test statistics of the number of valid reports and the independent and dependent variables for subjects with psychosis, with bipolar disorder and with depression and for the controls*

	M (SD)				F	p	Tukey-HSD test
	NAP (n=42)	BD (n=38)	MDD (n=46)	C (n=49)	df=3, 171		
Valid reports	45 (10)	45 (9)	45 (10)	51 (5)	4.9	.003	4>1, 2, 3[2]
Independent Variables							
1. Activity-related stress	2.5 (.7)	3.7 (.7)	2.7 (.6)	2.4 (.6)	39	.0001	2>1, 3, 4; 3>4
2. Social stress	1.8 (1.1)	1.7 (.9)	2.2 (1.1)	1.5 (.8)	4.2	.007	3>4
Dependent Variables							
1. NA	1.7 (.7)	1.5 (.8)	2.5 (1.2)	1.1 (.3)	22.7	.0001	1>4; 3>1, 2, 4
2. PA	4.4 (1)	3.8 (1.3)	2.2 (.8)	5.5 (.8)	96.1	.0001	4>1, 2>3

[1] For each subject, a mean was calculated over all reports, and the mean per subject was additionally aggregated over the group to obtain the group mean (sd)
[2] 1: subjects with psychotic disorder; 2: subjects with bipolar disorder; 3: subjects with depressive disorder; 4: control subjects

The MDD reported significantly higher NA than all other groups; NAP subjects reported higher levels of NA than the control subjects. The MDD group also reported the lowest level of PA, significantly lower than the NAP and BD groups. The NAP and BD groups reported significantly lower PA than the controls.

Predictors of mood states

The multilevel random regression analyses (table 3) showed that the two stress measures were both significantly associated with mood. In addition, group was also significantly associated with both PA and NA in the same fashion as reported in the unilevel analyses presented in table 2 (results not shown for multilevel analyses).

table 3. *Multilevel model estimates for standardized NA and standardized PA*

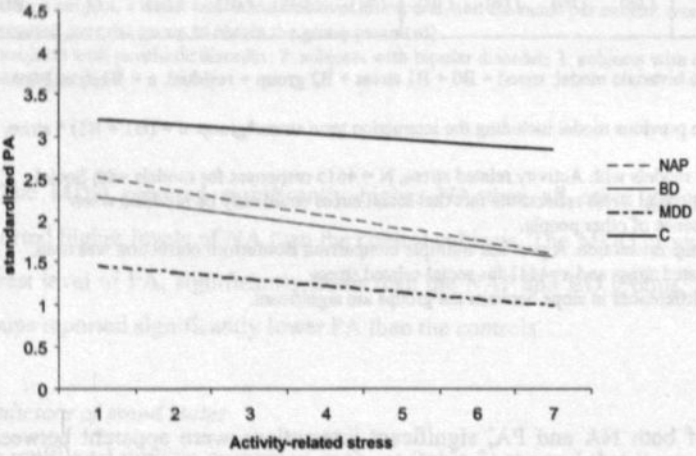
		Effect of stress on mood (a)[1]	Effect of group on mood[1] (intercept stratified by group (b))				Effect of stress on mood, stratified by group[2] (slope stratified by group)					
			NAP	BD	MDD	C	NAP	BD	MDD	C	F[4] (df=3, x)[5]	Bonferroni[6]
NA	Activity-related stress[3]	.07 (.01) ***	1.40 (.11)	1.17 (.12)	2.03 (.11)	0.88 (.10)	.13 (.01)	.02 (.01)	.10 (.01)	.03 (.01)	19.47 ***	C, BD < MDD, PD
	Social stress[3]	.07 (.01) ***	1.36 (.11)	1.20 (.11)	2.05 (.10)	0.93 (.10)	.08 (.01)	.06 (.01)	.09 (.01)	.03 (.01)	6.42 **	C < PD, MDD
PA	Activity-related stress[3]	-.10 (.00) ***	2.66 (.08)	2.40 (.08)	1.55 (.08)	3.28 (.07)	-.15 (.01)	-.12 (.01)	-.08 (.01)	-.06 (.01)	15.11 ***	C, MDD < BD, PD
	Social stress[3]	-.07 (.01) ***	2.58 (.08)	2.29 (.09)	1.39 (.08)	3.18 (.07)	-.09 (.01)	-.10 (.01)	-.07 (.01)	-.04 (.01)	4.23 **	C <PD, BD

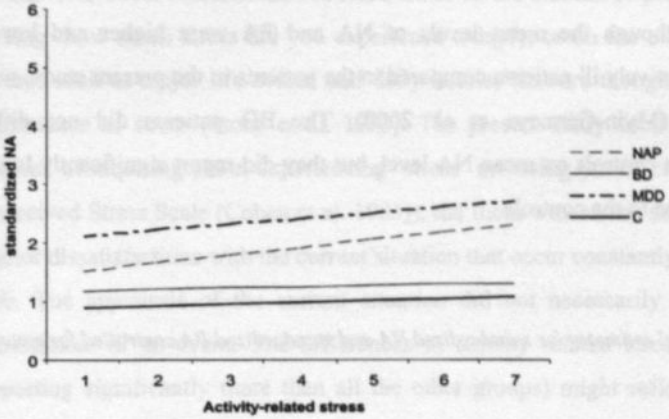
[1] Estimated effects in the bivariate model: mood = B0 + B1 stress + B2 group + residual. a = B1, b = B0 + B2 for each group.
[2] Estimated effects in the previous model including the interaction term stress*group. c = (B1 + B3) * stress for each group.
[3] N = 7949 responses for models with Activity related stress, N = 4615 responses for models with Social stress. The smaller N for social stress reflects the fact that social stress could only be reported when subjects were in the presence of other people.
[4] F test for the stress*group interaction. A post hoc multiple comparison Bonferroni correction was used.
[5] x=7772 for activity-related stress and x=4441 for social-related stress
[6] Indicates whether the differences in slope between the groups are significant.
** p<.001; *** p<.0001

In the models of both NA and PA, significant interactions were apparent between group, on the one hand, and both stress measures on the other. For example, the effect of *activity-related stress* on PA was -.15 for the NAP group, meaning that 1 unit change in *activity-related stress* resulted in a decrease in PA of 0.15 *SD*. The difference between the extremes of the scales (between 1 and 7 of the 7-point Likert scale), therefore, was 0.9 SD (6 * 0.15 *SD*). In the same model, a one unit change in *activity-related stress* resulted in a 0.12 *SD* decrease in PA for the BD, a 0.08 *SD* decrease for the MDD and a 0.06 *SD* decrease for the control group. This is depicted in figure 1a where the predicted values of PA for each group have been calculated according to the formula: PA = intercept + slope

for each of the seven levels of *activity-related stress.* Similarly, the model predicting NA with *activity-related stress* is depicted in figure 1b. For NA, the highest level of stress reactivity was found in MDD and NAP subjects, whereas the BD group did not differ significantly from the controls in stress-related NA. For PA, the NAP and BD subjects reported the largest decrease in PA related to subjective appraisals of stress, while the MDD group scored not significantly different from the controls. The *activity-related stress scale* differentiated more clearly between the three patient groups than *social stress,* for which no significant differences in stress-related NA or PA were found.

figure 1a and 1b. *Effect of activity-related stress on PA in the four groups, derived from the statistical model (see text)*





The mean per subject of NA and PA was added to the multilevel model as possible confounder. This revealed that mean NA was not a confounder for the models predicting PA; but its addition did reduce the effect size of the interaction between stress and group in the model of NA; PA was not a confounder for the models predicting NA, but did reduce the interaction effect between stress and group in the model of PA (table 4). However, all interaction effects remained significant, with the exception of the interaction between *social stress* and group in the model of PA.

Discussion

Subjective appraisals of stress and mood in daily life

The four groups differed significantly on the dependent measure 'mood'. The differences in mood were in the expected direction given their respective current psychiatric status. MDD, who were in a current episode of depression, reported significantly higher NA and lower PA than all the other groups. These results correspond with results found in another ESM study of MDD patients in a current episode (Barge-Schaapveld et al. 1999). The patients with NAP reported significantly higher NA and lower PA than the controls,

consistent with the results found in an ESM study of actively ill patients with a diagnosis of schizophrenia, although the mean levels of NA and PA were higher and lower, respectively, in the actively ill patients compared to the patients in the present study, who were in remission (Myin-Germeys et al. 2000). The BD patients did not differ significantly from the controls on mean NA level, but they did report significantly lower levels of PA compared to the controls.

table 4. *Multilevel model estimates for standardized NA and standardized PA controlled for mean NA and mean PA*

		Effect of mean NA on mood (a) [1]	Effect of stress on mood, stratified by group (b) [1]					
			NAP	BD	MDD	Controls	F [3] (df=3, x) [4]	Bonferroni [5]
NA	Activity-related stress [2]	.89 (.01) ***	.08 (.01)	.03 (.01)	.08 (.01)	.02 (.01)	12.19 ***	C, BD < MDD, NAP
	Social stress [2]	.86 (.01) ***	.05 (.01)	.05 (.01)	.07 (.01)	.02 (.01)	6.02 ***	C < MDD
		Effect of mean PA on mood (a) [1]	Effect of stress on mood, stratified by group (b) [1]					
			NAP	BD	MDD	Controls	F [3] (df=3, x) [4]	Bonferroni [5]
PA	Activity-related stress [2]	.53 (.01) ***	-.11 (.01)	-.09 (.01)	-.05 (.01)	-.06 (.01)	11.58 ***	C, MDD < BD, NAPNAP
	Social stress [2]	.53 (.01) ***	-.06 (.01)	-.07 (.01)	-.06 (.01)	-.03 (.01)	2.36	

[1] Estimated effects in the model: mood = B0 + B1 stress + B2 group + B3 mean Mood + B4 stress * group. a = B3, b = (B1 + B4) * stress for each group, (SE).
[2] N = 7949 for models with *activity-related stress*, N = 4615 for models with *social stress*. The smaller N for *social stress* reflects the fact that *social stress* is only reported when subjects were in the presence of other people.
[3] F test for the stress by group interaction term. A post-hoc multiple comparison with Bonferroni correction was conducted.
[4] x=7772 for *activity-related stress* and x=4441 for *social stress*
[5] Indicates whether the differences in slope between the groups are significant.
** p<.01; *** p<.0001

Previous stress research has focussed either on the amount of perceived stress (e.g. by asking 'how much stress did you experience today?), or on the occurrence of objective events such as major life events and daily hassles that are thought to be related to the experience of stress (Stone et al. 1993). The present study used the first method but instead of inquiring about experiencing 'stress' or 'being out of control' (such as in the Perceived Stress Scale (Cohen et al. 1983)), the focus was on the subjective appraisals of minor dissatisfactions with the current situation that occur constantly in the realm of daily life. The appraisals of the current situation did not necessarily reflect the objective seriousness of an event. The differences in *activity related* stress (with BD subjects reporting significantly more than all the other groups) might reflect differences in the amount of subjective stress a person experiences when confronted with an objective event. It has been hypothesised that NAP subjects experience more subjective stress than controls (Lukoff et al. 1984), although this has not been reported for BD.

Emotional reactivity to daily life stress in psychosis and affective disorder

The results show an overall association between the subjective appraisals of small disturbances in the natural flow of daily life and concurrent mood. The effect sizes were small but not negligible, especially considering that the kind of disturbances we assessed occur very frequently in daily life, and may therefore have considerable cumulative effects.

Emotional reactivity to daily life stress may constitute part of the underlying vulnerability for severe mental illness such as non-affective psychosis (Myin-Germeys et al. submitted). Previous ESM research found that not only psychotic patients in remission but also their healthy first-degree relatives, deviated from healthy controls in emotional stress-reactivity, with greater increases in stress-related NA and greater decreases in stress-related PA than shown by healthy controls. The results from the present study show that altered emotional stress-sensitivity is present in all investigated groups of patients, and although no healthy individuals at risk for MDD and BD were investigated and some of the effects are likely to be illness-related, it is attractive to speculate that altered emotional reactivity to daily life events is a general vulnerability marker for severe mental illness (Van Os et al. 1999).

Several studies have reported quantitative variation in indicators of risk for psychiatric disorders, especially in effect size of social adversity (Van Os et al. 1999). For example, the effect of life events is most pronounced in affective disorder (Paykel 1978; Bebbington et al. 1993; Dohrenwend et al. 1995), as is the effect of high levels of Expressed Emotion in family environments (Vaughn & Leff 1976; Butzlaff & Hooley 1998). The present study also found quantitative differences in emotional stress-reactivity between the three groups of patients in the study. However, emotional reactivity to minor events was not more prominent in MDD than in the other groups. To the contrary, the results suggest that patients with non-affective psychosis were most vulnerable, in that they experienced both an increase in NA, and a decrease in PA in response to small disturbances in their daily life, whereas MDD only differed from controls in stress-related increases in NA and BD in stress-related decreases in PA. The difference in findings may be related to the fact that the life event and high EE studies were focussing on direct causal links between stress and illness episodes, while emotional stress-sensitivity as assessed in this study may constitute part of the underlying vulnerability.

It could be argued that, given the current findings, the importance of stress-sensitivity, especially for minor daily hassles, is more important in non-affective psychosis than has previously been acknowledged. For example, the personality characteristic Neuroticism, which was originally conceived as a measure indicating vulnerability to stress (Eysenck 1958), has been widely investigated as risk factor for the development of depression e.g. (Rodgers 1990). However, a high level of neuroticism long before the onset of the illness appears to be an equally strong risk factor for schizophrenia (Van Os & Jones 2001), which again suggests an area of shared liability between non-psychotic affective disorder and non-affective psychosis.

The differences in emotional reactivity between two mood disorders apparently reflect a pathoplastic effect of mood disorder on stress-reactivity. The type of mood disorder thus influences the expression of the emotional vulnerability to stress, in this case resulting in an increase in NA for the MDD group and a decrease in PA for the BD group compared to the healthy controls.

An alternative explanation, equally relevant from the clinical point of view, for the differences between the groups is that reactivity is to some extent dependent on overall

mood levels. The MDD group consisted of patients in a current episode of the illness so that they were experiencing higher NA and lower PA than the BD and NAP subjects. However, when individual mood levels were included in the model, a significant stress by group interaction effect on mood remained. Most of the estimated coefficients were lowered by 25 to 30%, but 3 out of 4 interaction effects remained significant and the differences between the groups were the same. This indicates that any differences in overall levels of NA and PA can only partially explain the results.

The differences between the groups may also be related to differences in stress and coping, which may mediate the effects of stress on mood (Lazarus & Folkman 1984). However, the present study used appraised stress as the primary independent measure. Furthermore, coping efforts appear to have little effect on mood in within-day assessments (Marco et al. 1999).

Methodological issues

The present results should be viewed in the light of several methodological issues. First, the data are based on subjective reports. Although subjective reports are considered less reliable (e.g. do all subjects interpret or answer the questions identically?), they can be valid whereas the validity of objective approaches cannot be taken for granted (Strauss 1994). Second, the present study was a cross-sectional study, which made it impossible to establish causal relationships. Therefore, it is impossible to determine whether stress measures influenced mood, or mood influenced the subjective appraisals of stress. However, either explanation has clinical relevance.

Clinical implications

It is likely that emotional vulnerability to daily life stress is not merely a neutral indicator of vulnerability. Increased sensitivity to stress may be causally related to the development of psychopathological symptoms and the high rates of recurrence of symptoms seen in clinical practice. Longitudinal designs will clarify the role of stress-sensitivity in symptom formation and relapse rates. If such an association were established, reduction of sensitivity to stress would, for example, be a credible therapeutic target. Cognitive-

behavioral therapy is effective in reducing relapse rates in both affective and psychotic disorders (Jones et al. 2000; Scott 1996). It is attractive to hypothesise that part of the effect of cognitive-behavioral therapy on reduction of relapse rates is mediated through increased resilience to daily life stresses.

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CHAPTER 7

Epilogue

Summary and research findings

Patients suffering from schizophrenia are more emotionally active than has been assumed based on behavioral observations

By comparing the intensity and variability of positive and negative affect in patients suffering from schizophrenia and healthy controls, we found no evidence for a diminishing of subjective emotional experiences in patients with schizophrenia (*chapter 2*). Schizophrenia patients experienced equal amounts of negative affect and lower rates of positive affect than the control subjects, although their average score of positive affect (a score of 4 on a 7-point Likert scale) could hardly be called flat. The inner emotional experience was unrelated to the emotional expression of feelings, as no difference in experience could be found between blunted and non-blunted patients suffering from schizophrenia.

These results extended the laboratory findings showing that patients with schizophrenia are capable of experiencing the full range of intense emotions under simple experimental conditions such as looking at videotapes or drinking good- or bad-tasting beverages, to the complex natural situations of daily life (Berenbaum & Oltmanns 1992; Kring et al. 1993; Kring et al. 1994; Kring & Neale 1996).

These findings have clear clinical implications. First of all, it seems crucial for the clinician to realize that underneath an often expressionless face, there is a rich emotional world consisting of diverse and intense emotions. The understanding and assessment of the emotional richness inside patients suffering from schizophrenia, is important for practitioners in the rehabilitation process. Adequate assessments of the patient's positive experience can help clinicians to recognize effective coping and to stimulate patients to engage in emotionally rewarding activities.

The context does not characterize delusional experiences, but it might increase or decrease the risk to experience a delusional moment.

By comparing delusional moments with non-delusional moments in daily life, we found that delusional moments were characterized by more negative feelings and less positive feelings, by more introspective thoughts concerning one's psychological well-being, but not by differences in the environmental situation (*chapter 3*). The context, however, became relevant in predicting the future occurrence of a delusional moment. The presence of family members and acquaintances decreased the risk to become delusional while the withdrawing from all activities increased the risk to become delusional.

Delusional moments were experienced only 30% of the time. Previous research already reported the delusional experiences were subject to change (Brett Jones et al. 1987; Garety & Hemsley 1994). However, it has never been reported that the intensity of delusional experiences varies over the day, within minutes or hours. Diminishing the time actually spent in delusional thinking might be a valuable therapeutic approach, besides the reduction of distress and disability associated with symptoms (Tarrier 1992; Sensky et al. 2000).

The fact that context might increase or decrease the risk to become delusional, has implicitly been acknowledged by several researchers. For example, the climate in low EE family members has been reported to serve a protective function (Bebbington & Kuipers 1994; Ivanovic et al. 1994), as well as frequent social contacts (Jorgensen & Aagaard 1988). Inactivity, on the other hand, has been considered a factor contributing to poor outcome (Wing & Brown 1970; Curson et al. 1992). The study presented in *chapter 3*, however, was the first to show a direct link between these environmental factors and the occurrence of delusional moments later on.

ESM has shown to be an effective tool for the detection of antecedents of a delusional moment, as well as for the assessment of the degree of distress and disability associated with the symptom in daily life. Therefore, ESM could prove to be a useful tool in clinical practice, especially in Cognitive Behavioural Therapy (CBT) (Fowler et al. 1995; Kuipers et al. 1997; Sensky et al. 2000). The general approach in CBT for psychotic disorders is based on working towards a collaborative understanding of the development

of symptoms and the reduction of distress and disability, for example, by examining the antecedents of the emergence of psychotic symptoms. Furthermore, ESM might provide the therapist with a means to discuss the occurrence of delusional thinking in the context of the patient's actual daily experience.

Higher levels of genetic risk for psychosis are associated with higher levels of emotional reactivity to daily life stress in a dose-response fashion

The study of emotional reactivity to daily life stress in patients with psychosis, first-degree relatives of patients with psychosis, and control subjects, provided evidence that emotional stress-sensitivity might be a vulnerability factor for psychotic illness (*chapter 4*). Subjective stress was associated with an increase in negative affect and a decrease in positive affect in all the groups. However, quantitative differences in their pattern of reaction were detected. Psychotic patients reacted with more intense emotions to subjective appraisals of stress in daily life than controls. The decrease in positive affect in the relatives was similar to that of the patients, whilst the increase in negative affect in this group was intermediary to that of patients and controls.

Emotional reactivity to daily life stress was already reported in several studies investigating these effects in the general population (Bolger et al. 1989; Marco & Suls 1993; Stone et al. 1993; Affleck et al. 1994; Van Eck et al. 1998). The increased stress-sensitivity in psychotic patients who were in remission, and the increased stress-sensitivity in their first-degree relatives who did not develop the illness, suggest that altered stress-sensitivity may be interpreted as a behavioral expression of the underlying familial risk, thus possibly qualifying as a vulnerability marker for psychotic illness.

If emotional stress-reactivity is, in addition to being an indicator of familial risk, also causally related to the development of the symptoms of schizophrenia, it might be therapeutically useful to either reduce the stressfulness of the environment or to alter the personal reactivity to stress. The latter could be established with cognitive-behavioral therapy for psychosis, but rather than aiming to reduce the distress caused by psychotic symptomatology, it should aim at reducing the distress caused by daily life.

Altered emotional reactivity to daily life stress is not a consequence of cognitive impairments

The study reported in *chapter 5* examined the association in psychosis patients between the vulnerability marker described in *chapter 4*, namely altered stress-sensitivity, and another well-known vulnerability marker for schizophrenia, cognitive impairments. The relationship between cognitive impairments and altered stress-sensitivity has never been thoroughly investigated. Implicitly, it has often been assumed that cognitive impairments affect the way subjects react to stress, for example by limiting the coping capacities. The results presented in *chapter 5*, however, showed either no relationship or an inverse relationship between altered stress-sensitivity and cognitive impairments. Patients who performed best neurocognitively showed the highest levels of stress-sensitivity.

Different vulnerability markers might be related to different clinical pictures, according to the lines set out by Robins and Guze (Robins & Guze 1970): neuropsychological deficits might be related to a more chronic type of illness characterized by brain alterations and more negative symptoms, while altered stress-sensitivity might be related to a more episodic, reactive type of illness with a predominance of positive symptoms.

Therapeutically, the division into two sub-types of underlying vulnerability might be useful in directing therapeutic approaches (in case these vulnerability markers are actually causally related to the development and onset of symptoms). For example, some patients may benefit more from cognitive remediation therapies while others would be more helped by focussing on coping techniques in dealing with the stresses of daily life.

Altered emotional reactivity to daily life is not specific for non-affective psychosis, it has also been found in affective disorder, although quantitative differences have been reported

The comparison of stress-sensitivity in non-affective psychotic patients and affective patients (bipolar disorder and major depression), provided evidence that altered stress-sensitivity is a vulnerability marker for major psychiatric disorders in general (rather than

being specific for psychotic disorders). Quantitative differences, however, became apparent. Bipolar patients reacted to stress with a decrease in positive affect compared to controls, while patients with major depression reacted with a stress-related increase in negative affect. The patients with psychosis reported both an increase in negative affect and a decrease in positive affect, whenever they encountered stress.

Quantitative differences were expected based on the literature concerning the effects of life events (Paykel 1978; Bebbington et al. 1993; Dohrenwend et al. 1995) and high EE families (Vaughn & Leff 1976; Butzlaff & Hooley 1998) on onset and relapse in the major psychiatric disorders. However, these studies reported the most pronounced effect in affective disorder while the present study showed the largest effect in psychotic disorder. Apparently, altered stress-sensitivity is a vulnerability marker for all major psychiatric disorders, but it is most pronounced for non-affective psychotic disorders.

The phenomenology of schizophrenia

The single symptom approach, as was described in the introduction, was applied in the studies described in *chapter 2* and *chapter 3*. Two of the most prominent symptoms of schizophrenia were investigated. One main positive symptom, delusions, and one main negative symptom, flat affect, were studied with the Experience Sampling Method. Some of the problems connected with the single symptom approach were tackled. In the study of delusions, a broad definition of delusions was applied, which leaned closely to the general concept used by clinicians in daily practice. Furthermore, a dimensional approach was chosen, defining delusions along several dimensions which together constitute the symptom 'delusions'.

In addition, the Experience Sampling Study was applied in order to improve our insight into these basic symptoms of schizophrenia. In the study of flat affect, the boundaries of the concept 'flat affect' were tested. Although it is clearly stated in the DSM IV that flat affect concerns a lack *expression* of emotions, it was often implicitly assumed that a lack of expression includesa lack of *experience* of emotions. With the

current approach, it was clearly shown that patients who suffer from schizophrenia, have a rich emotional life, despite moments of flat *expression*.

One of the most interesting findings of the study of delusions with ESM, was that delusions have a fast fluctuating pattern, with quick changes between more and less intense moments of delusions. These results opened the way to the study of dynamic interaction patterns between the environment and these fast changing delusional experiences. As such, we ware able to identify triggers and protecting factors which increased or decreased the risk to experience a full blown delusional moment.

In relation to the subdivision of the clinical heterogeneous picture of schizophrenia in 2 or 3 subtypes, some evidence was put forward that independent vulnerability markers might exist, which might be related to different clinical pictures in schizophrenia. Research reported in *chapter 5* showed that altered stress-sensitivity and cognitive impairments were independent and, to some extend, mutually exclusive vulnerability markers for psychosis. These findings seem to support the hypothesis that multiple aetiological factors might lead to the development of the heterogeneous picture called schizophrenia.

However, a critical remark needs to be put forward at this point. It concerns the difference between vulnerability markers and causal mechanisms related to the onset of a disorder. So far, the relationship between two vulnerability markers was described, markers that are indicators of familial risk. Therefore, all we can conclude, is that both markers independently increase the risk for schizophrenia. Only if we were able to prove that these vulnerability markers actually constituted causal mechanisms, directly or indirectly leading to the onset or relapse of schizophrenia, we would be able to tell more about the underlying aetiology. There is some evidence that neurocognitive markers are causally related to the development of symptoms, as cognitive impairments have been reported to influence course and functional outcome (Green 1996; Harvey et al. 1998). For altered stress-sensitivity, the story is more complicated. It has already been reported that the occurrence of stressors such as life events (Lukoff et al. 1984; Bebbington et al. 1993) and daily hassles (Malla et al. 1990), influence the course of schizophrenia. Following the vulnerability-stress model, it is reasonable to assume that emotional

sensitivity for daily life stress is causally related to the occurrence of symptoms. However, as long as no direct link has been reported between altered stress-sensitivity and course and outcome of the disease, we should be careful in interpreting the results.

The vulnerability-stress model for schizophrenia

As was introduced in *chapter 1*, the most prominent model to investigate causes and aetiology of schizophrenia, is the vulnerability-stress model. One of the main problems to study this model, concerned the interactional aspect of the model.

The Experience Sampling Method provided the opportunity to study the reactions of vulnerable persons to stress. However, finding the right method is one thing, deciding on the variables that optimally should be investigated is another. First, one needs to decide which stressors should be studied. ESM samples moment-to-moment within-day self-reports, and is therefore better suited for the study of daily hassles, such as a discussion with your boss, than for the study of big life events, such as getting married. Previous research had already shown that the presence of smaller daily hassles might be a more important predictor of psychological symptoms in general (Kanner et al. 1981; Monroe 1983), of subjective distress (Norman & Malla 1991) and of relapse rates in schizophrenia (Malla et al. 1990). Therefore, sensitivity to daily hassles might be more interesting to investigate, especially in the search for vulnerability markers. Elaborating on this idea, we decided to move beyond the study of daily hassles and to study even smaller disturbances that continually happen in everyday life. A second aspect of stress research, involves the perspective one wants to use, either the subjective or the objective approach. You can focus on the amount of perceived stress (e.g. by asking 'how much stress did you experience today?') or you might measure the objective occurrences of events (e.g. by means of a checklist) (Stone et al. 1993). The first approach was chosen for the present studies, because (1) we believed that the subjective appraisal of stress is more important than the actual occurrence of a stressor and (2) it is hypothesised that the same amount of objective stress gives rise to more subjective stress in patients with schizophrenia. Therefore, if you want to investigate different populations, comparability

is enhanced by using the subjective approach. The subjective method was used, but rather than inquiring about experiencing stress (such as in the Perceived Stress Scale (Cohen et al. 1983)), the focus was put on the subjective appraisals of small dissatisfactions with the current situation that occur constantly in daily life.

Second, one should decide what reactions to stress should best be investigated. The findings reported in *chapter 2*, showing that patients who suffer from schizophrenia have a rich and intense emotional life, hinted in the direction of studying emotional reactivity. Furthermore, the fact that patients with schizophrenia showed high levels of moment-to-moment variability added to the idea that patients might emotionally react quite intense to their environment.

Can altered emotional reactivity to stress be considered a vulnerability marker for psychosis (Green 1998)? Altered stress-sensitivity was found in patients in remission. However, as was described in *chapter 1*, it is difficult to determine in this sample whether altered stress-sensitivity precedes or follows from the occurrence of psychiatric episodes. Therefore, subjects with increased familial liability namely first-degree relatives were investigated and they also showed increased emotional reactivity to daily life stress compared to controls. Furthermore, altered stress-sensitivity could be considered a *true* vulnerability marker as it tells us something about how vulnerable persons react to real life stressors, not just laboratory situations (Katschnig 1991). Finally, concerning the specificity of the vulnerability marker, the study in *chapter 6* reported a comparison of patients suffering from non-affective psychotic illness and non-psychotic affective disorder. We found differences in stress-reactivity between the three groups, indicating that patients suffering from psychosis are worst off. They report both the highest levels of increase in negative affect and decrease in positive affect related to daily life stress compared to the other groups. Therefore, altered stress-sensitivity does not seem uniquely related to schizophrenia. These findings add validity to the hypothesis that there is an area of shared vulnerability between non-psychotic affective disorder and non-affective psychosis (Van Os et al. 1999).

Do these studies provide evidence for the presence of a genetic liability, which is expressed as increased stress-sensitivity? The presented studies are limited in this perspective. The most important limitation is found in the composition of the study

groups. We investigated patients, first-degree relatives and control subjects. However, the patients and first-degree relatives were not all related. Some patients had no relatives in the study and some relatives had no patient. Therefore, familiality was not included as a variable in the statistical models. If you really want to investigate familial transmission patterns, you should investigate patients with several family members in order to discover patterns of familial clustering. Even more, if you want to investigate genetic heritability patterns, you need to investigate several patients and several relatives from the same family. However, the presented studies showed that stress-sensitivity is altered both in healthy relatives and patients in remission, indicating that it is at least a valuable variable to investigate in more selected subject samples

What does these findings tell us about the vulnerability-stress model? The vulnerability-stress model was originally developed to explain and predict the natural, episodic course of schizophrenia in daily life (Zubin & Spring 1977; Zubin et al. 1983). In this perspective, the studies presented in *chapter 4* and *chapter 6* did not provide evidence for a relationship between increased stress-sensitivity and the reoccurrence of psychotic symptomatology. Finding a direct relationship between the occurrence of small daily experiences of stress and the occurrence of psychopathology probably is difficult, as it appears to be the cumulative effect of experiencing increased levels of emotional reactivity to constantly occurring stressors in daily life that finally might push subjects over the edge to illness. The presented studies do fit in the vulnerability-stress model, as proposed by the UCLA group (Nuechterlein & Dawson 1984; Nuechterlein 1987; Green 1998), in which the emphasis has been put on the identification of subtle indicators of underlying vulnerability to schizophrenia. In that perspective, we did provide evidence that subjects who are vulnerable for schizophrenia and other psychiatric disorders, are more sensitive to daily life stress. As such, we added ecological validity to the vulnerability-stress model.

Directions for future research

The results of the research presented in this doctoral dissertation certainly gives rise to many more thoughts and ideas for future research. For one, other psychiatric symptoms, related to schizophrenia and related major psychiatric disorders could and should be investigated in the realm of daily life in order to deepen our understanding of psychopathological experiences. However, in this last part, I will introduce two lines of investigation that I hope to pursue in the near future.

The first concerns the study of associations between different vulnerability substrates, the so-called endophenotypes of schizophrenia. To date, limited attention has been devoted to the study of relations between endophenotypes and, implicitly, it has been assumed that all endophenotypes constitute one underlying vulnerability for schizophrenia. However, as shown in *chapter 4*, these endophenotypes might be independent and mutually exclusive mechanisms leading to different clinical pictures associated with schizophrenia. The relationship between different endophenotypes and their association with different clinical pictures, therefore, seem worthwhile investigating. Focusing on the interactional aspect of the vulnerability-stress model, it would be most interesting to study endophenotypes that are most closely related to the way subjects interact with their environment, such as: 1) cognitive functions which are impaired in patients and their first-degree relatives and which are related to course and functional outcome of schizophrenia, 2) problems with social cognition (e.g. 'Theory of Mind'), which are specific alterations in psychological mechanisms related to the way people form attributions about the world around, 3) altered emotional reactivity to daily life stress, which is reported in patients and first degree relatives, and 4) electrodermal anomalies which are considered vulnerability markers for schizophrenia, and which are related to information-processing difficulties.

One might think of several research questions, that can be investigated with these endophenotypes in a genetically sensitive sample of patients with schizophrenia and their first-degree relatives, for example:

1) how are the 4 endophenotypes related in patients with schizophrenia?

2) is the same pattern of association evident in first-degree relatives of these patients?

3) can we identify patterns of familial clustering in patients and their first-degree relatives, and to what degree is this quantitatively or qualitatively different from the pattern observed in controls and their relatives?

4) are levels of endophenotypes stable over time, and is this similar in patients, relatives and controls?

5) how are the endophenotypes related to symptom levels and global functioning in patients suffering from schizophrenia?

6) how are the endophenotypes related to sub-clinical symptom levels and global functioning in first-degree relatives of patients and controls?

These research questions will provide insight into transmission patterns of endophenotypes (possibly related to differentiation in phenotypes) and will illustrate quantitative and possibly qualitative differences between vulnerable subjects and the general population. In addition, studying these relationships will shed light on the importance of these endophenotypes as possible mechanisms underlying symptomatology and functional adaptation.

A second line of investigation, considers the importance of these different endophenotypes as predictors of outcome of Cognitive-Behavioral Therapy (CBT). The interest on the part of both clinicians and patients in CBT for schizophrenia is growing, mainly because of the high prevalence of medication-resistant symptoms, the patients' reluctance to take life-long medication (Garety et al. 2000) and CBT's appealing and emancipatory normalising rationale. CBT is of proven efficacy in reducing positive symptoms and relapse rates (Jones et al. 2000). However, it requires intensive patient-therapist interactions (typically 20 sessions), with high direct costs. Furthermore, the number of trained CB therapists is limited, not all patients benefit from CBT, and the mechanisms by which improvement is achieved remain unknown (Garety et al. 2000). The mechanism of improvement is an extremely important issue, as CBT can be considered as an environmental protective factor. The numbers needed to treat are estimated at 4 to 8, indicating that 3 to 7 patients are treated unsuccessfully for each

patient that benefits from CBT. Therefore, indicators of response to CBT are required, as well as research into the underlying mechanisms (Garety et al. 2000).

So far, only limited research has been devoted to the study of predictors of outcome of CBT, mainly focussing on symptom levels, insight and cognitive flexibility (Kuipers et al. 1997). It would be interesting to study this issue from a different angle and to focus on the different endophenotypes as possible predictors. It might be hypothesized that the change processes involved in CBT may act differently on the different vulnerability substrates, therefore adequately treating some patients while others do not benefit.One could assume that the assessment of underlying vulnerability before CBT might predict the outcome of treatment.

The primacy of context

To end, I want to spend a few words on the main title of this doctoral dissertation 'The Primacy of Context'. This title might seem provocative for some. It might bring back memories of the schizophrenogenic mother (Mitchell 1968), it might provoke thoughts on how the environment determines the way subjects behave, a kind of stimulus-driven behavior as was proposed by the early behaviorists.

However, the aim was to bring 'the context' back in the picture and to emphasise its importance in every study of the mind and behavior. In contemporary psychiatry research, a lot of interest has been put in the study of the brain. Sophisticated techniques, such as functional MRI and PET scans, have been used to study abnormalities in brain functions. Neuropsychological studies extensively documented abnormal psychological functions in patients with schizophrenia. However, as valuable as these studies are, they should be complemented with research that focuses on an important aspect of human behavior (deVries et al. 1997).

Humans are continuously interacting with the world. The context influences every aspect of human behavior. The mind is 'embodied' and cannot be seen as separate from the environment in which it is functioning. It is only by using an interactive approach, by studying the interaction between mind and context, between the person and the environment that we can come to a thorough understanding of human behavior. This

approach has been successfully applied to the study of visual perception (O'Regan & Noë 2001) and of cognitive psychology (Thelen et al. 2000).

This doctoral dissertation has shown that it is also a valuable approach for the study of psychiatry. Not only did it provide more information on the patterns of symptomological experience, it also showed that an important problem of subjects vulnerable to schizophrenia, and other psychiatric disorders, lies exactly in the way subjects interact with the environment.

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Summary

Humans are constantly interacting with the world; the context influences every aspect of human behavior. Therefore, the study of the interaction between mind and context, between the person and the environment, seems essential to come to a thorough understanding of human behavior. The studies presented in this doctoral dissertation use the Experience Sampling Method as interactive approach to study person-environment interactions in schizophrenia and other psychiatric disorders. Several issues are addressed, including (i) whether patients suffering from schizophrenia are able to experience emotions in daily life, (ii) the daily life characteristics of delusions in schizophrenia, (iii) whether delusions can be triggered by daily life context in schizophrenia, (iv) whether emotional reactivity to daily life stress can be considered a vulnerability marker for psychotic illness, (v) whether altered emotional reactivity to stress is related to cognitive impairments in psychosis, and (vi) whether altered emotional reactivity to daily life stress is specifically related to psychotic illness or whether it is more generally associated with major psychiatric disorders such as affective disorders.

Chapter 1 provides an introduction both in the phenomenology and the vulnerability-stress model of schizophrenia, the two major domains that the research questions are aimed at. Concerning the phenomenology, both the sub-classification of schizophrenia into different subtypes and the problems and advantages of the single symptom approach are considered. Regarding the vulnerability-stress model, the interactional aspect of the model is extensively discussed. The vulnerability-stress model is aimed to show how subjects who have a certain level of vulnerability for psychosis deal or fail to deal with stress, which results in an occurrence of symptoms. Especially this interactional aspect of the model remains difficult to investigate and is, therefore, often neglected both in the study of vulnerability markers and the study of stressors. In the third part, the Experience Sampling Method is introduced as reliable and valid method to study experiences and behaviors as they occur in the context of daily life. The Experience Sampling Method is

used in all the studies presented in this thesis. To end, the aims and outline of the study are described.

Chapter 2 reports a study concerning the presence of *experience* of emotions in patients suffering from schizophrenia. Flat affect, described as blunting of the *expression* of emotions, is considered an important negative symptom of schizophrenia. Much less is known about the *experience* of emotions in schizophrenia patients. The study sample included 65 control subjects and 58 patients with schizophrenia of which 30 were blunted and 21 were nonblunted in emotional expression (as measured with the BPRS item 'flat affect'). The subjective *experience* of emotions was measured with the Experience Sampling Method. Experience of emotions was conceptualised as 1) mean intensity of positive and negative emotions, 2) mean variability of positive and negative emotions from personal profile and 3) mean variability of positive and negative emotions over time. No evidence was found for lessened experience of negative emotions on any of the three definitions, nor for lessened variability over time for positive emotions. The results did indicate a diminishing of intensity and deviation of personal profile of positive emotions. The blunted patient group did not differ from the nonblunted group on any of the measures, indicating that the level of expression is not related to the level of experience of emotions. In conclusion, the present study showed that patients who suffer from schizophrenia do experience more emotions than has been assumed based on behavioral correlates.

Chapter 3 presents the findings of a study on the daily life characteristics and environmental risk factors of delusional experiences in schizophrenia. Data were collected with the Experience Sampling Method (ESM). Forty-eight chronic patients diagnosed with schizophrenia rated the intensity of pathological symptoms and mood states and described their thoughts and the environmental context during consecutive moments in daily life. Delusions were defined on the basis of self-rated suspicion, preoccupation, feeling controlled, and coded thought pathology. Daily context included current activity, persons present, and location. Characteristics of DMs and non-delusional moments (nDMs) were compared, and a multilevel logistic regression model was used to

identify contexts that might trigger or prevent DMs. On average, patients experienced delusions less than one-third of the time. DMs were characterised by higher negative affect and lower positive affect. The presence of family or acquaintances decreased the risk of subsequently experiencing a DM, whereas withdrawal from activities increased this risk. Data support the validity of ESM for investigating delusions in schizophrenia. Daily life contexts appear to alter the probability that delusions will occur. Knowledge about such contexts may therefore be useful in helping patients develop better coping strategies and in creating therapeutic interventions that can lessen emotional distress.

The study described in *chapter 4* investigated the interaction between personal vulnerability and environmental stressors, following the vulnerability-stress model. In a study sample of 42 patients with psychotic illness, 47 non-psychotic first-degree relatives and 49 control subjects, emotional reactivity to daily life stress was studied as possible vulnerability marker for schizophrenia. The Experience Sampling Method was used to assess 1) appraised subjective stress of daily events and smaller disturbances in daily life and 2) emotional reactivity conceptualised as changes in both negative affect and positive affect, in relation to stress. Multilevel regression analyses showed that an increase in subjective stress was associated with an increase in negative affect and a decrease in positive affect in all groups. However, the groups differed quantitatively in their pattern of reaction to stress. Psychotic patients reacted with more intense emotions to subjective appraisals of stress in daily life than controls. The decrease in positive affect in the relatives was similar to that of the patients, whilst the increase in negative affect in this group was intermediary to that of patients and controls. These results indicated that higher levels of familial risk were associated with higher levels of emotional reactivity to daily life stress in a dose-response fashion. Therefore, subtle alterations in the way persons interact with their environment may constitute part of the vulnerability for psychotic illness.

The study described in *chapter 5,* investigates the question whether altered emotional reactivity to daily life stress is associated with another well-known vulnerability marker for psychosis, namely cognitive impairments. The presented study investigated whether

they both constitute one underlying vulnerability, or whether they are independent mechanisms related to psychotic illness. The study sample consisted of 42 patients with psychotic illness. Neuropsychological tests were administered directed at the following cognitive domains: episodic memory, semantic fluency, attentional span and speed of complex information processing. Emotional stress-reactivity was assessed with the Experience Sampling Method, in the same manner as described in the previous section. Multilevel random regression analyses revealed that in some instances, cognitive functioning did not alter emotional reactivity to stress. In other instances, an inverse relationship was found, indicating that a better performance on neuropsychological tests was related to increased emotional stress reactivity. These results indicate that daily life emotional stress-reactivity may not be a consequence of cognitive impairments. The two mechanisms may act through different pathways that are possibly related to the extremes of clinical outcomes that have been observed in schizophrenia: an episodic, reactive, good outcome form and a more chronic form characterized by high levels of negative symptoms and cognitive impairments.

Chapter 6 describes a study, which compares emotional stress-reactivity in three groups of patients: patients with non-affective psychosis, patients with bipolar disorder and patients with major depression. Altered stress-reactivity has been identified as vulnerability marker for psychotic illness. Sensitivity to stress has been reported to explain aetiology and course in all major psychiatric disorders. Therefore, it is interesting to investigate whether altered emotional stress-reactivity is a specific marker for psychotic illness, or whether is more generally associated with major psychopathology. In 42 patients with psychotic illness, 38 patients with bipolar disorder, 46 patients with major depression, and 49 healthy controls, emotional reactivity to daily life stress was studied with the Experience Sampling Method (see summary chapter 4 for detailed description). The patients with major depression showed an increase in Negative Affect in relation to stress compared to controls. The patients with bipolar disorder reported a larger decrease in Positive Affect compared to controls. And the patients with psychotic illness showed both an increase in Negative Affect and a decrease in Positive Affect compared to controls. Therefore, it seems that altered emotional-reactivity to daily life

stress is important in all major psychiatric disorders. However, important differences were found. The type of mood disorder apparently exerts a pathoplastic effect on emotional reactivity in individuals with major depression and bipolar disorder. The patients with non-affective psychotic disorder seem to be most vulnerable to the effects of daily life stress.

Chapter 7 provides a summary of the findings and implications for clinical practice. It also emphasises again on the phenomenology and the vulnerability-stress model of schizophrenia. Regarding the phenomenology, evidence has been found that different underlying mechanisms might be related to different clinical pictures in schizophrenia. The division into sub-types of schizophrenia might be validated by the finding that several independent, and to some extend, mutually exclusive vulnerability markers for psychosis exist. With respect to the vulnerability-stress model, the Experience Sampling Method was used as interactive approach to study how subjects with different levels of vulnerability for psychosis reacted to daily life stress. Altered emotional reactivity to daily life stress is found in patients and their first-degree relatives and, therefore, seems to qualify as vulnerability marker for schizophrenia. It does not seem to be uniquely related to schizophrenia as patients with bipolar disorder and with major depression also show altered stress-sensitivity, although it seems most pronounced in patients with schizophrenia. Altered emotional stress-reactivity seems a valuable new vulnerability marker for psychotic illness, but some caveats are mentioned. First, the studies use a proxy-genetically sensitive design and, therefore, do not provide evidence for a genetic liability, which is expressed as increased stress-sensitivity. Second, no evidence was provided for a relationship between increase stress-sensitivity and the reoccurrence of psychotic symptomatology. The emphasis was put on the identification of subtle indicators of underlying vulnerability, in that perspective providing evidence that subjects who are vulnerable for schizophrenia are more sensitive to daily life stress. As such, ecological validity was added to the vulnerability-stress model.

Two directions for future research are discussed. The first aims at the investigation of the relation between underlying vulnerability markers. The assumption that all constitute one underlying vulnerability does not seem correct. Therefore, interrelationships and

patterns of familial transmission of these different vulnerability markers seem important to investigate. Second, the possible importance of different underlying vulnerability markers as predictors of outcome of Cognitive-Behavioral therapy is another interesting application of the results presented in this thesis.

In conclusion, the study of the interaction between mind and context, between the person and the environment, is a valuable approach for the study of psychiatry. Not only did it provide more information on the patterns of symptomatological experience, it also showed that an important problem of subjects vulnerable to schizophrenia, and other psychiatric disorders, lies exactly in the way subjects interact with their environment.

Samenvatting

Mensen zijn voortdurend in interactie met de wereld; de context beïnvloedt ieder aspect van het menselijk gedrag. Daarom is de studie van de interactie tussen de mens en de context, tussen de persoon en zijn omgeving, essentieel om tot een dieper begrip van het menselijk gedrag te komen. De studies die in dit proefschrift worden voorgesteld gebruiken de Experience Sampling Methode als een interactieve benadering om de persoon - omgevingsinteracties in schizofrenie en andere psychiatrische stoornissen te bestuderen. Verschillende onderwerpen worden behandeld, waaronder (i) of patiënten die aan schizofrenie lijden in staat zijn emoties te ervaren in hun dagelijks leven, (ii) de karakteristieken van waanideeën in het dagelijks leven bij schizofrenie, (iii) of de context in het dagelijks leven onmiddellijk kan leiden tot waanideeën, (iv) of emotionele reactiviteit ten opzichte van stress in het dagelijks leven kan beschouwd worden als teken van kwetsbaarheid voor een psychotische stoornis, (v) of veranderde emotionele reactiviteit ten opzichte van stress gerelateerd is aan cognitieve beperkingen bij psychose, en (vi) of veranderde emotionele reactiviteit ten opzichte van stress specifiek gerelateerd is aan een psychotische stoornis, dan wel meer algemeen geassocieerd kan worden met ernstige psychiatrische stoornissen zoals affectieve stoornissen.

Hoofdstuk 1 biedt een introductie zowel in de fenomenologie als in het kwetsbaarheid - stress model voor schizofrenie, de twee belangrijkste domeinen waarop de onderzoeksvragen gericht zijn. Op het gebied van de fenomenologie worden zowel de subclassificatie van schizofrenie in verschillende subtypes als de problemen en voordelen van onderzoek van individuele symptomen bekeken. Betreffende het kwetsbaarheid - stress model, wordt de nadruk gelegd op het interactionele aspect van het model. Het kwetsbaarheid - stress model is bedoeld om te tonen hoe subjecten met een zekere mate van kwetsbaarheid voor psychosen, moeite hebben gepast om te gaan met stress wat leidt tot het ontstaan van symptomen. Vooral dit interactionele aspect van het model blijft moeilijk om te onderzoeken en is daardoor vaak verwaarloosd zowel in de studie van markeerders van kwetsbaarheid als in de studie van mogelijke stressoren. In het derde

gedeelte wordt de Experience Sampling Methode geïntroduceerd als betrouwbare en valide methode om ervaringen en gedrag in het dagelijks leven te onderzoeken. De Experience Sampling Methode werd in alle studies van deze thesis gebruikt. Om te eindigen worden de doelen en het opzet van de studies beschreven.

Hoofdstuk 2 rapporteert een studie over de *ervaring* van emoties in patiënten die lijden aan schizofrenie. Vervlakt affect, dat wordt beschreven als een vervlakking van de emotionele *expressie*, wordt beschouwd als een belangrijk negatief symptoom van schizofrenie. Over de *ervaring* van emoties in schizofrenie patiënten is veel minder geweten. De onderzochte groep bestond uit 65 controle subjecten en 58 patiënten met schizofrenie, van wie er 30 vervlakt en 21 niet vervlakt waren in hun emotionele expressie (gemeten met de BPRS schaal 'vervlakt affect'). De subjectieve emotionele *ervaring* werd gemeten met de Experience Sampling Methode. Emotionele ervaring werd gedefiniëerd als 1) gemiddelde intensiteit van positieve en negatieve emoties, 2) gemiddelde afwijking van het persoonlijk profiel van positieve en negatieve emoties en 3) gemiddelde variabiliteit over tijd van positieve en negatieve emoties. De ervaring van negatieve emoties was volgens geen van de drie definities verminderd, noch was de variabiliteit over tijd van positieve emoties verminderd. De resultaten toonden wel een vermindering in intensiteit en afwijking van het persoonlijk profiel voor positieve emoties. De groep van vervlakte patiënten verschilde niet van de niet-vervlakte groep voor alle gebruikte maten, wat aantoont dat de mate van expressie niet gerelateerd is aan de mate van ervaring van emoties. Als conclusie kan men stellen dat patiënten die lijden aan schizofrenie meer emoties ervaren dan werd aangenomen gebaseerd op hun gedrag.

Hoofdstuk 3 stelt de bevindingen voor van een studie over de karakteristieken in het dagelijks leven van waanervaringen bij schizofrenie en beschrijft mogelijke risicofactoren in de omgeving. Gegevens werden verzameld met de Experience Sampling Methode (ESM). Achtenveertig chronische patiënten met de diagnose schizofrenie beoordeelden de intensiteit van hun pathologische symptomen en hun gemoedsgesteldheid en beschreven hun gedachten en de omgeving gedurende opeenvolgende momenten in het dagelijks leven. Wanen werden gedefiniëerd op basis

van zelf-gerapporteerde achterdocht, preoccupatie, het gevoel gecontroleerd te worden en gecodeerde pathologie van de gedachten. De dagelijkse context bestond uit de huidige activiteit, de mensen aanwezig en de locatie. Karakteristieken van waanmomenten (WM) en niet-waanmomenten (nWM) werden vergeleken en een multilevel logistisch regressiemodel werd gebruikt om de omgevingsfactoren te identificeren die als risico- of beschermingsfactor voor het voorkomen van wanen kon dienen. Patiënten ervoeren WMs gemiddeld minder dan één derde van de tijd. WMs werden gekarakteriseerd door meer negatieve en minder positieve gevoelens. De aanwezigheid van familieleden of bekenden verlaagde het risico om een WM te ervaren, terwijl het terugtrekken uit een activiteit dit risico verhoogde. De resultaten ondersteunen de validiteit van ESM om wanen bij schizofrenie te onderzoeken. De dagelijkse context lijkt de kans op het voorkomen van wanen te veranderen. Kennis over deze context kan patiënten helpen om betere coping strategieën te ontwikkelen en kan bijdragen tot de creatie van therapeutische interventies die het emotionele ongemak verminderen.

De studie beschreven in *hoofdstuk 4* onderzoekt de interactie tussen persoonlijke kwetsbaarheid en omgevingsstressoren, volgens het kwetsbaarheid – stress model. In een groep van 42 patiënten met een psychotische stoornis, 47 niet-psychotische eerstegraads familieleden en 49 controle subjecten, werd emotionele reactiviteit ten opzichte van stress in het dagelijks leven onderzocht als mogelijk teken van kwetsbaarheid voor schizofrenie. De Experience Sampling Methode werd gebruikt om 1) de ervaren subjectieve stress bij dagelijkse gebeurtenissen en kleinere verstoringen in het dagelijks leven en 2) de emotionele reactiviteit geconceptualizeerd als veranderingen in zowel positieve als negatieve gevoelens in relatie tot stress, te meten. Multilevel regressie analyses toonden dat een stijging van subjectieve stress geassocieerd was met een stijging van negatieve gevoelens en een daling van positieve gevoelens in alle groepen. De groepen verschilden echter kwantitatief in hun reactiepatroon op stress. Psychotische patiënten reageerden met meer intense gevoelens op subjectief ervaren stress dan controles. De daling in positieve gevoelens bij de familieleden was vergelijkbaar met die van de patiënten terwijl de stijging in negatieve gevoelens tussen dat van de patiënten en de controles lag. Deze resultaten tonen aan dat een grotere mate van familiaal risico gepaard gaat met een

grotere mate van emotionele reactiviteit ten opzichte van stress in het dagelijks leven. Subtiele veranderingen in de manier waarop een persoon omgaat met zijn omgeving zijn daarom mogelijk een deel van de kwetsbaarheid voor een psychotische stoornis.

De studie beschreven in *hoofdstuk 5* onderzoekt de vraag of veranderde emotionele reactiviteit ten opzichte van stress in het dagelijks leven geassocieerd is met een andere welbekende markeerder van kwetsbaarheid voor schizofrenie, namelijk de cognitieve beperkingen. De studie onderzocht of beiden samen 1 onderliggende kwetsbaarheid vormen, of ze daarentegen als onafhankelijke mechanismen gerelateerd zijn aan psychosen. Tweeënveertig patiënten met schizofrenie werden onderzocht. De uitgevoerde neuropsychologische testen waren gericht op de volgende cognitieve domeinen: episodisch geheugen, semantische vlotheid, aandachtsspanne en snelheid van complexe informatieverwerking. Emotionele stress reactiviteit werd gemeten met de Experience Sampling Methode, op dezelfde manier als beschreven in het vorige gedeelte. Multilevel random regressie analyses toonden dat in sommige gevallen het cognitief functioneren de emotionele reactiviteit ten opzichte van stress niet wijzigde. In andere gevallen werd er een omgekeerde relatie gevonden waarbij een betere prestatie op de neuropsychologische testen samenging met een verhoogde stress reactiviteit. Deze resultaten tonen aan dat emotionele stress reactiviteit ten opzichte van stress in het dagelijks leven mogelijk niet het gevolg is van cognitieve beperkingen. De twee mechanismen opereren mogelijk via verschillende wegen, gerelateerd aan de extremen van het klinische beeld dat hoort bij schizofrenie: een episodische, reactieve vorm met goede uitkomst en een meer chronische vorm gekarakteriseerd door een hoge mate van negatieve symptomen en cognitieve beperkingen.

Hoofdstuk 6 beschrijft een studie die de emotionele stress reactiviteit vergelijkt in drie groepen patiënten: patiënten met een niet-affectieve psychose, patiënten met een bipolaire stoornis en patiënten met een ernstige depressie. Veranderde stress reactiviteit werd geïdentificeerd als teken van kwetsbaarheid voor psychosen. Gevoeligheid voor stress wordt ook genoemd als factor in de etiologie en het verloop van alle belangrijke psychiatrische ziekten. Daarom is het interessant te onderzoeken of veranderde

emotionele stressgevoeligheid een specifieke markeerder is voor psychotische stoornissen, of het daarentegen meer algemeen geassocieerd is met ernstige psychopathologie. In 42 patiënten met een psychotische stoornis, 38 patiënten met een bipolaire stoornis, 46 patiënten met een ernstige depressie en 49 gezonde controles werd emotionele reactiviteit ten opzichte van stress in het dagelijks leven bestudeerd met de Experience Sampling Methode (zie hoofdstuk 4). Patiënten met een ernstige depressie vertoonden een stijging van negatieve gevoelens in relatie tot stress vergeleken met de controles. De patiënten met een bipolaire stoornis vertoonden een grotere daling van positieve gevoelens vergeleken met de controles. En de patiënten met een psychotische stoornis vertoonden zowel een stijging in negatieve gevoelens als een daling in positieve gevoelens vergeleken met de controles. Hieruit blijkt dat veranderde emotionele stress reactiviteit in het dagelijks leven belangrijk is voor alle grote psychiatrische stoornissen. Er werden echter belangrijke verschillen gevonden. Het type van affectieve stoornis heeft een pathoplastisch effect op de emotionele reactiviteit in individuen met een depressie of bipolaire stoornis. De patiënten met een niet-affectieve psychotische stoornis lijken het meest kwetsbaar voor de effecten van stress in het dagelijks leven.

Hoofdstuk 7 biedt een samenvatting van de bevindingen en de implicaties voor de klinische praktijk. Bovendien wordt er opnieuw gekeken naar de fenomenologie en het kwetsbaarheid – stress model voor schizofrenie. Op het vlak van de fenomenologie werden aanwijzingen gevonden dat er mogelijk verschillende onderliggende mechanismen gerelateerd zijn aan de verschillende klinische beelden van schizofrenie. De verdeling van schizofrenie in subtypes kan mogelijk gevalideerd worden door de bevinding dat er verschillende onafhankelijke, en in zekere mate elkaar uitsluitende, kwetsbaarheid markeerders bestaan voor psychosen. Wat betreft het kwetsbaarheid – stress model werd de Experience Sampling Methode gebruikt als interactieve benadering om te bestuderen hoe subjecten met verschillende maten van kwetsbaarheid voor psychosen reageerden op stress in het dagelijks leven. Veranderde emotionele reactiviteit ten opzichte van stress in het dagelijks leven werd gevonden in patiënten en in hun eerstegraads familieleden, en lijkt dus te voldoen als kwetsbaarheid markeerder voor schizofrenie. Het lijkt niet uitsluitend gerelateerd aan schizofrenie, vermits patiënten met

een bipolaire stoornis en met een ernstige depressie ook veranderde stressgevoeligheid vertoonden, al was het het meest uitgesproken in patiënten met schizofrenie. Veranderde emotionele stress reactiviteit lijkt een waardevolle nieuwe kwetsbaarheids markeerder, al moeten een aantal valkuilen worden vermeld. Ten eerste gebruikten de studies een proxy-genetisch gevoelig design, zodat zij geen uitsluitsel kunnen geven over een genetische erfelijkheid die mogelijk uitgedrukt wordt als verhoogde stressgevoeligheid. Ten tweede werd er geen evidentie geleverd voor een relatie tussen verhoogde stressgevoeligheid en het voorkomen van psychotische symptomatologie. De nadruk werd gelegd op de identificatie van subtiele indicatoren van onderliggende kwetsbaarheid. In dat opzicht werd aangetoond dat subjecten die meer kwetsbaar zijn voor schizofrenie, ook meer gevoelig zijn voor stress in het dagelijks leven. Aldus werd er ecologische validiteit toegevoegd aan het kwetsbaarheid – stress model.

Twee richtingen voor toekomstig onderzoek worden bediscussieerd. De eerste heeft als doel de relatie tussen onderliggende kwetsbaarheid markeerders te onderzoeken. De aanname dat zij allemaal deel uitmaken van 1 onderliggende kwetsbaarheid lijkt niet correct. Daarom is het belangrijk de onderlinge relaties en de patronen van familiale transmissie van deze verschillende kwetsbaarheid markeerders te onderzoeken. In de tweede plaats wordt het belang van de verschillende onderliggende kwetsbaarheid markeerders als mogelijke voorspellers van het succes van cognitieve–gedragstherapie als interessante toepassing van de resultaten uit deze thesis naar voor geschoven.

Concluderend kan men stellen dat de studie van de interactie tussen de mens en de context, tussen de persoon en zijn omgeving, een waardevolle benadering is voor de studie van de psychiatrie. Niet alleen verkregen we zo meer informatie over de patronen van de ervaring van de symptomen, het toonde ook aan dat een belangrijk probleem van personen die kwetsbaar zijn voor schizofrenie en andere psychiatrische stoornissen precies ligt in de manier waarop zij met hun omgeving omgaan.

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Curriculum vitae

Inez Myin-Germeys werd geboren op 11 april 1972 in Wilrijk (België). Na het afronden van de studie Latijn-Wiskunde aan het Regina Pacis Instituut in Hove (België), begon zij met de studies Psychologie aan de Katholieke Universiteit Leuven. Zij specialiseerde zich in de 'fysiologische psychologie' en in 'functieleer'. Zij verbleef 1 academiejaar in de Verenigde Staten waar ze haar wetenschappelijke stage deed aan de State University of San Diego en in het Veterans Administration Medical Centre in San Diego, Californië. Zij deed daar onderzoek naar aandachtsstoornissen bij het Wernicke-Korsakoff Syndroom. Haar afstudeerscriptie schreef zij in het domein van de psychofysica. In 1995 behaalde zij het diploma van Licentiaat in de Psychologie met grote onderscheiding.

Sinds 1996 was zij werkzaam als assistent in opleiding bij de vakgroep Psychiatrie en Neuropsychologie, sectie Sociale Psychiatrie en Psychiatrische Epidemiologie, van de Universiteit Maastricht. In 1999 verbleef zij 2 maanden aan de State University of New York at Stony Brook. Het resultaat van het wetenschappelijk werk dat zij de laatste 5 jaar verrichtte, staat beschreven in deze dissertatie. Zij zal de volgende jaren verbonden blijven aan de sectie Sociale Psychiatrie en Psychiatrische Epidemiologie in een postdoc onderzoekspositie in samenwerking met de Mondriaan Zorg groep.

Inez Myin-Germeys is gehuwd met Erik Myin en is mama van Elise, Charlotte en Laure.

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