Stress Sensitivity in Psychosis

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Assessment, Mechanism & Intervention

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Stress Sensitivity in Psychosis:
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Dissertation

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Contents

Chapter One

Introduction

This introduction is based on a book chapter published in Dutch in the "Handboek Psychose". Its first two paragraphs are citations of the online book chapter Stress Assessment using Experience Sampling: Convergent Validity and Clinical Relevance (2016). In P. Fauquet-Alekhine (Ed.), *Stress Self-assessment & Questionnaires: choice, application, limits,* (21-35). Retrieved from http://hayka-kultura.org/larsen.html

(from: Vaessen et al (2015). Stress Assessment using Experience Sampling: Convergent Validity and Clinical Relevance)

"During the last century the concept of "stress" has taken a central position in both preclinical and clinical research. Its implications range from an organism's most basic survival tactics to physical and mental well-being[1]. In humans, aside from major stressors such as abuse, unemployment, divorce, or death of a loved one, minor stressors that occur naturally in the flow of daily life are believed to pose a risk to those individuals who are predisposed to somatic or psychological illness[2]. In order to identify, understand, and possibly influence this complex concept and its consequences, accurate assessment of the stress response is crucial. So, what do we mean when we say stress or stress response?"

Stress

(from: Vaessen et al (2015). Stress Assessment using Experience Sampling: Convergent Validity and Clinical Relevance)

"The definition of stress remains topic of discussion. Public speaking, important deadlines, and rumination are just a few examples of situations in which people may express that they are 'stressed'. On the other hand, we refer to stress as that what an animal experiences when faced with a hungry predator, or *is* a hungry predator. Indeed, stress is a complex concept that encompasses several components. One such component is a stressor, which can be conceptualized as anything that causes disbalance to an organism's homeostatic equilibrium[3]. This imbalance triggers an innate, automatic reaction in the organism's physiology aimed at reinstatement of homeostasis through allostasis, known as the acute stress response. This immediate reply to threat is highly adaptive and functions ultimately to secure survival. However, when the stress response is triggered repeatedly or persists over a longer period of time (i.e. becomes chronic) this protective mechanism may have devastating consequences for the organism.

In addition to the beneficial effects of increased chances of survival, the stress response may have detrimental effects on an organism's biology- a phenomenon coined allostatic load. Especially when exposure to a stressor is prolonged or recurrent (i.e. chronic), the excessive release of stress hormones may impair

cardiovascular, metabolic, and immune functioning, and promote neuroinflammation[4]. In humans, chronic stress is implicated in the epidemiology of a broad range of mental disorders[5-9], urging for a better understanding of its dynamics. Thus, whereas a single, short-lived stress response may not pose a direct threat to a person's well-being, a prolonged or recurrent stress response to either a physical or cognitive stressor can have detrimental effects on both somatic and psychological health."

The physiological stress response

(from: Vaessen et al (2015). Stress Assessment using Experience Sampling: Convergent Validity and Clinical Relevance)

"From an evolutionary viewpoint, the stress response is seen as an adaptive reaction to (life)threatening situations, promoting immediate behavioral action. In humans and other vertebrates, two major biological systems mark the human stress response. First, activation of the sympathoadrenal system (SAS) results in a fast release (within seconds of stress-onset) of peripheral and central catecholamines, activating the sympathetic nervous system and bringing the organism in a state of high-energy that is characteristic for the behavioral stress response. Second, the hypothalamic-pituitary-adrenal (HPA) axis sets in motion a slower cascade of neuroendocrine activity (over a course of 30 minutes after stress-onset) resulting in corticotrophin releasing factor (CRF), adrenocorticotrophic hormone (ACTH) and cortisol release. The boost of sympathetic activation and the fast effects of the neuroendocrine system that a stressor triggers are aimed at successful coping, typically in a *fight-or-flight* fashion, whereas the slow effects of neuroendocrines reverse these effects to restore balance[10]. This response offers opportunities to escape the stressor and secure survival."

Because of its double-edged nature, stress is a well-known culprit in psychiatry research. A disorder that has been often associated with stress is psychosis. Majorly aversive experiences such as childhood trauma or negative life events, as well as

continuous stressors such as having an outsider status or being discriminated against, all have been implicated in the development of psychotic complaints.

Psychosis

Psychosis is a state that is characterized by loss of contact with reality, which can range from minor changes in perception or ideation to more serious, debilitating aberrances. Psychotic-like experiences are not uncommon – about 5.8 % of the general population may have them at least once[11], and in most cases it has no large impact on their everyday lives. Individuals higher on the continuum, however, may have episodes in which they have strong, often paranoid, convictions that are misplaced or out of touch with reality (i.e. delusions), or see, hear, feel, smell, or taste something that is not there (i.e. hallucinations). A psychotic episode can have a large impact on a person's daily functioning, and greatly increases the risk for subsequent episodes[12, 13]. Around 3.5% of all people is diagnosed with a psychotic disorder at one point in their lives[14]. 0.5-1% is ever diagnosed with schizophrenia[15] – a severe psychotic disorder characterized by recurrent psychotic episodes and persistent cognitive complaints and negative symptoms. The term "negative symptoms" refers to diminished affect, motoric behavior, motivation, and experience of pleasure, which prove considerably harder to treat than positive symptoms and are associated with poor functional outcome[16]. Psychosis is difficult to treat and some may suffer its consequences for the rest of their lives.

Stress as a risk factor for psychosis

The Diathesis-Stress Model

That enviromental factors play a role in the emergence of psychotic illnesses is not a new concept. In the '70 and '80 of the last century, a model was proposed that stated that under the influence of stressors, psychotic symptoms can develop in individuals who carry a biological vulnerability[17-19]. This so-called stress-diathesis model has later been used and modified by different researchers and is still considered to be one of the most influential approaches to developing psychosis. A later version of this model states

that stressors can add to the etiology of schizophrenia through the influence of the HPA axis on the dopamine system[9]. In this model, the central notion states that increased cortisol release by stress-induced HPA activity augments dopamine synthesis. A causal relationship between cortisol release and dopamine levels was mainly based on animal studies where administration of corticosterone directly leads to an increase in dopamine in the striatum[20]– a brain structure that is associated with reward-learning, motivation, and salience attribution. In humans, administration of 2-deoxyglucose, a metabolic stressor that elicits a robust activation of the HPA axis, results in augmented dopamine release in the striatum of healthy volunteers[21]. To date, dopamine is the most important biomarker for psychosis and a primary target of first-generation antipsychotics. The interaction between biological vulnerability and stress then disturbs the dopamine system and may eventually facilitate psychosis.

The Sensitization Model

Not all stressors seem to have the same effect on the HPA axis. An extensive meta-analysis shows that, at least under laboratory circumstances, particularly the uncontrollable, social-evaluative threats to reach important aims are successful in eliciting a cortisol reaction[22]. Large psychosocial environmental stressors, such as childhood trauma[23, 24], migration[25] and discrimination[26] have been linked to an increased risk of the development of psychosis. However, the underlying mechanism explaining how psychosocial environmental stressors lead to psychotic symptoms is not yet clear. An often proposed theory is the sensitization model for example, see[27], which suggests that stressors elicit a larger response depending on the organism's prior exposure to life-stressors (see figure 1). This theory is based on the "*kindling*" hypothesis of mood disorders[28] that states that whereas a first depressive episode is often preceded by multiple larger stressors, later episodes may be triggered by smaller and less stressors due to a developed sensitivity to stressors of the same or lower intensity. In psychosis, the sensitization model assumes that this increased sensitivity particularly increases the risk of developing a psychosis in individuals who have a vulnerable genetic predisposition[29]. Not only large stressful experiences can lead to sensitization of the system; smaller, everyday stressors appear to play a role as well[30].

Stress sensitivity in daily life can be studied with the experience sampling method[31]. The experience sampling method is a structured diary method that can map momentary fluctuations in subjective experiences that individuals have, within the context of everyday life. With it, several studies have shown that psychotic vulnerability is associated with a heightened emotional and psychotic reaction to daily hassles, both in patients[32, 33], in family members of patients[32-34], in individuals with subclinical psychotic experiences[35], and in individuals at clinical high risk to develop a psychotic episode[36-38]. This last group appears more stress sensitive than individuals who already have developed a psychotic disorder[36, 39]. Furthermore, in this group psychotic experiences were found to induce stress, possibly leading to a vicious cycle in which stress elicits symptoms, which are stressful things to have. A recent network analysis underlines the notion that daily-life stressors play a central role in the variation of psychosis[40]. In line with the sensitization hypothesis it was furthermore found that prior exposure to larger stressors, such as life stressors[41] or childhood trauma[42], increases sensitivity to smaller daily stressors.

Together, the evidence confirms the notion that psychosis is associated with heightened sensitivity to daily stressful situation. However, an important question is whether this marker can be used to predict clinical outcome. In line with this reasoning, Collip and colleagues[43] found that increased stress reactivity predicted persistence of psychotic experiences. No study has investigated if increased stress sensitivity is a risk factor for the onset of psychotic symptoms.

Biological Mechanisms of Stress Sensitivity

At the biological basis of the sensitization model lays the HPA axis, serving as a mediator between exposure to stressors and increased stress reactivity, especially of the neurotransmitter dopamine[44]. In the next paragraphs I will summarize the evidence for increased stress sensitivity in biological systems and discuss the role of stress as a risk factor. Lastly, I will discuss the effectivity of new psychological treatments that are specifically aimed at coping with stress.

HPA Sensitivity

That there is a link between cortisol and psychosis becomes immediately clear when we see that administration of exogenous corticosteroids elicit psychotic symptoms[45, 46]. Also, syndromes that are associated with increases in cortisol, such as Cushing syndrome, are associated with psychotic symptoms. Within the psychosis spectrum we observe heightened cortisol levels in individuals who have subclinical psychotic experiences[47], individuals at high risk of developing psychosis[48], and first-episode psychosis patients[49]. However, during an acute metabolic stress task, psychosis patients show an attenuated increase in plasma cortisol compared to healthy volunteers[50]. A similar effect is observed in patients with schizotypal personality disorder[51]. Medication-free first-episode psychosis patients too show a blunted cortisol and ACTH response to stress[52], indicating that it is not a result of antipsychotic medication. During an experimental psychosocial stress task, individuals at high clinical risk of developing psychosis show the same flattened cortisol response when compared to healthy volunteers[53], suggesting this effect to be present before receiving a possible diagnosis of psychotic disorder. Interestingly, this flattened cortisol response is associated with a higher quality of life[54]. It thus seems that, especially in early stages, psychotic vulnerability is associated with increased basal HPA activity, and a blunted HPA reaction to stressors, compared to healthy volunteers[55, 56]. The observation that individuals diagnosed with major depression show no difference in cortisol reactivity compared to healthy volunteers may suggest that this pattern is specific to psychosis[57]. However, there remain inconsistencies about the HPA response in psychosis. For example, the blunted cortisol response is typically observed after exposure to psychosocial stressors, but not always to physiological stressors[58] or during a pharmacological challenge[44]. Also, cortisol reactivity to daily stressors has been shown to be increased instead of blunted in individuals at high familial risk of developing psychosis in an experience sampling study[34]. No study has investigated basal cortisol levels and cortisol stress reactivity in daily life in psychosis. Hence, it remains unclear how cortisol behaves under natural circumstances in psychosis and how this relates to cortisol in at-risk individuals. Finally, it is unclear what the role is of antipsychotics use on cortisol. Answering these questions may provide further insight into the role of

cortisol in the developmental course of psychosis. Summarizing, most evidence indicates increased tonic HPA axis activation and a flattened response to stress in individuals across the psychosis spectrum, and these alterations have an impact on the brain.

Changes in the dopamine system

Glucocorticoids influence dopamine release[59-61], an important catecholamine in psychosis. Peripherally, an increased concentration of homovanillic acid, a dopamine metabolite, is observed in the plasma of psychosis patients during a metabolic stress task compared to healthy volunteers[50, 62]. First-degree relatives of individuals diagnosed with psychotic disorder similarly show an increase compared to healthy volunteers without a first-degree family member with psychosis, although here the difference is smaller[63]. Thus, it seems that, in contrast to cortisol, dopamine reactivity is sensitized in psychosis, and that the magnitude of the difference covariates along the psychosis continuum. In first-degree relatives, homovanillic acid reactivity to metabolic stress (i.e. the relative increase compared to a rest condition) is associated with psychotic reactivity (i.e. the relative increase of psychic experiences) to daily stressors[64]. This suggests that the sensitized catecholaminergic response not only is seen under artificial laboratory circumstances; it also has relevance for daily life.

When looking at the brain, across the psychosis spectrum deviances are observed with regard to dopamine release. In particular in the striatum dopamine release is increased in individuals with psychosis[65]. During an acute stress task, psychotic patients show more striatal dopamine release than healthy volunteers[66], which is in line with the hypothesis that striatal dopamine release is sensitized in psychosis. Individuals at high familial[67] and clinical[66, 68] risk of developing psychosis likewise show more dopamine activity in the striatum, affirming the notion that this hypersensitivity is more likely to be an etiological factor than a symptom. In addition to increased striatal dopamine, there is possibly a decrease in dopamine release in prefrontal brain areas during stress[69, 70], although a study directly tapping into this found no difference between psychosis patients and healthy volunteers[71]. Psychotic reactivity was, however, associated with stress-related dopamine release in the prefrontal cortex in first-degree

relatives of psychosis patients [72], and therefore seems to be related to psychosis sensitivity. In a sample of both healthy volunteers and individuals at familial risk for psychosis, prefrontal dopaminergic activity was directly related to daily-life stress sensitivity[73]. Concluding, whereas there seems to be no direct difference in prefrontal dopaminergic stress reactivity, it nonetheless appears to be associated with stress sensitivity in individuals at different stages of the psychosis continuum. In addition, there seems to be an association between childhood trauma and acute stress-induced prefrontal dopamine in healthy volunteers, but not in psychosis patients[74]. Possibly, this reflects an abnormal development of the dopaminergic stress response after childhood trauma in individuals who eventually develop psychosis. Although the exact mechanisms are not clear yet, it seems that changes in HPA activity have structural implications for dopaminergic activity in the brain, and that this plays an important role in the etiology of psychosis. A systematic review of the literature on the role of stress-induced dopamine could shed light on this.

Research on sensitization of the stress response shows alterations in endocrine and neural systems in the development of psychosis. Large psychosocial life stressors, but also everyday hassles, increase the risk of the development of psychosis in individuals with a genetic vulnerability. Considering this, a logical next step is to see if it is possible to timely intervene and stop the development of psychosis. Because evermore evidence suggests that traditional treatment using antipsychotic medication actually further sensitizes the dopamine system, increasing the risk of relapse[75], a solution may be lying in psychotherapies. New-generation behavioral therapies are aimed specifically at learning new strategies to cope with stressors.

Coping with stressors

Whereas traditional cognitive-behavioral therapies mainly target the symptoms and cognitions associated with them, new generation behavioral therapies generally try to improve coping with stressors. Especially strategies aiming to avoid negative experiences (so called experiential avoidance) are deemed ineffective. Recent research within the psychosis spectrum shows that experiential avoidance is associated with higher stress levels as a result of hearing voices[76]. New-generation behavioral therapies

teach an individual to change their attitude towards negative thoughts, feelings, and sensations, to improve quality of life. A meta-analysis on the effectiveness of these therapies for psychosis reveals a moderate effect compared to treatment as usual[77]. Furthermore, it seems that some of these treaments, called Acceptance and Commitment Therapies, specifically are effective in treating psychosis. For instance, Acceptance and Commitment Therapy shows significant improvements in coping with negative experiences in psychosis patients[78-80]. Arguably even more important are the improvements of psychotic symptoms[80, 81] and the halving of the readmission rates after a 1 year follow-up period when a short form of Acceptance and Commitment Therapy is compared to treatment as usual[79, 82]. These effects are mediated by coping with symptoms[83], confirming the idea that this treatment works through the teaching of skills to cope with stressors. In addition, Acceptance and Commitment Therapy aims at behavioral activation, possibly explaining the improvements in negative symptoms[78]; a symptom cluster where traditional cognitive-behavioral therapy has achieved limited success[84]. Although the sample sizes are yet suboptimal, these studies provide hope for a new development in the area of psychotherapies for psychosis. A both logical and necessary next step is the application of Acceptance and Commitment Therapy in individuals at ultra-high risk for psychosis, as we have seen that especially in these early stages the sensitization of the stress system plays an important role.

Aims of this thesis

The current thesis has three principal aims. First, it provides a critical evaluation of the methods that have been used to measure stress in daily life. Second, it reviews the evidence for altered stress sensitivity in psychosis and discusses the mechanisms in which stress is believed to influence the developmental course of psychotic symptoms. Finally, it considers treatment strategies that target stress reactivity in an mHealth format.

Outline of the thesis

Chapter Two gives an overview of how stressors and stress reactivity have been measured in daily life using the ESM and assesses its construct validity and clinical

relevance. It further reviews the role of stress as measured with ESM in the development of psychotic and affective disorders.

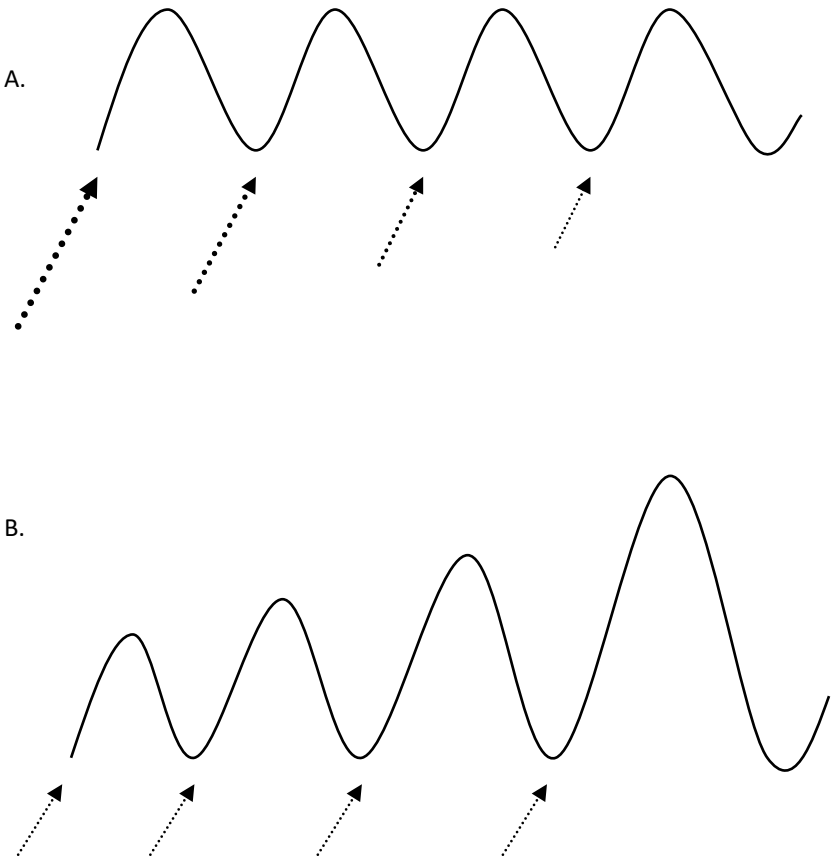
Chapter Three discusses the mechanism of increased stress sensitivity in the development and persistence of psychotic and affective symptoms. This is presented in a longitudinal study assessing the predictive value of stress sensitivity on symptom development in a cohort of adolescents and young adults.

Chapter Four presents a study on the endocrine stress response in daily life. Moreover, it investigates the hypothesis that cortisol levels and reactivity are altered in psychosis and psychosis liability. Finally, it assesses the effect of antipsychotic medication use on the HPA axis.

Chapter Five reviews the role of cerebral dopamine release during experimental stress induction. Particularly, the evidence for a sensitization of the dopamine system in psychosis and other psychopathology is discussed here. This chapter further looks into the efficacy of different types of stress tasks that have been used for this purpose.

Chapter Six proposes a novel approach for treatment of stress-related mental disorders. This mHealth treatment is based on a short form of Acceptance and Commitment Therapy and aims to train alternative stress coping skills in a patient's daily life. Development of a new, effective psychotherapy may prove invaluable in the treatment of psychosis.

Figure 1: Sensitization



Sensitization can express itself as a similar reaction to stressors of lower intensity (figure A) or as a stronger reaction to stressors of the same intensity (figure B).

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Chapter Two

Stress Assessment using Experience Sampling: Convergent Validity and Clinical Relevance

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Abstract

Subjective appraisal and experience are key aspects of stress, but most questionnaires fail to assess these measures within the transitory time-window of the acute stress response. The experience sampling method (ESM) overcomes this issue and allows for in-the-moment assessment of subjective appraisal of a situation and the stress response reflected in current subjective distress or increases in negative affect and symptomatology. The current manuscript discusses these measures and attempts to assess their validity and clinical relevance based on previous literature. Several established physiological markers of the stress response were shown to relate to ESM measures of subjective distress and affective and psychotic reactivity to daily life stressors. Across the psychopathology spectrum, ESM measures indicated increased stress sensitivity and a pathology-specific physiology. Childhood trauma and stressful life events are likewise associated with a sensitized affective response to daily stressors as measured with ESM, and in these groups psychotic stress reactivity specifically increased in psychotic individuals. Thus, although there remains room for improvement, the evidence suggests that ESM measures of subjective distress and affective and psychotic reactivity are indeed valid and meaningful.

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Introduction

During the last century the concept of "stress" has taken a central position in both preclinical and clinical research. Its implications range from an organism's most basic survival tactics to physical and mental well-being[1]. In humans, aside from major stressors such as abuse, unemployment, divorce, or death of a loved one, minor stressors that occur naturally in the flow of daily life are believed to pose a risk to those individuals who are predisposed to somatic or psychological illness[2]. In order to identify, understand, and possibly influence this complex concept and its consequences, accurate assessment of the stress response is crucial. So, what do we mean when we say stress or stress response?

The concept of stress

The definition of stress remains topic of discussion. Public speaking, important deadlines, and rumination are just a few examples of situations in which people may express that they are "stressed". On the other hand, we refer to stress as that what an animal experiences when faced with a hungry predator, or *is* a hungry predator. Indeed, stress is a complex concept that encompasses several components. One such component is a stressor, which can be conceptualized as anything that causes disbalance to an organism's homeostatic equilibrium[3]. This imbalance triggers an innate, automatic reaction in the organism's physiology aimed at reinstatement of homeostasis through allostasis, known as the acute stress response. This immediate reply to threat is highly adaptive and functions ultimately to secure survival. However, when the stress response is triggered repeatedly or persists over a longer period of time (i.e. becomes chronic) this protective mechanism may have devastating consequences for the organism.

In addition to the beneficial effects of increased chances of survival, the stress response may have detrimental effects on an organism's biology- a phenomenon coined allostatic load. Especially when exposure to a stressor is prolonged or recurrent (i.e. chronic), the excessive release of stress hormones may impair cardiovascular, metabolic, and immune functioning, and promote neuroinflammation[4]. In humans, chronic stress is implicated in the epidemiology of a broad range of mental disorders[5-9], urging for a

better understanding of its dynamics. Thus, whereas a single, short-lived stress response may not pose a direct threat to a person's well-being, a prolonged or recurrent stress response to either a physical or cognitive stressor can have detrimental effects on both somatic and psychological health.

The physiological stress response

From an evolutionary viewpoint, the stress response is seen as an adaptive reaction to (life-) threatening situations, promoting immediate behavioral action. In humans and other vertebrates, two major biological systems mark the human stress response. First, activation of the sympathoadrenal system (SAS) results in a fast release (within seconds of stress-onset) of peripheral and central catecholamines, activating the sympathetic nervous system and bringing the organism in a state of high-energy that is characteristic for the behavioral stress response. Second, the hypothalamic-pituitary-adrenal (HPA) axis sets in motion a slower cascade of neuroendocrine activity (over a course of 30 minutes after stress-onset) resulting in corticotrophin releasing factor (CRF), adrenocorticotrophic hormone (ACTH) and cortisol release. The boost of sympathetic activation and the fast effects of the neuroendocrine system that a stressor triggers are aimed at successful coping, typically in a *fight-or-flight* fashion, whereas the slow effects of neuroendocrines reverse these effects to restore balance[10]. This response offers opportunities to escape the stressor and secure survival.

Subjective appraisal of stress

In today's western society, rather than situations where we need to fight or run for our lives, stress usually arises from psychological stressors such as daily hassles, interpersonal quarrels, or a high workload. Whereas they do not directly pose an immediate threat to one's somatic well-being, and effective coping strategies typically involve no fighting or running, these situations may cause considerable problems when a person appraises them as a stressor. Under identical circumstances, a daily hassle such as a delayed train may be a stressor to one person but not to another, depending on their respective evaluation of the situation. Subjective appraisal is a process that influences whether or not something becomes a source of stress (i.e. a stressor), and, at

least in the case of negative (i.e. stressful) appraisal, consequently induces a stress response reflected by subjective feelings of distress and increased negative affect. Furthermore, subjective appraisal predicts the acute physiological stress response[11, 12]. Thus, a physiological stress response may be set in motion solely by the perception of a threat, even when an "actual" threat to homeostasis is lacking.

The implications of this becomes clear when we consider that prolonged or recurrent exposure to major life events, traumatic experiences, or daily life stressors may occur through memories, flashbacks and rumination, which in itself may again trigger a full-blown stress-response, depending on the subjective appraisal. Indeed, negative appraisal may contribute to the development of posttraumatic stress disorder[13], and constitutes one of its core features. The next paragraph discusses the complex interplay between the potential stressor, cognitive appraisal, subjective distress, affectivity, and physiology.

The relation between physiological and subjective responses

The human physiological stress response thus seems to depend at least in part on the subjective cognitive appraisal of a situation. This, however, does not imply a one-to-one relationship, or directionality, between subjectively experienced distress and the physiological stress response. For instance, some situations, such as suddenly almost getting hit by a car when you cross the street, immediately trigger a sympathetic response for which no elaborate cognitive appraisal is required. Moreover, subsequent positive (i.e. non-stressful) appraisal of the stressor might reduce the initiated stress response quickly. So, how do feelings of distress and negative affect, induced by a perceived stressor, relate to a physiological stress response?

Multiple studies that experimentally induced stress in a lab have associated subjective reports of distress or negative affect with cortisol levels. Whereas physical stressors, such as nociceptive stimulation, are relatively easy to implement in experimental research, they form a particular category of stressors that have relatively low ecological validity. Psychological stressors on the other hand may represent more daily life stressors, but confront researchers with some challenges. Several experimental tasks have been proposed to mimic psychological stressors in attempts to investigate the

acute stress response. In an extensive meta-analysis, Dickerson, Kemeny [14] compared 208 studies that made use of a psychological stress task on their effectiveness to elicit a cortisol response. They found a considerable amount of variation between stressors, with some tasks that did not significantly increase cortisol levels, and some that yielded very strong responses. The most robust cortisol increases were obtained with tasks that induced a sense of uncontrollability and posed a social evaluative threat. Of these tasks, the Trier Social Stress Task[15], where participants are confronted with an unpredictable public speech scenario, cognitive pressure, and negative feedback, is generally the most effective in terms of cortisol-induction. Interestingly, increases in cortisol were not associated with measures of subjective distress and negative affect, which were increased in all types of tasks, suggesting that subjective feelings of stress are not always predictive of HPA-axis involvement. While acknowledging the complex interplay of subjective appraisal, mood, and physiology, this finding is unexpected when considering that several studies found negative affect to mediate the relation between daily stressors and HPA-axis reactivity[16-18]. Apart from the issues that have been discussed to confound the relation between subjective reports and cortisol, measurement of physiological measures comes with several methodological complications such as timing and practicality. Also, stress is not the only influence on cortisol levels, and omission of important covariates results in more unexplained variance. On the other hand, subjective reports are similarly subject to much variation, for instance due to memory bias or social desirability, hence decreasing the likelihood of finding an association. Questionnaires such as the Perceived Stress Questionnaire[19], have been developed to measure the subjective appraisal of stress. However, it remains questionable to what extend these questionnaires reliably and validly tap onto the stress response. Particularly, since stress refers to a transient state, timely and accurate assessment is key to capturing its immediate effects in the moment. Ambulatory strategies may overcome some of the biggest issues by assessing appraisal, subjective distress, and affect in the current moment, diminishing recall bias and allowing for brief, in-the-moment measurement.

Aim of this manuscript

As a person's assumed introspective capacities allow for assessment of the subjective experience of stress, the important issue arises whether verbal reports on subjective appraisal, distress, and affect form a meaningful source of information. As arguably the most suitable candidate to accurately capture this transient process, it would be valuable to see to what extent ambulatory stress assessment, such as experience sampling, constitutes a valid and meaningful method. As such, associations are expected with established physiological and psychological derivatives of the stress response to provide a case for its validity as an estimator of the subjective appraisal of daily life stressors. The current manuscript aims to assess the construct and convergent validity of experience sampling stress measures through associations with established measures of the stress response and its relevant consequences. It first describes the subjective assessment of stress (§2.1), the associated subjective response (§2.2) and it suggests a protocol of validation through comparative analysis with other techniques and with physiological assessments.

Subjective stress in daily life

As discussed earlier, stress and the stress response refer to a transient state, it originates in interaction with environmental contexts that change over time. In order to capture this moment-to-moment variation, we need a method that allows us to assess stress real-time in daily life. The Experience Sampling Method (ESM)[20, 21], also known as Ecological Momentary Assessment (EMA)[22] or Ambulatory Assessment (AA)[23] is a structured diary technique, assessing subjective experiences in the context of daily life. Individuals fill out questionnaires throughout the day in their natural environments, where daily hassles and small disturbances from a natural source of stressful events and situations. ESM may thus provide an excellent method to study stress and the stress response.

The ESM consists of multiple measurements over the day at a number of consecutive days (typically 8 to 10 reports over 5 to 6 consecutive days)[24]. Participants receive a watch and a paper and pencil diary, a palm-top or an application on their smartphone. They receive an auditory signal at semi-random occasions throughout the day, referred

to as “beeps”. Following a beep, participants are required to fill out a questionnaire assessing their current mood, (sub)clinical symptoms, activities, social context and events. The ESM reports thus provide multiple assessments per person, within the moment avoiding recall bias, and in direct relation to the context.

Subjective appraisals of stress

ESM is typically used to assess subjective experiences of stress, what we referred to earlier as appraisals of stress[25, 26]. Different stress-appraisals have been used (see table 1 for an overview).

Event-related stress

Event-related stress is most closely related to the concept of daily hassles. Participants are asked to fill out the most important event that happened between the previous and the current beep (time frame ranging between 15 minutes and 3 hours). Participants are invited to always fill out a response (no matter how unimportant the event). This is to avoid biases in response style, such as people only filling out the questionnaire when extreme events have happened. People are then asked to report how pleasant – unpleasant this event was on a bipolar Likert scale (-3 ‘very unpleasant’ to 3 ‘very pleasant’) and how important this event was (-3 ‘not important at all’ to 3 ‘very important’). Events that were rated as unpleasant and important are considered stressful events (although many studies have only used the pleasant-unpleasant variable).

Instead of directly asking about the stressfulness of events, this approach is deriving experienced stressfulness from a combination of unpleasantness and importance. The reason for using an implicit approach is that an ESM questionnaire is designed to assess current state as accurately as possible, thus avoiding questions that may be vulnerable to social desirableness or may be influenced by general ideas about the self. As stress, nowadays, is a widely used but poorly defined concept that may be vulnerable to triggering global self-reflections, an implicit approach was chosen. However, it still remains to be shown that the implicit approach indeed is preferential over an explicit approach.

Activity-related and social stress

Whereas event-related stress is reflecting on a period of time (between two beeps) and is closely related to the concept of daily hassles, ESM also provides the opportunity to investigate even smaller levels of disturbances and annoyances that happen in the flow of daily life. We refer to appraisals of current context that may be considered as stressful.

The first context relates to activities that one is involved in. Participants are asked to report the activity that they are currently doing and subsequently provide an appraisal of these activities. The items 'I am skilled to do this activity' (reverse scored), 'I would rather do something else' and 'This activity requires effort' (all scored on a Likert scale from 1 'not at all' to 7 ' very') constitute activity-related stress.

The second context is the social context. Participants are asked about their current social context ("Whom are you with at this moment?" and subsequently, they appraise this context. The items 'I like this company' (reverse scored) and, 'I would rather be alone' constitute social stress.

The subjective stress-response

ESM can also be used to examine the stress response. This has been done in two different ways. Either one directly assesses subjective experiences of feeling distressed. Alternatively, a number of studies have investigated the impact of subjective stress-appraisals on current mood or (sub) clinical symptoms (i.e. psychotic symptoms). The latter is often referred to as reactivity to stress.

Subjective experiences of distress

Subjective distress includes items such as 'I'm in control' (reversed), 'I feel pressured', 'I feel comfortable among these people', 'I feel relaxed' (reversed), 'I feel judged', 'I do not live up to expectations'. These items thus refer to experiences of control and pressure. Although not often used in ESM stress studies, the composite measure including these items has been externally validated using an established experimental psychosocial stress task (the Montreal Imaging Stress task – inducing stress by

combining performing aritmetics under time pressure combined with psychosocial stress[27] that has been shown to trigger an endocrine stress response in multiple samples[27-29]. During this task, substantial task-induced increases in ESM subjective distress ratings were observed in samples of healthy subjects, psychotic patients, and first-degree relatives of psychotic patients[30-32], suggesting that this method of assessment indeed indicates a response to a stressful situation.

Reactivity to stress

ESM has also been used to examine how people react to subjective appraisals of stress, what we then would call the stress-response. One could examine how subjective experiences of stress are related to changes in mood. Mood mostly is defined as two separate variables, either positive affect (a composite score of items such as "I feel satisfied", "I feel relaxed", I feel cheerful") or negative affect (a composite score of items such as "I feel down", "I feel anxious", "I feel lonely", "I feel guilty", "I feel insecure"). This emotional response has been investigated in relation to event-related stress, activity-related stress, and social stress, both in healthy populations as well as in individuals suffering from psychopathology. It is important to note that emotional stress-reactivity is not assessed with a reflective question. Participants do not report how they feel in a certain situation (e.g. In this social context, I feel down or cheerful). Rather, participants report on their current mood, symptoms, context and appraisals of this context. The association between subjective appraisal and emotional reaction has later been made statistically by the investigator. This again precludes social desirability and response biases.

Within psychiatric populations, a stress response can also consist of increases in psychopathology. This has especially been investigated in relation to psychotic experiences[33-38]. Psychosis has been assessed with items such as 'I feel suspicious', 'I feel unreal', 'My thoughts are being influenced by others', 'I can't get rid of my thoughts', 'I see things that aren't really there', 'I hear voices', and 'I'm afraid I'll lose control'. These psychotic experiences have also been associated with subjective experiences of stress.

In sum, various ESM measures of subjective stress appraisal and stress-response have been put forward to capture important aspects of the subjective stress experience.

However, the question remains whether subjective stress measures and the stress-response as measured with ESM are a valuable and valid measure of stress. In the next paragraph, we will discuss the validity of the subjective stress response as assessed with ESM. In light of construct validity using the "known groups" method[39], we will compare ESM subjective stress-reactivity in samples with different psychopathologies known to be associated with vulnerability to stress. Furthermore, we will investigate convergent validity, by associating these subjective stress measures with the physiological stress response. Finally, we will investigate whether subjective ESM stress measures are related to assessments of childhood trauma or Life Events.

Validity of ESM subjective stress measures

ESM stress reactivity in psychopathology

If the subjective stress response as measured with ESM truly is a reflection of a stress response, we would expect populations with a theoretical increased vulnerability to stress to report more ESM emotional reactivity to stress. This technique is called the "known groups" method[40] and has been used to assess construct validity. Following the vulnerability-stress model, psychiatric populations in general are considered to be more stress-reactive compared to healthy controls. This may be particularly true for patients with depression (who overall report higher exposure rates to life events) and patients with psychotic disorder. Several studies have investigated subjective emotional reactivity to stress in different patient populations.

Patients with major depressive disorder (MDD) showed increases in negative affect associated with activity-related and social stress[36]. Similarly, higher negative affect reactivity to event and activity stressors was found in patients with non-remitted MDD compared to remitted patients in whom the stress-reactivity was normalized[41]. This supports the notion that the subjective stress response as measured with ESM is capturing meaningful variation at the level of the stress-vulnerability.

Similarly, many studies have been conducted in patients with a psychotic disorder. It was shown that patients diagnosed with a psychotic disorder[25, 36, 42], their first-degree relatives[25, 43] as well as people at psychometric risk for psychosis[44] and people at ultra high risk for psychosis[38], showed increased emotional and psychotic reactions to stress

as measured with ESM compared to healthy controls. Furthermore, increased stress-reactivity was particularly found in patients with positive symptoms of psychosis[33, 45], and was more pronounced in women[46]. In these studies, it was particularly relevant to use subjective stressors to examine the stress response, as patients with psychosis are thought to experience to environment as more stressful compared to controls (e.g. buying a bread in a bakery for a patient may be appraised as stressful as giving a lecture for a full auditorium would be for a healthy individual). However, using the subjective stress appraisal provides us with the opportunity to compare the stress response across populations.

These data thus seem to underscore that the subjective stress response as measured with ESM is distinguishing psychiatric from healthy populations as well as patients with more versus less symptoms, in the expected direction. These data thus support construct validity and provide a first suggestion that the ESM subjective stress response is capturing meaningful variation, which is possibly related to stress.

Hypothalamic-adrenal-pituitary axis

In order to provide more direct arguments, we now move to associations with biological markers of the stress response. Increased HPA-axis functioning poses itself as a prime target of reference when validating a stress questionnaire. ESM measures of emotional reactivity to stress should, therefore, be associated with derivatives of increased HPA-axis activation.

Several structural changes are associated with prolonged HPA-axis hyperactivity. For example, the size of the pituitary gland is increased in psychosis due to a sensitized hormonal stress response[47]. Likewise, a smaller hippocampal volume is associated with excessive hormonal release due to a hyperactive HPA-axis; experimentally increased cortisol release decreases hippocampal volume already within three days[48]. Indeed, ESM stress measures seem to relate to these markers of a sensitised stress response. Variations in daily life emotional reactivity to stressful events (i.e. event-related stress) were directly associated with both reduced hippocampal volume[49] and increased pituitary volume[50]. This suggests that, at least on a structural level, subjective emotional responsivity to stressful events in daily life as measured with ESM reflects altered

physiological and neuroendocrine functioning due to excessive exposure to stress. However, to investigate whether subjective stress also varies with the acute neuroendocrine stress response we need more functional measures, such as hormones. Salivary cortisol is a valid and reliable measure of free (unbound) cortisol in the blood[51] and can be easily implemented in an ESM approach. Following the onset of a psychological stressor, increases in salivary cortisol can be measured within 5-10 minutes after stressor onset, but peak-levels are reached after 15-30 minutes[52, 53]. ESM cortisol sampling in daily-life is done with cotton salivettes (Salivette, Sarstedt, Etten-Leur, The Netherlands). Following a beep, after filling-out a digital questionnaire, participants collect a saliva sample using a salivette, record the exact time of sampling, and store the sample in their home freezer until transport to the lab. This method yields 81% compliance rates as measured with an electronic monitoring device[54].

Several studies related daily-life stress as measured with ESM questions to fluctuations in free cortisol. For instance, during acute experimentally induced stress using the Montreal Imaging Stress Task, higher task-induced subjective distress ratings (using ESM questions) are indicative of increased levels of free cortisol in healthy volunteers[31], indeed linking ESM subjective distress rates to the endocrine stress response. However, a study by Hernaus and colleagues[30] failed to find this association in samples of healthy volunteers and psychotic patients under similar circumstances. Interestingly, the study by Hernaus et al did not find an increase in blood plasma cortisol levels during experimental stress, suggesting that no robust endocrine stress response occurred in these samples, which could possibly explain the lack of an association. Replication studies will have to indicate whether ESM subjective distress rates are indeed related to cortisol levels.

As ESM stress measures aim to assess subjective appraisal of stress under more ecologically valid circumstances, we have to move beyond laboratory settings and into daily life. Studies have looked at daily life measures of subjective stress appraisal and compared them with salivary cortisol levels to see if the two measures are related. Although Collip, van Winkel, Peerbooms, Lataster, Thewissen, Lardinois, Drukker, Rutten, Van Os, Myin-Germeys[55] indeed found that ESM event-related stress is predictive of increased free cortisol levels in a sample of first-degree relatives of

psychotic patients (a group that shows increased sensitivity to daily life stressors[33, 35]), this association was not observed in a large sample of healthy women[56], suggesting that ESM subjective stress is only related to a cortisol stress response in stress-sensitive individuals. However, considering that event-related stress is operationalized as a rating of the most important event since the last beep on a scale ranging from very unpleasant to very pleasant, the time period between the reported event and cortisol sampling may vary up to 180 minutes, possibly exceeding the optimal cortisol sampling time-frame. As subjective experiences can outlast the physiological stress response, the effect of event-related stress on levels of free cortisol might be less pronounced because the timing of the ESM event-stress assessment. The association found in first-degree relatives of psychotic patients may reflect an increased reaction of cortisol to daily hassles in this sample, large enough to measure under these circumstances.

Other ESM subjective stress measures assess stressful situations at the time of beep; activity stress and social stress allow for in-the-moment response assessment[37]. With these real-time stress measures, reactivity is related to the stress measures within the same beep. If ESM assessment of subjective stress reactivity is reflective of a full-blown stress response, associations should be observed between these real-time measures and the neuroendocrine response. Indeed, the study by Jacobs, Myin-Germeys, Derom, Delespaul, van Os, Nicolson [56] showed that both activity-related stress and social stress are associated with salivary cortisol levels at the time of assessment, and that in both cases the effect is mediated by negative affect, affirming the hypothesis that ESM stress and salivary cortisol may be sides of the same coin. A subjectively reported daily life stressful activity or social situation and the subsequent increase in negative mood thus seem to co-occur with activation of the HPA-axis, indicative of a neuroendocrine stress response.

Sympathoadrenal system (SAS)

In addition to HPA-axis measures, the immediate effects of stress on sympathetic nervous system activation allow for a directly measurable association between ESM stress (reactivity) and central and peripheral measures of stress-induced catecholaminergic increase. For instance, following an experimental acute psychosocial

stress task, increases in subjective stress are related to task-induced dopaminergic (DAergic) activity in the medial prefrontal cortex (vmPFC), as measured with positron emission tomography[32].

That the DAergic system particularly has been ascribed a role in psychosis[57] specifically forecasts a link with ESM psychotic stress reactivity. Indeed, in first-degree relatives of psychotic patients (individuals at increased genetic risk for psychosis), daily life psychotic reactivity to event-related stress is predictive of increased plasma levels of homovanillic acid, a major DA metabolite, during an acute metabolic stress task[35]. Regarding the central nervous system, psychosis is marked by increased DAergic activity in regions of the midbrain and striatum[58]. In addition, it has been suggested that prefrontal DAergic activity is reduced in psychosis[59]. In line with this suggestion, increased psychotic reactivity to task-induced stress signals less task-induced DAergic activity in the prefrontal cortex in first-degree relatives of psychotic patients[32]. One study combined a neuro-imaging PET stress approach with ESM in daily life. This study found increased psychotic reactivity to activity-related stress to be related to decreased mPFC DAergic activity during an acute psychosocial stress task[60], possibly linking ESM-based measures of psychotic stress reactivity with a DAergic stress response. However, results on prefrontal DAergic functioning in psychosis are limited and inconsistent[61]. For example, no increased DA-ergic response was observed in a PET stress study using a sample of non-medicated psychotic patients[30]. This renders statements on the relation with ESM measures of psychotic reactivity to stress speculative.

Summarizing, ESM assessment of subjective stress and stress reactivity have been directly associated with the peripheral and central catecholaminergic stress response. The evidence suggests that ESM-based assessment of subjective stress and stress reactivity reflects the physiological response to both task-induced and daily-life stress, affirming its convergent validity.

Childhood trauma and life events

A final argument in the validation of the ESM subjective stress approach is to investigate whether subjective stress reactivity as measured with ESM is related to exposure to major stressors such as childhood trauma or adversity and stressful life events.

Childhood trauma refers to a range of early negative and potentially harmful experiences[62]. Studies have focused on a wide variety of different types of childhood trauma, ranging from accidents[63], poverty[64], parental death[65], war[66], to neglect and abuse[67], and peer victimization[68]. Adult life events refer to "situations or occurrences that bring about a positive or negative change in personal circumstances and/or involve an element of threat" (Beards et al., 2013, p. 740). While the concept of life events overlaps to a degree with that of childhood trauma, the former will be used here to refer exclusively to events in adulthood.

In this paragraph, we are examining whether exposure to major stressors can be picked up and detected at the micro-level of daily life. It has been hypothesized that prolonged or repeated exposure to environmental stressors may increase sensitivity to minor day-to-day stresses through a process of sensitization[69], the latter being an important factor in increasing risk of mental disorder. In the following, we will synthesize and discuss the available evidence of the impact of large environmental exposures on the subjective stress response as measured with ESM.

Childhood trauma

Childhood trauma is usually assessed with structured interviews or (self-report) questionnaires. Some examples of self-report questionnaires are the frequently used Childhood Trauma Questionnaire (CTQ)[70], or the Childhood Experiences of Care and Abuse Questionnaire (CECA.Q)[71]. In the CTQ, items are divided over five subscales of childhood trauma (physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect), and each item is recorded on a frequency scale. The CECA.Q includes similar items, but for each item the severity of the experience is recorded, using pre-selected examples (e.g. levels of physical abuse, ranging from spanking to more sever forms) indicating the level of severity.

Although many childhood trauma studies have been published, which all have a different focus (e.g. importance of type of trauma, or focus on different types of psychopathology), the general consensus of most studies is that experiencing (severe) childhood trauma can lead individuals to have an increased stress sensitivity throughout life[72-75]. This increased stress sensitivity is thought to stem from a

sensitization of the mesolimbic DA system, which leads to a heightened DA response to future stressors[76]. Thus, if ESM is a valid measure to capture the subjective stress response, individuals exposed to childhood trauma should show an increased emotional reaction to small daily life stressors compared with non-traumatized individuals.

A few studies have investigated daily life stress sensitivity in traumatized individuals using ESM[77-80]. All these studies converge on the same result; individuals exposed to childhood trauma compared to non-traumatized individuals show increased emotional and psychotic reactivity to daily life stress as adults[77-80]. Moreover, these findings were similar using different childhood trauma questionnaires, and across samples, such as individuals from the general population[79, 80], patients with a psychotic disorder[78], and frequent GP visitors[77].

In a sample of psychotic disorder patients, Lardinois and colleagues showed that patients exposed to childhood trauma, as measured with the CTQ, had a higher psychotic and NA reactivity to event related and activity related stress[78]. Glaser and colleagues investigated frequent attenders of the GP without a clear somatic problem. He also reported an increased NA reactivity to event-related and activity-related stress in individuals who were exposed to severe sexual or physical abuse[77]. Two other studies used a general population sample, and an adapted childhood trauma questionnaire (the CTQ with the most explicit questions on sexual or physical abuse omitted), reporting similar findings of increased ESM stress sensitivity in traumatized individuals[79, 80].

Adult life events

Elevated sensitivity to minor stressors in daily life, as measured with the ESM, has also been investigated as a potential mechanism through which exposure to adult life events may impact on the development of mental disorder. Adult life events are commonly measured with questionnaires, checklists or interviews. So for example, the Life Events and Difficulties Schedule (LEDS)[81] is a semi-structured interview that allows for a very detailed assessment of life events, commonly in a 6-month or 12-month time-frame prior to interview and/or onset of a specific mental disorder[81]. Life events are rated

based on an extensive manual, case vignettes and consensus discussion considering extensive information about the nature of, and context surrounding, the life event as well as the individual's biographic circumstances. Life events can then be grouped according categories of threatening, loss, humiliation, and non-severe events as well as independent, possibly independent and dependent events[81, 82]. Using this and other validated measures, consistent evidence has accrued that implicates adult life events in the development of mood disorders, in particular, depression[83-88]. Further, some evidence has emerged that life events are associated with an increased risk of psychosis[89].

Overall, there has been relatively less research on the association between life events, stress sensitivity, and mental disorders. One study by Myin-Germeys et al[36] of individuals with psychotic disorder found elevated negative affect and reduced positive affect in response to both event- and activity-related stress in those exposed to stressful life events, measured with the Life Events and Difficulties Schedule (LEDS)[81]. Similarly, increased emotional reactivity to event-related stress has been reported in general population twins exposed to negative life events, as assessed by a modified version of Paykel's Interview of Recent Life Events[90, 91]. While, overall, research investigating this issue has been limited in amount, what there is does tentatively suggest that elevated sensitivity to minor stressors in daily life may be underlying the association between life events and mental disorder.

Although all these studies on both life events and childhood trauma report relatively small effect sizes (i.e. small increases in stress sensitivity), these effects were measured frequently during the day, for several consecutive days, and in reaction to small daily life stressors.

Overall, these findings again support the notion that the assessment of the subjective stress response with ESM is feasible, capturing valid and valuable indicators of the stress-response.

Summary and Conclusions

The current manuscript provided an overview of the evidence for the validity and clinical relevance of ESM-based subjective stress assessment. Validity was affirmed by

the finding that ESM subjective distress increased after experimental acute stress induction, and seemed to directly relate to increased cortisol levels. Furthermore, increased emotional reactivity to stressful events was found to relate to structural changes associated with prolonged stress exposure, and momentary emotional stress reactivity to increases in cortisol, directly linking these subjective reports to established measures of the physiological stress response. Moreover, the sensitized emotional stress reactivity observed in several samples suffering from psychopathological symptoms, groups that are known for their heightened stress sensitivity, stipulates both the meaningfulness and specificity of these measures. On a similar note, psychotic stress reactivity as measured with ESM was found to relate to DAergic changes associated with psychosis, which not only affirms its validity as a subjective measure of stress responsiveness, but also its clinical relevance in terms of psychopathological specificity. Finally, groups associated with heightened stress sensitivity as a result of childhood trauma or the experience of stressful life events in adulthood showed an increased affective and psychotic responsiveness to daily stressors. This further affirms that ESM subjective stress measures adequately tap onto the stress response and indicate meaningful group differences.

Although we have provided compelling evidence for ESM to be a useful and meaningful tool to assess subjective stress, this does not preclude further methodological improvement. Both the assessment of the subjective appraisal as well as the stress-response could be further improved. For example, although event-related stress seems to be an indicator of subjective stress measures, it serves suboptimally as a predictor of the physiological stress response. Adding appraisals of "importance" and "control" could possibly further improve the assessment of event-related stress. A few studies inquired about negative events specifically (Did something negative happen?). This approach, however, may be more subject to response biases (which may be specifically relevant when comparing psychopathological populations. Also, very few studies examined subjective distress directly. It would be interesting to investigate whether direct assessments of feeling stressed yield similar results to our indirect approach. Likewise, no study compared ESM subjective distress measures with other measures

regularly used for subjective distress assessment, such as the state-trait anxiety inventory.

This manuscript describes the construct and convergent validity as well as clinical relevance of ESM measures of subjective stress and stress response. Based on the findings reported here, ESM measures comprise a valid and useful tool to measure daily life stress.

Table 1: ESM measures of stress appraisals and stress response

Subjective Stress Appraisals	Stress Response
Event-related stress (-3=very unpleasant; 3=very pleasant) *'Think about the most important event since the last beep. This event was…'*	Subjective stress (1=not at all; 7=very) *'I'm in control'* (reversed), *'I feel pressured', 'I feel comfortable among these people', 'I feel relaxed'* (reversed), *'I feel judged', 'I do not live up to expectations'*
Activity-related stress (1=not at all; 7=very) *'I am not skilled to do this activity', 'I would rather do something else', 'This activity requires effort'*	Emotional stress reactivity (1=not at all; 7=very) Negative affect: *('I feel down / guilty / insecure / lonely / anxious'*) Positive affect: (*'I feel cheerful / relaxed / satisfied'*)
Social stress (1=not at all; 7=very) *'I don't like this company', 'I would rather be alone'*	Psychotic stress reactivity (1=not at all; 7=very) *'I feel suspicious'*, *'I feel unreal'*, *'My thoughts are being influenced by others'*, *'I can't get rid of my thoughts'*, *'I see things that aren't really there'*, *'I hear voices'*, and *'I'm afraid I'll lose control'*.

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Chapter Three

Is Sensitivity to Daily Stress Predictive of Onset or Persistence of Psychopathology?

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Abstract

The aim of the current study was to replicate findings in adults indicating that higher sensitivity to stressful events is predictive of both onset and persistence of psychopathological symptoms in a sample of adolescents and young adults. In addition, we tested the hypothesis that sensitivity to mild stressors in particular is predictive of the developmental course of psychopathology. We analyzed experience sampling and questionnaire data collected at baseline and one-year follow-up of 445 adolescent and young adult twins and non-twin siblings (age range: 15 – 34). Linear multilevel regression was used for the replication analyses. To test if affective sensitivity to mild stressors in particular was associated with follow-up symptoms we used a categorical approach adding variables on affective sensitivity to mild, moderate, and severe daily stressors to the model. Linear analyses showed that emotional stress reactivity was not associated with onset ($\beta = .02$; $p = .56$) or persistence ($\beta = -.01$; $p = .78$) of symptoms. There was a significant effect of baseline symptom score ($\beta = .53$; $p < .001$) and average negative affect (NA: $\beta = .19$; $p < .001$) on follow-up symptoms. Using the categorical approach we found that affective sensitivity to mild ($\beta = .25$; $p < .001$), but not moderate ($\beta = -.03$; $p = .65$) or severe ($\beta = -.06$; $p = .42$), stressors was associated with symptom persistence one year later. We were unable to replicate previous findings relating stress sensitivity linearly to symptom onset or persistence in a younger sample. Whereas sensitivity to more severe stressors may reflect adaptive coping, high sensitivity to the mildest of daily stressors may indicate an increased risk for psychopathology.

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Introduction

Stress plays a major role in the aetiology and persistence of psychopathology[1-3]. It is hypothesised that stress impacts on psychopathology through a process called stress sensitisation[4, 5], according to which repeated exposure to stressors results in an increased response to stressors of the same intensity, or a heightened response to stressors of lower intensity. These low intensity stressors, or daily hassles, as well as an individual's emotional reactivity to those stressors, have been studied using the experience sampling method (ESM) - a structured diary technique assessing momentary affect, behaviour and context in an individual's real life[6]. Using ESM, greater hypothalamus-pituitary-adrenal (HPA) responsivity to daily-life stressors has been associated with an increased genetic risk for psychosis[7]. Moreover, higher emotional reactivity to daily hassles has been linked to mood[8-10] and psychotic disorders[9, 11-15]. However, this has mainly been found in cross-sectional studies. Two longitudinal studies found that high emotional reactivity to daily stressors is associated with the prospective risk of developing chronic physical health impairments in a general population sample[16], and increased mortality in elderly men[17]. With regard to psychopathology, two longitudinal studies have studied the effects of affective reactivity to stressors on symptoms. Wichers and colleagues[18] reported high emotional reactivity to daily stressors to be predictive of depression onset and general increase in affective symptoms in general population female twins. A second prospective study in the same sample linked higher emotional reactivity to daily events not to the onset, but to the persistence of psychotic symptoms[19], raising questions about the relationship between emotional stress reactivity and psychopathology. Is high emotional stress reactivity a marker of emerging psychopathology or rather a signal of risk for persistence or recurrence? Furthermore, the sample used in these two studies consisted of adult female twins. As the onset of psychopathology often occurs early in life during the critical period of adolescence[20], it may be more relevant to study the relationship between emotional stress reactivity and psychopathology in a sample of both male and female adolescents and young adults.

Emotional reactivity to daily stressors in ESM is typically measured as the linear association between stressor intensity and negative affect[14], assuming that an increased

association between stressor intensity and negative affect across all levels of stress reflects hyperreactivity. However, this may not always be the case. In mood disorders, the kindling hypothesis[21] describes how, especially in vulnerable individuals, sensitisation to stressors of smaller magnitude may trigger depressive symptoms. In a healthy population, a hypersensitised stress system may be more reflected in a relatively strong response to milder daily stressors in particular, whereas a strong affective response to more unpleasant or stressful circumstances may actually be adaptive. However, no prospective study to date has investigated whether sensitisation reflected in stronger responses to smaller stressors in particular is a better predictor of developmental course of psychopathological symptoms.

In the current study, we investigate the effect of increased emotional reactivity to stressful daily events as measured with ESM on the development of psychopathological symptoms one year later using a prospective design in a general population sample of adolescents and young adults using both a linear and a non-linear, categorical approach to stress sensitisation. We hypothesised that 1) increased emotional reactivity to daily stressors using a linear approach is associated with future symptoms, replicating the results of Wichers and colleagues [18], 2) emotional stress reactivity is particularly predictive of future symptoms in individuals with higher levels of symptoms at baseline (i.e. symptom persistence), and 3) using a categorical approach, the predictive value of emotional stress reactivity depends on the stress severity level, where reactivity to milder stressors is more strongly associated with future symptoms than reactivity to stressors of larger magnitude.

Methods

Participants

Participants were recruited as part of the TwinssCan study, an ongoing longitudinal adolescent/young adult twin study. Individuals were recruited through a population based twin register (East Flanders Prospective Twin Survey, EFPTS[22]), which prospectively registers multiple births from 1964 onwards. In order to oversample adolescent participants, twins between 15 and 18 years of age were sent letters inviting them to participate. Additionally, all twins and their (non-twin) siblings between 15 and

34 years were eligible to participate and could register via the twin register newsletter. Approval from the local Ethics Committee (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, No. B32220107766) was obtained. Participants provided written informed consent before study inclusion. If participants were younger than 18 years, parents provided additional written informed consent. Participants were assessed using online questionnaires at baseline (t0), and one year later at follow-up (t1).

Experience sampling method

ESM is a well-validated structured diary technique that assesses individual and contextual measures in the current moment, throughout the day on six consecutive days[6, 23-25]. During the assessment period participants are prompted to fill out a brief questionnaire assessing their current mood, thoughts, context, and their appraisal of the context, at a frequency of 10 times a day at an unpredictable moment in each of ten 90-minute time blocks between 7:30 and 22:30. For the current study, participants received a digital device that allowed them to fill out the questionnaires electronically. Participants who completed less than 30% of the ESM questionnaires were excluded for analyses[26].

Negative affect (NA) was calculated using a weighted mean score of ESM items *"I feel insecure", "I feel anxious", "I feel down", "I feel guilty"*, and *"I feel lonely"*, each rated on a 7-point Likert scale (1=not at all; 7=very). Cronbach's Alpha for these items was .74. For the stressor assessment, participants were asked to think about the most important event that happened since the previous report and then report *"How pleasant was this event?"* (-3 very unpleasant; 3 very pleasant). If the event was rated lower than 0 (i.e. unpleasant events) the event was considered stressful; all scores higher than 0 (i.e. pleasant events) were recoded to 0. Emotional stress reactivity was calculated per person as the within-person average effect size of event unpleasantness on NA[18]. For the categorical analyses, we calculated separate emotional stress reactivity scores as the effect size of mild- (i.e. event pleasantness -1), moderate- (i.e. event pleasantness -2) and severe- (i.e. event pleasantness -3) stressors on NA, each compared to neutral events (score 0).

Symptoms

The Symptom CheckList 90 (SCL-90)[27] was used to assess symptoms indicative of psychopathology. The SCL-90 is a 90-item self-report questionnaire assessing the extent to which an individual was bothered by psychopathological symptoms during the last week on a 4-point Likert scale, ranging from "not at all" to "extremely". Internal consistency was high at both t0 (α = .97) and t1 (α = .97). Affective symptoms were constructed using the weighted mean of the depression and anxiety subscales (26 items; α = .93 at t0; α = .93 at t1[18]). As Collip and colleagues[19] used a measure of overall psychotic experiences, and we had no hypotheses involving specific psychotic symptom clusters, we assessed psychotic symptoms using the weighted mean of both the paranoid ideation and psychoticism symptom subscales (16 items; α = .87 at t0; α = .84 at t1). Both scales correlate strongly with the schizophrenia subscale of the Comprehensive Psychopathological Rating Scale[28, 29].

Analyses

To analyse if daily-life emotional stress reactivity was predictive of future psychopathological symptoms we conducted a linear multilevel regression analysis. SCL-90 total score at t1 served as outcome variable with emotional stress reactivity as predictor, while controlling for baseline SCl-90 total symptoms score, average NA at baseline, age, and gender (coding: male = 0; female = 1). Intercepts were allowed to vary within family by adding twin identification number as a level in the regression. Next, we added the interaction term [emotional stress reactivity*baseline total symptom score] to the model in order to test whether emotional stress reactivity was particularly predictive for future symptoms in individuals with a vulnerability for psychopathology (i.e. symptom persistency). These analyses were repeated for the affective and psychotic symptoms subscales separately.

For the categorical approach, we tested the hypothesis that the association between emotional reactivity to unpleasant events and future symptoms depends on the level of unpleasantness by creating a model that tested emotional reactivity scores to mild, moderate and severe stressors as predictor variables and general psychopathology as outcome variable. This analysis was repeated in a model that included the three

interaction terms with baseline symptoms for each levels of event unpleasantness. The same analyses were carried out in the model of affective and psychotic symptoms. In case at least one predictor showed to be significant, direct comparison analyses were done using STATA's *lincom* command. All variables were transformed into z scores in order to report standardised effect sizes.

Results

Sample

A total of 828 participants filled out the ESM questionnaires, 50 of which were excluded because of insufficient ESM data during six days of measurement; two more were excluded because of missing data on demographic variables. Of these 776 participants (467 female), belonging to 380 families (of which 41 were non-twin siblings), 755 filled out the SCL 90 at t0, and 445 also at t1 (41% dropout). There was no difference in baseline symptoms (t(634.639) = .0626, p = .9501) between those participants who completed the study and those who were lost for follow-up. Completers, however, were significantly older than non-completers (mean age completers = 18.29(SD = 3.93); mean age non-completers = 17.55(SD = 3.15); t(738.752) = 2.8365, p = .0047) and more likely to be female (χ^2(2, N = 755) = 20.7144; p < .001). Also, completers showed significantly higher emotional stress reactivity than non-completers (t(657.922) = 2.363, p = .018; for a sample description see table 1). Out of the 445 completers, 315 participants reported at least one mildly unpleasant event, 296 reported at least one moderately unpleasant event, and 272 reported at least one very unpleasant event; 171 participants reported stressors of all unpleasantness ratings during the assessment period.

The effect of baseline stress reactivity on follow-up symptoms

First, we tested the hypothesis that overall emotional stress reactivity (defined with a linear approach) at baseline is positively associated with symptoms at follow-up. While controlling for baseline symptoms, average NA, gender and age, we found no significant main effect of emotional stress reactivity on follow-up total symptoms (β = .02; SE = .04; p = .56; 95% CI = -.05 - .10). Baseline symptoms and average NA, on the

other hand, were significant predictors (baseline symptoms: β = .53; SE = .04; p < .001; 95% CI = .45 - .62; NA: β = .19; SE = .04; p < .001; 95% CI = .10 - .27). To replicate the results of Wichers and colleagues[18], we repeated the analysis for affective symptoms, but again we found no significant main effect (β = .03; SE = .04; p = .453; 95% CI = -.05 - .11). Repeating the analysis for psychotic symptoms likewise did not indicate a significant main effect for emotional stress reactivity on follow-up symptoms (β = .03; SE = .04; p = .52; 95% CI = -.06 - .11). In both analyses, baseline symptoms (affective symptoms: β = .49; SE = .04; p < .001; 95% CI = .41 - .58; psychotic symptoms: β = .45; SE = .05; p < .001; 95% CI = .36 - .54) and average NA (affective symptoms: β = .18; SE = .04; p < .001; 95% CI = .09 - .26; psychotic symptoms: β = .17; SE = .04; p < .001; 95% CI = .08 - .26) again significantly predicted symptoms. When we included the interaction effect, we found no significant interaction effect between overall emotional stress reactivity and baseline symptoms on symptoms at follow-up for total symptoms (β = -.01; SE = .04; p = .779; 95% CI -.08 - .06), affective symptoms (β = -.02; SE = .04; p = .587; 95% CI = -.10 - .06), or psychotic symptoms (β = -.04; SE = .04; p = .327; 95% CI = -.12 - .04), indicating overall emotional stress reactivity not to be related to persistence in particular, and again failing to replicate the results of a previous study[19]. Since one major difference with these previous studies was the inclusion of males in the current sample, we conducted two post-hoc analyses testing possible gender effects. However, the two-way interaction of emotional stress reactivity and gender (β = .03; SE = .08; p = .671; 95% CI -.12 - .19), nor the three-way interaction between emotional stress reactivity, gender and baseline total symptoms (β = .07; SE = .10; p = .522; 95% CI -.14 - .27) significantly predicted follow-up total symptoms. When we used the categorical approach to emotional stress reactivity, we found no difference between stress severity levels as predictors of follow-up symptoms; none of the measures were significantly associated with either total, affective, or psychotic symptoms (see table 2), refuting the hypothesis that emotional reactivity to mildly stressful events is a more suitable predictor of follow-up symptoms than emotional reactivity to moderately or very stressful events. In these models, again baseline symptoms and average NA were the strongest predictors (see table 2).

However, a significant interaction with baseline total symptoms was found for mild stressors (β = .25; SE = .06; p < .001; 95% CI = .13 - .36), but not for moderate (β = -.03; SE = .07; p = .654; 95% CI = -.17 - .11) or severe stressors (β = -.06; SE = .08; p = .422; 95% CI = -.22 - .09; see figure 1). This effect remained significant after Bonferroni correction for multiple testing. Similar effects were found for affective and psychotic symptoms (see table 2), affirming the hypotheses that increased emotional reactivity to the mildest daily stressors may at least be a more predictive measure of persistence of psychopathology than emotional reactivity to moderately or very stressful events. Direct comparisons indicated that the interaction term composed of emotional reactivity to mildly unpleasant events and baseline symptoms was more predictive of follow-up total symptoms than that of moderately (β = .28; SE = .10; p = .004; 95% CI = .09 - .46) or very stressful events (β = .31; SE = .11; p = .005; 95% CI = .10 - .53). Similar results were obtained for affective symptoms (compared to moderately stressful events: β = .26; SE = .09; p = .002; 95% CI = .09 - .43; compared to very stressful events*baseline symptoms: β = .25; SE = .10; p = .016; 95% CI = .05 - .45). Psychotic symptoms showed the same trend, but here lincom comparisons failed to reach significance (compared to moderately stressful events: β = .21; SE = .13; p = .12; 95% CI = -.05 - .47; compared to very stressful events*baseline symptoms: β = .17; SE = .12; p = .152; 95% CI = -.06 - .41).

Discussion

The current study investigated whether emotional reactivity to stressful daily events is predictive of psychopathological symptoms later in time in general population adolescents and young adults, and whether this association is moderated by baseline symptoms. In addition, it aimed to investigate whether increased emotional reactivity to milder stressors was more predictive for the developmental course of future symptoms than emotional reactivity to more severe stressors. Our findings did not confirm the first two hypotheses. Emotional reactivity to stress assessed in a linear fashion did not predict psychopathological symptoms one year later. There was also no interaction with baseline symptoms suggesting that it was not associated with onset or persistence of symptoms. Average levels of NA and baseline symptoms were the

strongest predictors of future psychopathology. With regard to the categorical approach, emotional reactivity to events of either severity was not directly related to follow-up symptoms. However, emotional reactivity specifically to the smallest stressors was related to follow-up symptoms in those with higher symptoms at baseline. These findings suggest that high emotional reactivity to the smallest daily stressors may put adolescents at risk for worsening or persistence of psychopathology.

Emotional stress reactivity and psychopathology

This study was not able to replicate previous findings indicating that general emotional stress reactivity assessed with a linear approach is associated with the development of future affective symptoms[18], and that higher emotional stress reactivity is related to persistence of psychotic symptoms[19]. This may be due to the difference between the studies. First, whereas the previous studies included an adult sample, the current study included predominantly adolescents and young adults. Other studies show that younger adults report more daily stressors and higher levels of NA than older adults[30], and show a weaker association between daily stressors and NA[31]. As young adults encounter more stressors and feel more NA on average, it may be more difficult to differentiate between healthy and unhealthy stress sensitisation, possibly requiring a more sensitive measure to make meaningful predictions. Second, whereas the current study had only one follow-up moment after one year, the sample used by Wichers et al and Collip et al averaged over four follow-up moments between three and 12 months after the first measurement. Linear emotional stress reactivity may be more predictive of future symptoms on the shorter term, therefore increasing the association. Also, Collip et al used a different approach to study the persistency of psychotic symptoms based on latent growth model see[32], possibly explaining part of the incongruence in results between their study and ours. However, if general emotional stress reactivity is associated with symptom persistence in adolescents and young adults, we expected to a find significant relationship also using the method we opted for in the current study.

A categorical approach to emotional stress reactivity

In individuals reporting more symptoms at baseline, a larger increase in NA in response

to mildly unpleasant events was associated with follow-up symptoms. This finding seems to support the hypothesis that, at least in adolescents and young adults, emotional reactivity to the smallest stressors constitutes a more clinically relevant measure of early emotional stress reactivity. In the search for better predictors for emerging and recurring psychopathology, more sensitive markers of stress vulnerability are needed. Emotional stress reactivity in daily life is typically measured in one of two ways: 1) the association between event-unpleasantness and NA; 2) the association between stressor frequency and NA. A potential problem with these methods is that they do not necessarily tap into hypersensitised or maladaptive coping, especially in the general population. A higher increase in NA following negative events is a response seen in most general population samples and probably reflects adaptive coping. After all, in general population samples higher general NA reactivity to daily stressors is associated with increases in cortisol[33, 34], which is part of the body's adaptive response to stressors. A sensitised increase assumes that the reaction is of greater magnitude, or longer duration than expected based on the objective severity of frequency of the stressors. The alternative method of measuring emotional stress reactivity as increased emotional reactivity to specifically the smallest stressors has proven more successful in predicting clinical outcome after one year in individuals who already report more symptoms at baseline, suggesting that a relatively strong affective response to mild stressors might be a more sensitive measure of inefficient coping. This study may thus contribute to new ideas and insights on measures that capture the hyperreactive emotional response to stress that may reflect aversive development.

Emotional reactivity to stress and persistence of symptoms

Baseline symptoms proved the strongest predictor for future symptoms, affirming the vulnerability to symptom persistence and worsening of those who experienced psychopathological complaints before. Previous studies show that affective reactivity to daily stressors is increased in individuals at clinical risk for psychosis, and that this effect is even stronger than reactivity in individuals diagnosed with a psychotic disorder[15, 35], suggesting that this mechanism plays a larger role in the early stages of disorder development. Interestingly, in the current study increased emotional

reactivity to the smallest stressors was particularly predictive of future psychopathology in individuals who already experienced symptoms at baseline. This is in line with the kindling and stress sensitivity hypotheses stating that recurrence or persistence of psychopathology is predicted by relatively small stressors[5, 36, 37]. The current study demonstrates that this process can be observed at a micro-level, where increases in NA following especially the smallest of daily hassles reflect a risk of symptom worsening in individuals with a psychopathological vulnerability. A very interesting finding is that low emotional reactivity to mild stressors seems to be associated with resilience in this high-risk group. Although the finding that emotional stress reactivity predicts clinical outcome is not a new one, the fact that we find an effect of the mildest stressors on symptom development in adolescents and young adults emphasises the importance of early detection and learning of adequate coping skills to increase psychological resilience in early age. Promising initiatives that aim to reach more youth with mental health problems, such as the headspace model, may play an important role in this. We also found that average levels of self-reported NA were robustly associated with symptom development, such that individuals reporting higher levels of NA at baseline tended to report more symptoms one year later. Interestingly, when considering biological markers of the stress response, a similar pattern of baseline activation of the HPA[38, 39] and sympathoadrenal[40] stress axes is observed in children and adolescents at the higher end of the psychopathology spectrum. Arguably, the association between NA and the development of future symptoms observed in the current study similarly reflects a heightened overall stress severity level in those individuals (at risk for) psychopathology. However, these findings warrant further investigation.

Limitations

There are several factors that warrant caution when drawing conclusions from these results. First, after correction for multiple comparisons only the models testing the interaction between baseline symptoms and emotional stress reactivity remained significant. Although the initial sample size was large enough to detect small effects, due to considerable dropout and the operationalisation of emotional stress reactivity (i.e.

only including those instances where the participant appraised an event as mildly/very unpleasant) the analyses were performed using less than half of the total number of participants included in the study. The selective dropout of young male participants with lower levels of emotional stress reactivity may also have had an influence on the results, although gender did not moderate the association between emotional stress reactivity and follow-up symptoms. Still, however, replication of these results in a larger sample is necessary for strong conclusions. Second, appraisal on stressor intensity (i.e. event unpleasantness) was assessed by the participants at the same time their NA response was assessed. Although we have no reason to assume that an explicit link between NA and the stressor was implied by filling out an ESM questionnaire, there may be cross-contamination of mood on appraisal of the events. For example, a high NA state might influence the judgment about the stressor's unpleasantness at the time. Future studies should replicate the results with more objective determination of stressor intensity, for instance using remote assessment of physiological responses, to determine the extent of this possible effect.

Conclusions

The aim of this study was to explore more sensitive and clinically meaningful measures of emotional stress reactivity in a sample of general population adolescents and young adults. Its results suggest that whereas high emotional responsiveness to very unpleasant daily hassles is not directly associated with a worse clinical outcome, high emotional reactivity to smaller stressors is, especially in those already struggling with psychopathological symptoms. As effect sizes are still small, however, future research should continue to develop more sensitive methods to assess first signs of maladaptive stress coping strategies that put an individual at risk for developing psychopathology. The exact relationship between stressors and emotional reactivity remains to be eluded. However, the results of the current study imply that emotional reactivity to daily hassles may in itself not be a risk factor for psychopathology in a group of adolescents and young adults as a whole. Instead, they offer a new approach to differentiate between adaptive and maladaptive emotional reactivity, and may stimulate new ideas about the daily-life assessment of affective sensitisation.

Table 1: Descriptive characteristics of the sample at baseline and one-year follow-up

	Baseline (n = 755)	Follow-up (n = 445)
	Mean(SE)	Mean(SE)
Age	18.0(.13)	19.3(.19)
Gender	61% female	67% female
SCL-90 total scale	.49(.02)	.43(.02)
Negative affect	1.63(.02)	n.a.
Negative affect at baseline[AC]	1.57(.02)	n.a.
Sensitivity to mildly unpleasant events[BC]	1.75(.03)	n.a.
Sensitivity to moderately unpleasant events[BC]	1.9(.04)	n.a.
Sensitivity to very unpleasant events[BC]	2.07(.04)	n.a.

[A] Negative affect after neutral or pleasant events
[B] Negative affect after unpleasant events minus negative affect at baseline
[C] n < 755

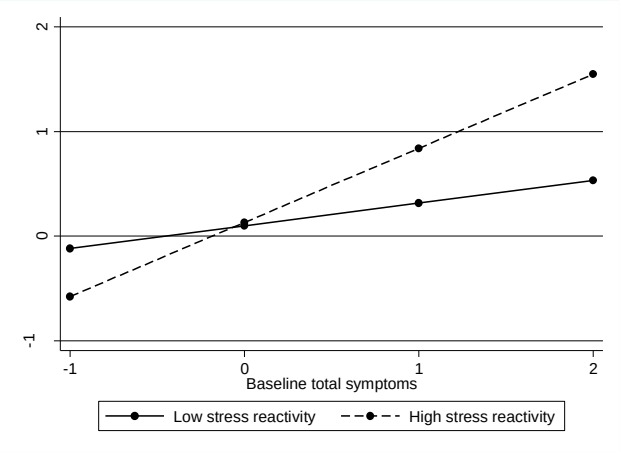
Table 2: Results from multilevel regression analyses of the categorical effects of stress sensitivity on follow-up symptoms

	SCL-90 total symptom score		SCL-90 affective symptom score		SCL-90 psychotic symptom score	
	β^A (SE), p (95% CI)	β^B (SE), p (95% CI)	β^A (SE), p (95% CI)	β^B (SE), p (95% CI)	β^A (SE), p (95% CI)	β^B (SE), p (95% CI)
Mild stressors	.105 (.067), .116 (-.026 - .236)	.246 (.06), <.001** (.128 - .364)	.102 (.068), .135 (-.032 - .235)	.208 (.056), <.001** (.098 - .317)	.052 (.073), .476 (-.091 - .195)	.209 (.072), .004* (.068 - .35)
Moderate stressors	-.064 (.076), .397 (-.214 - .085)	-.031 (.07), .654 (-.168 - .105)	-.043 (.077), .578 (-.194 - .108)	-.053 (.062), .392 (-.175 - .069)	-.06 (.083), .472 (-.222 - .103)	.002 (.092), .979 (-.177 - .182)
Severe stressors	.058 (.078), .458 (-.095 - .211)	-.065 (.08), .422 (-.222 - .093)	.068 (.08), .396 (-.088 - .223)	-.039 (.076), .607 (-.189 - .11)	.106 (.086), .219 (-.063 - .274)	.034 (.089), .702 (-.141 - .209)

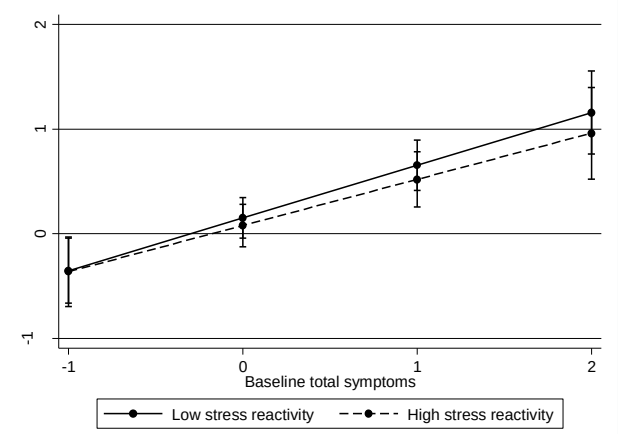
* significant at α .05
** significant at α .004 (Bonferroni corrected: p = .05/12)
A main effect of stress sensitivity, adjusted for baseline symptoms, average negative affect, age and gender
B two-way interaction of stress sensitivity x baseline symptoms, adjusted for average negative affect, age and gender

Figure 1: The effect of stress sensitivity, moderated by baseline total symptoms, on follow-up total symptoms for mildly (a), moderately (b), and very (c) stressful events

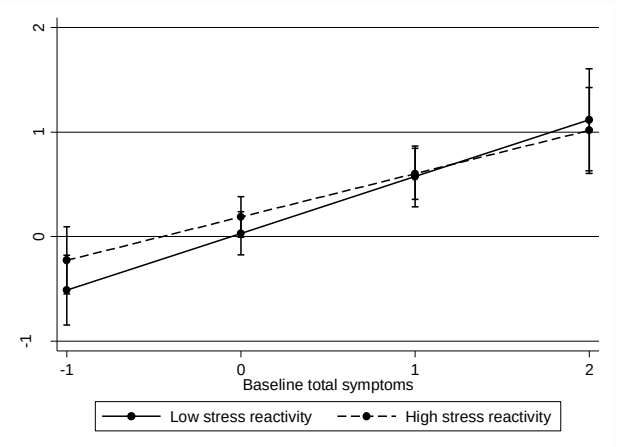
(a)



(b)



(c)



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Chapter Four

Cortisol Reactivity to Daily-Life Stressors in Psychosis

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Abstract

Results from experimental studies suggest that psychosis and psychosis liability are associated with increased cortisol levels and blunted cortisol reactivity, and that use of antipsychotics may reduce these aberrations. However, no study to date has investigated these observations in daily life. Here, we report for the first time, overall cortisol, diurnal slope, and cortisol stress reactivity in everyday life in psychosis and psychosis liability using the experience sampling method (ESM).

Our sample consisted of individuals diagnosed with psychotic disorder currently on (MPD; n=53) or off antipsychotic medication (NMPD; n=20), first-degree relatives of psychotic patients (REL; n=47), and healthy controls (HV; n=67). Saliva samples were collected throughout the day on six consecutive days and analyzed for cortisol levels. Simultaneously, stressfulness of the current activity was assessed with ESM questionnaires.

We found no group differences in overall cortisol level between groups, but REL had a steeper diurnal slope than HV; in MPD a trend was found in the same direction. Regarding reactivity to stressful activities, results indicated attenuation of the cortisol response in both patient groups compared to HV.

These results do not confirm reports of increased cortisol levels in psychosis, but provide further evidence of stress-related blunting of cortisol and as such contribute to the development of an inclusive biomarker for psychosis.

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Introduction

Stress, both at the experiential and biological level, has been reported to play a major role in psychosis[1-4]. For example, research using the experience sampling method (ESM), a structured diary technique, found that individuals across the psychosis continuum show heightened emotional reactivity to daily stressors[5-9], suggesting that psychosis liability is associated with a sensitization of the stress response. Secretion of cortisol, the end-product of the hypothalamus-pituitary-adrenal (HPA) axis and principal marker of the endocrinal stress response, is altered in psychosis as well[10]. However, several meta-analyses and systematic reviews of experimental studies suggest that this pattern is more complex than a mere elevation of cortisol levels after stress. For instance, basal cortisol levels were shown to be increased in individuals at ultra-high risk (UHR) for psychosis[11], individuals at familial risk for psychosis[12], and chronic patients[10] compared to healthy volunteers. Similarly, morning cortisol levels were heightened in patients, and seemed to increase with illness chronicity and severity[13], although results have been mixed[10-17]. In addition, there is evidence that antipsychotic medication use attenuates both basal and morning cortisol levels in psychosis[11, 13], although some recent reports found no such effect[18, 19].

Whereas overall cortisol levels appear to be increased, cortisol reactivity is blunted in both chronic and first-episode psychosis (FEP) patients, as indicated by flattened cortisol awakening responses (CAR)[20] and blunted responses to experimental psycho-social stress[17, 21], although there are indications of a publication bias[17]. Use of antipsychotic medication may have normalizing effects on the CAR in chronic patients[18, 22], although no relation was observed in FEP[22]. With regard to cortisol reactivity to stress, antipsychotic medication use has been associated with blunting of cortisol response in bipolar[23], but not in psychotic disorder[17, 18], further obscuring the relationship between antipsychotic medication use and cortisol levels. In UHR individuals, there is less evidence for a flattening of the CAR[20] and cortisol reactivity to stress may even be increased[24], whereas individuals at familial risk for psychosis show unaltered cortisol reactivity to experimental stressors[14, 15]. One study used ESM to assess cortisol responses to daily stressors, and reported increased cortisol reactivity to stressful daily events in individuals at familial risk for psychosis compared to healthy

volunteers[25]. ESM is a well-suited, ecologically valid approach to study diurnal fluctuations in cortisol and their relationships to the current context, and can provide valuable information about cortisol fluctuations throughout the day. No study to date, however, has used ESM to investigate diurnal cortisol, nor cortisol responses to daily stressors, in individuals diagnosed with a psychotic disorder.

Taken together, the empirical evidence from experimental studies suggests dynamic alterations in both overall and reactive cortisol levels across the developmental course of psychotic illness. Individuals at increased risk may show elevated cortisol levels, with mixed findings on cortisol reactivity. In patients, cortisol reactivity seems to flatten over the course of psychotic illness whereas overall cortisol levels remain high. The impact of antipsychotic medication on both overall cortisol levels and cortisol reactivity in psychosis is inconclusive. Given the highlighted inconsistencies, and the artificial nature of laboratory research settings, a comprehensive study of HPA axis function in a naturalistic environment may shed new light on the relationship between cortisol and psychosis.

In this manuscript, we investigated, for the first time, cortisol levels in the daily lives of medicated and unmedicated individuals diagnosed with psychotic disorder, their first-degree relatives, and healthy controls. More specifically, we aim to investigate 1) if differences in overall cortisol levels between the three groups observed in experimental settings are also present in a natural setting; 2) the cortisol response to daily stressors in these groups; and 3) the effect of antipsychotic medication use on cortisol stressor reactivity and its relation to psychotic experiences and symptoms. We therefore include an additional group of individuals diagnosed with psychotic disorder who have not used antipsychotic medication during the past two years.

Methods

Participants

For the current study, the samples of the Stress Reactivity in Psychosis (STRIP) 1 and 2 studies were combined[26, 27]. The STRIP1 sample consisted of individuals diagnosed with a psychotic disorder (PD; n=48), non-psychotic first-degree relatives (REL; n=48), and a healthy control group (HV; n=54). Of the PD group, ten participants did not use any

antipsychotic medication during the last year (NMPD); 38 had been on antipsychotic medication during the last year (MPD). Participants in the STRIP2 study were MPD (n=24), NMPD (n=12), and HV (n=23), thus resulting in a sample of 209 individuals (HV=77; REL=48; MPD=62; NMPD=22). Inclusion criteria for both studies were i) age 18 – 65 years and ii) sufficient command of the Dutch language to provide informed consent. Exclusion criteria were i) head trauma with loss of consciousness or presence of a central neurological disorder, ii) endocrine disorder, iii) cardiovascular disorder, iv) current/previous illicit drug use (lifetime: >15 times cannabis, >5 times other drugs; illicit drug use in the past year), and v) current alcohol use (>5 standard units of alcohol per day). Both HV and REL were excluded if they i) at any point had been diagnosed with a psychiatric disorder according to the DSM-IV-TR criteria, either as generated with the OPCRIT[28] program (STRIP1) or assessed with the Comprehensive Assessment of Symptoms and History[29] (STRIP2), or ii) currently used psychotropic medication. Ethical approval for both studies was provided by the medical ethics committee of Maastricht University.

Experience sampling method

The ESM is a structured diary technique that assesses current experiences and contexts in everyday life[9]. Participants in STRIP1 received a wristwatch and a paper diary; those in STRIP 2 were provided with an electronic dedicated device (PsyMate). The watch and device emitted 10 signals per day on random moments between 7:30 AM and 10:30 PM, on six consecutive days. Upon these prompts, participants were instructed to fill out a brief questionnaire assessing current mood, thoughts, psychotic symptoms and context. Reports were considered valid when they were provided within 15 minutes after prompting. Participants who responded to less than 20 of the total of 60 prompts were excluded from analyses due to concerns about the data quality[30]. During the six days of ESM assessment, study compliance was verified by the researchers via telephone calls with the participants, and following the assessment period during an in-person debriefing interview.

Salivary cortisol sampling

Immediately following a prompt, participants were instructed to collect a saliva sample using a cotton swab (Salivette; Sarstedt, The Netherlands) and to record the collection time. Samples collected more than 15 minutes after a prompt were not taken into account for the analyses. Subjects kept the samples in their home freezers for the duration of the study. Afterwards they were transported to the lab where the samples were stored at -20°C before being analyzed.

Questionnaires

We used the positive and negative symptom scale (PANNS)[31] to assess psychotic symptom severity. The PANSS is a 30-item interview assessing positive symptoms (7 items), negative symptoms (7 items), and general illness (16 items). Symptom severity for every item is scored on a 7-point scale (total range 30-210). Internal consistency was acceptable (Cronbach's alpha: positive symptoms=0.81; negative symptoms=0.69; general illness=0.75).

ESM measures

Daily-life stress was operationalized as the stressfulness of the activity the participant was engaged in at each assessment moment[5, 9, 32], defined as an average score on the items: "I am good at this" (reversed coded), "I would rather do something else", and "This requires effort", all rated on 7-point Likert scales, resulting in a scale ranging from 1 to 7 where higher scores indicated higher levels of current stress (Cronbach's alpha = 0.55).

To account for relevant confounders, the use of nicotine and caffeine was assessed with two questions: "Since the last beep, did you use nicotine/caffeine?" using YES/NO response options.

Salivary cortisol

All samples were analyzed at Dresden LabService GmbH (Dr. Clemens Kirschbaum laboratory in Dresden, Germany). Time-resolved radio-immunoassays with fluorescence detection were determined in duplicate[33]. The lower detection limit was

0.2 nmol/l. Intra- and interassay coefficients were <10%. Samples with cortisol >44 nmol/l were excluded from further analysis[25, 32, 34, 35].

Statistical analyses

All analyses were carried out in Stata version 13.1[36]. Group (0=HV; 1=REL; 2=MPD; 3=NMPD) differences on demographic variables and relevant ESM measures were analyzed using ANOVA and chi-square tests. Multilevel analyses were used to test the main hypotheses, with individual assessments (level 1) nested within days of assessment (level 2), which are nested within individuals (level 3). The diurnal cortisol curve was estimated using the time of assessment in hours centered on 3 PM (time), and the square of this variable ($time^2$). Initial analyses using the raw cortisol values indicated a significant effect of both time and $time^2$ variables (see Figure 1). Next, the raw cortisol values were log-transformed to account for skewed distributions. The log-transformed cortisol variable (lncort) was used as dependent variable in all analyses. Time-invariant covariates that were added to all models unrelated to stress were age, gender (0=Male; 1=Female), and current oral contraceptive use (0="No"; 1="Yes"); time-variant covariates were recent (since the previous assessment moment) use of nicotine and caffeine (0="No"; 1="Yes").

Group differences in overall cortisol levels were tested by investigating the main effect of group on lncort. Wald tests[37] were used to produce the overall group effect sizes in the form of a χ^2 value. In case of a significant effect, the *Lincom* command was used for pairwise comparisons. Next, we tested group differences in diurnal slope by adding the interaction term group*$time^2$ to the model. To compare the groups on their cortisol response to activity-related momentary stressors, we included the term activity stress in the model. We did not expect the association between cortisol and activity stress to necessarily be linear, as minor subjective stressors are unlikely to increase HPA axis activity. We therefore ran two statistical models – a linear and a quadratic one – and compared the two using the log of the likelihood function as a measure of model fit. We furthermore included log-transformed cortisol level at the previous assessment (t-1) as covariate in all analyses to account for autoregressive effects. Random slopes were added for stress, as well as time, $time^2$, lncort at t-1, nicotine use, and caffeine use.

Results

Sample characteristics

Of 209 participants, 7 did not provide enough valid ESM reports, and an additional 11 provided no valid cortisol samples and were therefore excluded from analyses. The PANSS data were missing from another four participants. The final sample thus consisted of 187 participants (HV=67; REL=47; MPD=53; NMPD=20), providing a total of 7,653 valid ESM measurements (68% compliance). Groups did not differ in age, gender, education, average reported activity stress, or caffeine use (table 1). There were significant group differences in marital status, work situation, living situation, total PANSS score, and nicotine use (table 1).

Overall cortisol levels and diurnal slope

Regarding the first aim of the study, there were no group differences in overall cortisol levels (χ^2=2.92, p=0.404; table 2 Model 1), in contrast to previous work. There was, however, a trend for a significant interaction between time and group (χ^2=6.81, p=0.078; table 2 Model 2), with REL showing significantly steeper diurnal cortisol slopes than HV (B=-0.016, p=0.013). Patients did not differ from HV with respect to their diurnal cortisol slope (MPD: B=-0.009; p=0.142; NMPD: B=-0.003, p=0.754).

Cortisol reactivity to daily stressors

Concerning the cortisol response to daily stressors we tested a linear and a quadratic model. In the linear model, we observed a significant interaction between group and activity stress (χ^2=9.54; p=0.023; table 2 Model 3). Compared to HV, MPD (B=0.054; p =0.002) but not NMPD (B=0.025; p=0.322) or REL (B=0.018; p=0.271) showed stronger associations between activity stress and cortisol. In the quadratic model (χ^2=8.46, p=0.037; table 2 Model 4), activity stress was differentially related to cortisol in HV relative to MPD (B=-0.030; p =0.013) and NMPD (B=-0.034; p=0.049). The same was true for the difference between REL and both patient groups, although this effect failed to reach significance (MPD: B=-0.021; p =0.061; NMPD: B=-0.025; p=0.131). There was no significant difference between HV and REL (B=-0.009; p=0.412), or between both patient groups (B=-0.004, p=0.809). The plot of predictive margins suggested that

whereas in HV both ends of the activity stress scale were associated with greater momentary increases in cortisol, both patient groups showed a blunted response under these conditions (see Figure 2). Model comparison indicated that the quadratic model had a significantly better fit than the linear model (LR χ^2=10.57; p=0.032).

Post-hoc analyses

To investigate whether the difference between HV and both patient groups on stress reactivity was related to the degree of psychotic symptom severity, we ran three additional analyses of the quadratic model, each including one of the PANSS subscales. Results did not change, however, and there was no association between the PANSS scales and cortisol (positive symptoms: B=-0.001, p=0.886; negative symptoms: B=-0.006, p=0.493; general illness: B=0.001, p=0.920).

Discussion

The current study investigated daily life salivary cortisol in groups of MPD, NMPD, REL, and HV. We observed no group differences in overall cortisol levels, although REL showed steeper diurnal slopes compared to the other groups. With regard to stress, both patient groups showed blunted reactivity compared to HV.

Overall cortisol and diurnal slope

The absence of a difference between HV and both patient groups on overall cortisol levels is in line with a meta-analysis reporting that cortisol levels are not altered in FEP[11]. However, especially in NMPD higher overall levels would be expected based on previous literature[10, 11, 13]. Possibly, our sample was underpowered to detect a group difference. However, given the low B value in the NMPD compared to the HV group, the current study provides no evidence for any group differences. Interestingly, PANSS scores were considerably lower in our patient samples than in a larger sample of schizophrenia patients[31]. If increased overall cortisol is related to psychotic symptom severity, this may explain the absence of an effect in the current study. Still, findings on associations between psychotic symptoms and cortisol levels are mixed[10]. Similarly, we found no difference between HV and REL in overall cortisol levels, which is in line with

previous reports[14-16], but not with results of a previous ESM study, which indicated elevated cortisol levels in REL[25]. Increased cortisol levels have been shown to be predictive of transition to psychosis in UHR[38]. If increases are a marker of vulnerability, the absence of increased overall cortisol levels in our sample may indicate that our REL sample was in fact not at high risk of developing psychosis. This possibility is supported by the low levels of reported symptoms in the REL group and the REL's average age, which was beyond the critical period of 15-25 years when psychotic disorder typically emerges.

We further found a steeper diurnal curve for REL compared to HV, which is not in line with Collip and colleagues[25], who found no difference in slope between HV and REL. We found a similar trend of steeper slopes in MPD, which failed to reach statistical significance, however. Steeper diurnal slopes have been associated with psychotic illness[39], and the steeper day curves observed in REL could thus reflect sensitivity to psychosis. However, previous work has found no difference in diurnal slope between patients with chronic schizophrenia and healthy controls[40], and a flattened diurnal slope to be related to more symptoms and higher levels of perceived stress[41].

Reactivity to stressful activities

Considering that the quadratic model had a better fit than the linear model, our results suggest that daily-life cortisol reactivity to stressful situations is decreased in both patient groups. This is in line with findings of two meta-analyses showing a blunting of cortisol reactivity to experimental stressors in psychosis[17, 21]. Controlling for PANSS score did not change the results, suggesting that the alterations in cortisol reactivity are not a direct or indirect effect of psychotic symptomatology. This confirms previous reports failing to find an association between psychotic symptoms and cortisol reactivity[22, 42, 43]. Furthermore, total PANSS score was not associated with cortisol, suggesting that other mechanisms underlie cortisol aberrations in psychosis. In psychosis, blunting of the cortisol response has been negatively related to cognitive functioning[44], and even in high-risk youth this association has been observed[45]. Flattening of cortisol responsivity has been proposed to be a byproduct of elevated cortisol levels[46], possibly as a result of changes in hippocampal and pituitary volume[47-

[49]. However, associations between the endocrine and affective stress responses are found only in a minority of studies[50]. In fact, one study found that suppressing the HPA axis did not have any influence on subjective stress reports[51], suggesting that the endocrine stress response may be dissociated from subjective experience.

Effects of antipsychotic medication

We did not find any significant differences between MPD and NMPD in overall cortisol levels, diurnal curve, or stress reactivity when looking at a quadratic association. The literature provides evidence for a "normalizing" effect of antipsychotic medication use on cortisol patterns[18, 44], but this effect has not been robust across studies. In a study in FEP, antipsychotic medication use was associated with lower diurnal cortisol levels, but unrelated to the CAR[22]. Likewise, a recent meta-analysis found no relation between antipsychotic medication dose and the cortisol stress response in individuals diagnosed with schizophrenia[17]. It thus seems that antipsychotic medication, in particular second-generation antipsychotics[52], attenuate overall cortisol levels, but not HPA axis reactivity. As for the overall cortisol levels, Cohrs and colleagues[52] found that antipsychotic medication in healthy volunteers also decreased cortisol levels, suggesting that there is no direct relationship between symptoms and medication use in the context of the HPA axis.

Individuals at familial risk for psychosis

In the current study, individuals at familial risk for psychosis showed a steeper diurnal cortisol curve, but similar overall cortisol levels and cortisol stress reactivity compared to healthy control subjects. The HPA axis is yet a relatively unexplored topic in this population. Although one study found increased cortisol levels in individuals at familial risk for psychosis[12], others found no such effect[14-16]. Furthermore, two studies that investigated reactivity to experimental stress found no altered cortisol sensitivity in individuals at familial risk for psychosis[14, 15]. On the other hand, affective stress sensitivity in daily life has been associated with pituitary and hippocampal volume, indicating stress-related alterations in the HPA axis[49, 53]. The only ESM study to date to investigate the cortisol stress response in REL did find evidence for increased reactivity

in this group compared to healthy controls[25]. This contrasts with our current findings. A possible explanation for this discrepancy is that, whereas the current study operationalized stress reactivity as the cortisol response to stressful current activities, Collip and colleagues[25] measured the cortisol response to unpleasant events. This typically concerns the time span between two assessment moments, which arguably is too large for optimal peak cortisol detection. Individuals at familial risk for psychosis pose an interesting group. With a tenfold risk increase in siblings of an individual diagnosed with schizophrenia[54], familial risk remains among the largest predictor of psychotic disorder. At the same time, however, relative absence of psychosis in an individual exposed to a similar environmental load as his or her psychotic family member may indicate the presence of (genetic) protective factors. After all, the majority of individuals at familial risk for psychosis do not develop a psychotic disorder. The familial risk sample used in the current study is more likely to be at the lower end of the psychosis spectrum, as indicated by the relatively low levels of symptoms and subjective stress reported, and, importantly, high average age to be at risk for psychosis[55].

Strengths and limitations

This study bridges the gap between lab assessment and daily life, thereby providing insight in cortisol reactivity to real-life stressors. As such, it opens up the way for more detailed assessment of physiological responses to everyday stressors and its relationship with subjective stress measures. It furthermore directly compares individuals at familial high risk, PD, and HV, providing for an overview of HPA activity during different stages of the psychosis continuum. Similarly, the direct comparison between MPD and NMPD allows for a better understanding of the effects of antipsychotics.

There are also several limitations to this study. First, although compliance to the ESM protocol was acceptable, systematic reasons for missing values may be problematic in stress research. For instance, adherence may be subject to situational circumstances, such as high levels of perceived stress. If this were to be the case, our results would underestimate levels of daily-life stress. We have, however, no reason to believe that

possible systematic "missingness" would be group-dependent and thus confound the current results.

Second, we did not take into account the years of medication use in patients. We cannot exclude the possibility that medication use in the past has long-term effects on cortisol levels in both our patient groups, possibly explaining the lack of differences on overall cortisol. The effects of antipsychotics on HPA axis functioning are not clear at present, however, and future research must further investigate its long-term effects.

Third, although activity-related stressors as operationalized here have been found to be associated with an abundance of measures that are relevant for stress research[9, 32, 56-59], it may not be an optimal measure for daily life stress assessment. As daily hassles are often short-lived moments, momentary assessment in time-sampling protocols such as these most likely fail to capture stressors that occur in between assessment moments. Other sampling protocols have been used to overcome this issue, such as inquiring about stressors that occurred in between assessment moments or event-related designs, but they have their own disadvantages (i.e. recall bias, problems with cortisol peak sampling, overt focus on the occurrence of stressors).

Conclusions

The current study is the first to assess cortisol levels in daily life in PD. Our results do not provide evidence for increased overall cortisol levels in psychosis in everyday life, but did reveal that cortisol reactivity to daily stressors is attenuated in PD, irrespective of their antipsychotic medication use. These findings add evidence for a blunting of the cortisol stress response in psychosis and as such may contribute to the development of an inclusive biomarker for psychosis[60].

Table 1: Basic sample characteristics

	HV (n = 67)	REL (n = 47)	MPD (n = 53)	NMPD (n = 20)	Test Statistic	p-value
Age mean (SD)	39.9 (14.3)	42.9 (14.6)	43.0 (10.9)	46.0 (11.7)	F = 1.31	.27
Gender						
Male	35 (52%)	17 (36%)	30 (57%)	10 (50%)	$\chi^2(3)$ = 4.61	.20
Female	32 (48%)	30 (64%)	23 (43%)	10 (50%)		
Education						
Secondary school or less	15 (22%)	8 (17%)	20 (38%)	5 (25%)	$\chi^2(3)$ = 6.27	.10
Higher education	52 (78%)	39 (83%)	33 (62%)	15 (75%)		
Marital status						
Married or living together	34 (51%)	27 (57%)	18 (34%)	6 (30%)	$\chi^2(3)$ = 8.23	**.041**
Never married/single divorced	34 (49%)	20 (43%)	35 (66%)	14 (70%)		
Work situation						
Working/significant housework/studying	60 (90%)	38 (81%)	24 (45%)	14 (70%)	$\chi^2(6)$ = 38.95	**< .01**
Disabled/unemployed	6 (9%)	7 (15%)	29 (55%)	5 (25%)		
Other	1 (1%)	2 (4%)	0	1 (5%)		
Living situation						
Alone	19 (28%)	9 (19%)	26 (49%)	15 (75%)	$\chi^2(9)$ = 45.82	**< .01**
With partner/family/children	38 (57%)	34 (72%)	17 (32%)	5 (25%)		
With parents/relatives	10 (15%)	4 (9%)	4 (8%)	0		
In healthcare institution	0	0	6 (11%)	0		
PANSS total score	33.3 (4.7)	35.4 (4.8)	45.5 (12.7)	42.1 (12.6)	F = 22.29	**< .01**
PANSS positive score	7.4 (1.3)	7.6 (1.0)	11.2 (5.2)	11.5 (5.9)	F = 16.12	**< .01**
PANSS negative score	7.6 (1.3)	8.0 (1.5)	10.0 (3.7)	8.6 (1.8)	F = 11.83	**< .01**
PANSS general score	18.3 (3.1)	19.7 (3.5)	24.3 (6.4)	22.5 (5.7)	F = 18.25	**< .01**
ESM variables						
Activity stress	2.3 (.6)	2.5 (.5)	2.5 (.6)	2.4 (.9)	F = .96	.41
Nicotine use	2.5 (8.7)	6.1 (13.8)	13.0 (17.7)	6.2 (15.6)	F = 5.79	**< .01**
Cafeine use	8.5 (8.4)	10.1 (7.6)	11.4 (9.9)	9.7 (9.8)	F = 1.10	.35

HV = healthy volunteers; REL = first-degree relatives; MPD = patients currently on antipsychotic medication; NMPD = patients currently not on antipsychotic medication; PANSS = positive and negative symptom scale; ESM = experience sampling method.

Table 2: Multilevel analyses on group differences in overall cortisol levels, diurnal slope, and cortisol stress reactivity

	χ^2(df), p	REL – HV B (SE), z	MPD – HV B (SE), z	NMPD – HV B (SE), z	MPD – REL B (SE), z	NMPD – REL B (SE), z	NMPD – MPD B (SE), z
Model 1 Group	2.92(3), .40						
Model 2 Time x Group	6.81(3), .08	**-.02 (.01), -2.49***	-.01 (.01), -1.47	.00 (.01), -.31	.01 (.01), .94	.01 (.01), 1.48	.01 (.01), .75
Model 3 Activity stress x Group	9.54(3), .02	.02 (.02), 1.10	**.05 (.02), 3.06****	.02 (.02), .99	**.04 (.02), 2.13***	.01 (.02), .28	-.03 (.03), -.1.17
Model 4 Activity stress^2 x Group	8.46(3), .04	-.01 (.01), -.82	**-.03 (.01), -2.49***	**-.03 (.02), -1.97***	-.02 (.01), -1.88	-.03 (.02), -1.51	-.01 (.02), -.24

SE = standard error; CI = confidence interval; REL = first-degree relatives; MPD = patients currently on antipsychotic medication; NMPD = patients currently not on antipsychotic medication; PANSS = positive and negative symptom scale.

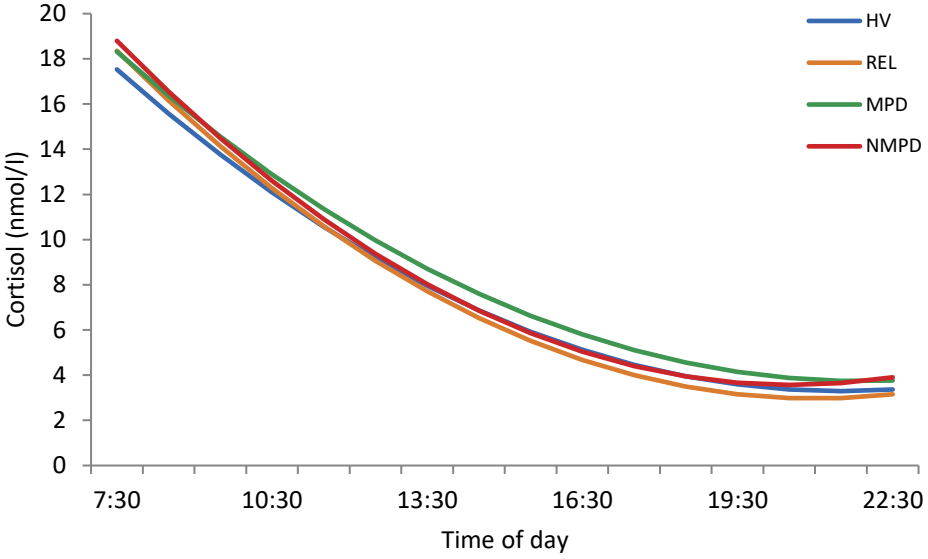
For each model, χ^2 represents the overall group effect. In case of (trend-level) significance, the pairwise comparisons are presented in B values.

Dependent variable in all models is lncort. All models control for time, time2, age, gender, oral contraceptive use, recent caffeine intake, and recent smoking.

* $p < .05$ (uncorrected)

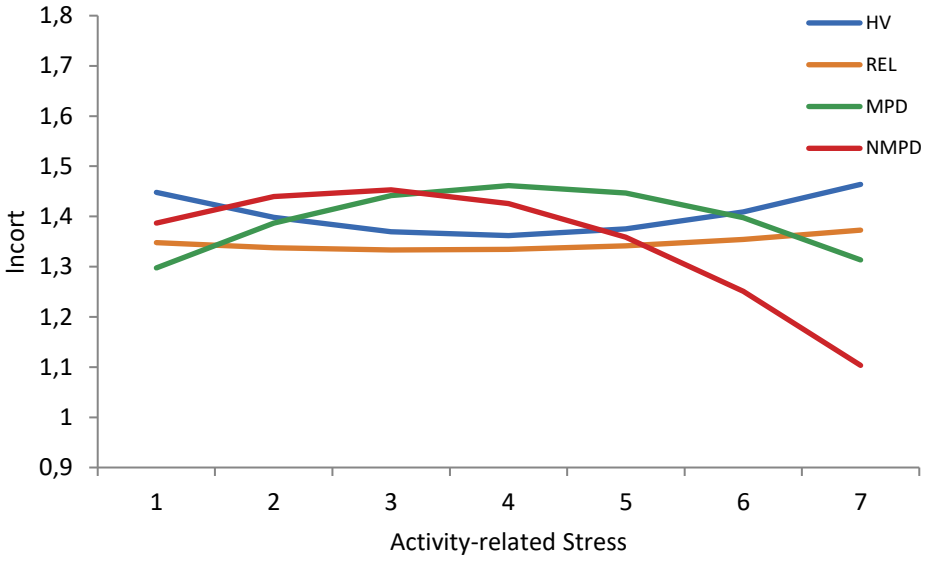
** $p < .01$ (uncorrected)

Figure 1: Diurnal slopes per group



HV: healthy volunteers; REL: first-degree relatives; MPD: patients currently on antipsychotic medication; NMPD: patients currently not on antipsychotic medication

Figure 2: The effects of activity-related stressors on cortisol



lncort: log-transformed cortisol values; HV: healthy volunteers; REL: first-degree relatives; MPD: patients currently on antipsychotic medication; NMPD: patients currently not on antipsychotic medication.

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Chapter Five

The Dopaminergic Response to Acute Stress in Health and Psychopathology: a Systematic Review

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Abstract

Previous work in animals has shown that dopamine (DA) in cortex and striatum plays an essential role in stress processing. For the first time, we systematically reviewed the *in vivo* evidence for DAergic stress processing in health and psychopathology in humans. All studies included (n studies=25, n observations=324) utilized DA D2/3 positron emission tomography and measured DAergic activity during an acute stress challenge. The evidence in healthy volunteers (HV) suggests that physiological, but not psychological, stress consistently increases striatal DA release. Instead, increased medial prefrontal cortex (mPFC) DAergic activity in HV was observed during psychological stress. Across brain regions, stress-related DAergic activity was correlated with the physiological and psychological intensity of the stressor. The magnitude of stress-induced DA release was dependent on rearing conditions, personality traits and genetic variations in several SNPs. In psychopathology, preliminary evidence was found for stress-related dorsal striatal DAergic hyperactivity in psychosis spectrum and a blunted response in chronic cannabis use and pain-related disorders, but results were inconsistent. Physiological stress-induced DAergic activity in striatum in HV may reflect somatosensory properties of the stressor and readiness for active *fight-or-flight* behavior. DAergic activity in HV in the ventral striatum and mPFC may be more related to expectations about the stressor and threat evaluation, respectively. Future studies with increased sample size in HV and psychopathology assessing the functional relevance of stress-induced DAergic activity, the association between cortical and subcortical DAergic activity and the direct comparison of different stressors are necessary to conclusively elucidate the role of the DA system in the stress response.

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Introduction

The biological stress response can be described as the bodily reaction to a perceived threat (i.e. a stressor) to homeostasis[1]. Whereas acute, moderate, stress serves as a vital adaptive mechanism by shifting available resources to a survival network[2], chronic, recurrent or extremely intense stress may lead to dysregulation of the stress system and predispose an individual to a broad range of psychopathology[3-7].

The neurobiological mechanism of the stress response has been extensively studied in psychobiological experiments. What has become apparent is that many neurochemical messengers play an essential role: adrenaline, noradrenaline, dopamine (DA), serotonin, glutamate[8] and glucocorticoids[9, 10] have all been shown to be involved in the stress response. That these chemical messengers work in different time frames and that they are differentially affected by the duration of stress (acute vs. chronic)[2, 11] indicates the system's daunting complexity.

Given that many neurotransmitters play a unique role in stress-related functions, new mechanistic insights into the stress response can be gained by studying the contribution of single neurotransmitter systems. In recent years, the DA system has been studied with great interest in the context of stress. DA is a catecholamine that is functionally involved in cognition, movement, reward motivation and salience attribution - the assignment of importance to a stimulus[12-14]. Most importantly however, changes in brain DA function have been related to stress-related psychopathological conditions such as substance abuse[15], post-traumatic stress disorder[16-21] and psychosis[22, 23]. Especially the latter disorder has consistently been associated with increased striatal DA synthesis capacity and release[24, 25]. Altered DA function in these disorders therefore renders DA a highly relevant target for stress research.

In the brain, DA acts primarily on D1 (D1 and D5) and D2 (D2, D3, D4) receptor families[12, 14] and is mainly synthesized in the ventral tegmental area (VTA) and substantia nigra (SN) of the midbrain from its precursor tyrosine. From these regions, three major pathways extend to the prefrontal cortex (mesocortical pathway), the nucleus accumbens (NAcc; mesolimbic pathway) and the basal ganglia (nigrostriatal pathway). A fourth pathway originates in the hypothalamus and projects to the pituitary gland (tuberoinfundibular pathway).

In animal models, the DA system has been shown to be consistently associated with acute and chronic stress[26]. In healthy rodents, increases in extracellular DA levels are specifically observed in the medial prefrontal cortex (mPFC) and, to a lesser extent, the NAcc and dorsal striatum after a pain[27-29] and social defeat[30] stressor. On the other hand, in animal models of mental illness (i.e. previously chronically stressed rats), a novel pain stressor consistently elicits a hyperactive DA response in the PFC[31-33], while DA transmission in subcortical areas is blunted or unaltered[32-34].

To our knowledge, no manuscript to date has reviewed the *in vivo* evidence for dopaminergic (DAergic) involvement in the stress response in humans. Here we aim to investigate i) the role of DA in the acute stress response, ii) the effects of different stressors on brain DA function and iii) the evidence for alterations in the DAergic stress response in those at increased risk for or diagnosed with a psychiatric disorder (i.e. dysregulated stress system). This review includes and is limited to all studies that have used emission tomography techniques (single-photon emission computed tomography (SPECT) or positron emission tomography (PET)) in combination with a DAergic radiotracer (DA receptor or synthesis ligand) and acute stress paradigm in humans. In emission tomography studies, task-induced reductions in binding potential relative to non-displaceable radiotracer (BP_{ND})[35] at the DA receptor are assumed to reflect increased endogenous DAergic activity[36].

Methods

PUBMED was searched for studies published before January 8th 2015 using the following Boolean phrase: ("positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" OR "single photon emission tomography" OR "SPET") AND ("dopamine") AND ("stress" OR "pain"). Studies were only considered if they i) were published in a peer-reviewed journal, ii) were written in the English language, iii) used human subjects, and iv) measured DAergic activity during experimental stress-induction. In addition to studies using psychological or psychosocial stressors, those that induced acute metabolic stress or pain were also included in the review.

Results

Based on the criteria mentioned above, a total of 22 studies were included in this review through PUBMED literature search. Additionally, two unpublished manuscripts were included after an author correspondence concerning the initial search results; one final manuscript was identified after cross-referencing (see figure 1 for a literature flowchart according to the PRISMA Statement[37]). All 25 studies used PET to measure DAergic activity during acute stress compared to a non-stress control or rest condition, reporting results on a total of 275 individuals without a diagnosis of mental disorder and 49 individuals with a diagnosis of a mental disorder. All results pertaining to stress-related DAergic activity are summarized in table 1.

Pain stress

Eleven studies investigated striatal DAergic activity in response to pain-induced stress. To induce pain, participants were all subjected to an injection of hypertonic saline to the masseter muscle.

Dorsal striatum- Pain stress-induced reductions in caudate and putamen [11C]raclopride BP_{ND} were consistently reported in healthy volunteers (HV)[38-40] and in a mixed sample of HV and patients with chronic non-neuropathic back pain (CNBP), where CNBP showed a relative increase in pain stress-induced [11C]raclopride BP_{ND} in the caudate compared to HV[41]. Positive correlations were reported between pain stress-induced reductions in caudate and putamen [11C]raclopride BP_{ND} and sensory and affective pain ratings in HV[38, 40, 41]. However, these associations were not replicated by Peciña and colleagues[42]. In HV, pain stress-induced changes in dorsal striatal [11C]raclopride BP_{ND} were reported to be associated with genetic variations in leptin gene[43], oxytocin gene[44], serotonin 2C receptor gene[45] and DA receptor subtype 2 gene[46], but not with fatty acid amide hydrolase gene[47].

Ventral striatum- One study reported pain stress-induced [11C]raclopride BP_{ND} reductions in the NAcc in HV[38], suggesting increased DAergic activity. However, this effect was only present in a contrast focused on pain-nonspecific effects of pain stress. There was a positive association between reductions in NAcc BP_{ND} and pain-related negative affect and fear[38]. Pain stress-induced reductions in NAcc [11C]raclopride BP_{ND}

were also demonstrated in a mixed sample of HV and CNBP[41]. As in the dorsal striatum, associations were reported between pain stress-induced changes in NAcc [11C]raclopride BP_{ND} in HV and genetic variations in brain-derived neurotrophic factor[48], leptin gene[43], DA receptor subtype 2[46], serotonin 2C receptor gene[45] and μ-opioid receptor gene [42], but not with fatty acid amide hydrolase gene[47].

Other regions- One study reported pain stress-induced reductions in [11C]raclopride BP_{ND} in the globus pallidus (GP) of HV[40]. In fibromyalgia subjects, no pain stress-induced changes in [11C]raclopride BP_{ND} were observed in any brain region[40].

Metabolic Stress

Both studies that investigated metabolic stress used a bolus infusion of 40 mg/kg of 2-Deoxyglucose (2DG) to induce stress.

Dorsal striatum- In HV, metabolic stress-induced reductions in [11C]raclopride BP_{ND} were observed in the whole striatum[49] and the caudate and putamen specifically[50], again suggesting increased DAergic activity.

Ventral striatum- Although metabolic stress-induced reductions in [11C]raclopride BP_{ND} were not observed in unaffected siblings of schizophrenia patients, asymmetry between metabolic stress-induced reductions in [11C]raclopride BP_{ND} in left and right NAcc was observed in this group. More specifically, metabolic stress-induced reductions in [11C]raclopride BP_{ND} were greater in the left NAcc compared to the right NAcc[50]. Asymmetry in the entire sample was positively associated with psychometric measures of psychosis liability.

Psychological stress

Twelve studies used a paradigm consisting of mathematical problems and negative feedback as a means of psychological stress-induction. Of these studies, 11 applied the Montreal Imaging Stress Task (MIST) to induce stress; one used a stressful subtraction paradigm.

Dorsal striatum- In the associative striatum (AST), psychological stress-induced reductions in [11C]-(+)-PHNO BP_{ND} were negatively associated with an angry-hostile personality trait[51]. Psychological stress-induced salivary cortisol was reported to

positively correlate with reductions in [11C]-(+)-PHNO BP_{ND} in the AST and the sensorimotor striatum (SMST) in a mixed sample of HV, individuals at clinical high risk for psychosis (CHR) and individuals with schizophrenia (SZ)[52], but this association was not found in other samples[53, 54]. Compared to HV, psychological stress-induced reductions in [11C]raclopride BP_{ND} in the AST were increased in individuals reporting physical anhedonia[54], CHR and SZ[52]. Mizrahi and colleagues[52] furthermore reported greater psychological stress-induced reductions in [11C]-(+)-PHNO BP_{ND} in the SMST in CHR and SZ, compared to HV. Although psychological stress-induced reductions in [11C]-(+)-PHNO BP_{ND} in AST and SMST were observed in CHR, psychological stress increased BP_{ND} in these areas in cannabis-using CHR (CHR-CU)[55].

Ventral striatum- Compared to HV, greater psychological stress-induced reductions in [11C]raclopride BP_{ND} in the limbic striatum (LST) were observed in individuals reporting low maternal care[54, 56] and physical anhedonia, but not in those reporting perceptual aberrations[54]. Positive correlations with psychological stress-induced levels of salivary cortisol were reported for psychological stress-induced reductions in [11C]raclopride BP_{ND} in the LST in a mixed sample of high and low maternal bonding individuals[56]. However, studies using a HV sample[53] and a mixed sample of HV and individuals scoring high on schizotypy[54] did not find this association. Psychological stress-induced reductions in LST [11C]-(+)-PHNO BP_{ND} were reported to negatively correlate with the vulnerability personality trait (e.g. anxiousness, hopelessness)[51]. Psychological stress-induced increases in [11C]-(+)-PHNO BP_{ND} in the LST were observed in CHR-CU, suggesting reduced DAergic activity[55].

Cortical regions- In HV, psychological stress was reported to increase [18F]fallypride displacement in vmPFC and the percentage of voxels displaying stress-induced [18F]fallypride displacement in vmPFC, reflective of increased DAergic activity[57]. Moreover, a significant positive association between task-induced subjective stress and the percentage of voxels displaying stress-induced [18F]fallypride displacement in vmPFC was observed in a sample of HV[57] and a mixed sample of HV and patients with a diagnosis of non-affective psychotic disorder (PDNA)[58]. Psychological stress-induced reductions in [18F]fallypride BP_{ND} that were observed in the dorsomedial prefrontal cortex (dmPFC) of HV were associated with increased heart rate, linking increased

DAergic activity in this area to a physiological stress response[59]. In addition to the mPFC, significant stress-induced [18F]fallypride displacement and percentage of voxels showing stress-induced [18F]fallypride displacement were observed in the temporal cortex of HV and PDNA[58]. No group differences were found in extrastriatal regions between HV and PDNA, or first-degree relatives of individuals with a psychotic disorder[60]. However, the latter showed a negative association between the percentage of voxels displaying stress-induced [18F]fallypride displacement in vmPFC and both task-induced subjective stress and task-induced subclinical psychotic symptoms[60]. Finally, psychological stress-induced [18F]fallypride displacement in inferior and superior frontal gyri was reported to be dependent on catechol-o-methyltransferase genotype[61].

Other regions- A negative association between psychological stress-induced reductions in the GP [11C]-(+)-PHNO BP_{ND} and a depressive personality trait was observed as well as a negative association between psychological stress-induced reductions in [11C]-(+)-PHNO BP_{ND} in SN and GP and openness to values personality trait[51]. Psychological stress-induced reductions in [11C]-(+)-PHNO BP_{ND} in the GP were smaller in CU compared to HV[62].

No psychological stress-induced changes in subcortical radiotracer BP_{ND} were reported in HV[52-54], individuals scoring high on a questionnaire assessing early-life maternal care[56] or in CU[62].

Discussion

Summary of main findings

In this review we investigated the DAergic response to acute stress in humans. In a healthy human stress system, the DAergic response to stress is dependent on the stress source. Physiological (i.e. pain, metabolic) stressors are consistently associated with increased dorsal striatal DAergic activity; the ventral striatal DAergic response is less robust. This contrasts with psychological stress, which does not consistently increase striatal DAergic activity in HV but seems to increase DAergic activity in the mPFC, an observation reported in three independent samples of healthy participants. Moreover, several genetic polymorphisms and personality traits have been shown to modulate the

DAergic stress response in striatal and extrastriatal regions, stipulating its variation and complexity. The dysregulated stress-system in humans is associated with increased DAergic activity to psychological, but not physiological, stress in dorsal and ventral striatal regions. In cortical regions, there are hints suggesting that a decreased DA response to psychological stress is a feature of the dysregulated stress-system, but further research is especially needed here. Important to note is that all studies reviewed used DA D2/3 radioligands to investigate DAergic activity.

The healthy stress-response

The healthy dorsal striatal response

The striatal DAergic stress response seems to depend on the stressor employed. None of the reported studies found a mean change in psychological stress-induced DAergic activity, suggesting significant variation in the response to psychological stress. In contrast, physiological stressors consistently increase DAergic activity in the dorsal striatum; only one study reported a significant increase in the ventral striatum.

The consistent increase of dorsal striatal DAergic activity observed during pain and metabolic stress in healthy humans is in line with results of animal studies using intense stressors[63]. The dorsal striatum receives input from prefrontal, motor and somatosensory cortices[64] and is involved in a broad range of neural processes involving cognition, as well as learning and execution of behavior and somatosensation[65].

The strongest evidence for stress-related DAergic activity in the dorsal striatum seems to point towards a role in somatosensation. The observations that dorsal striatal baseline DAergic activity is a predictor of individual pain threshold and pain tolerance[66-68] and that dorsal striatal stress-induced DAergic activity is related to subjective pain experience[38, 40, 41] suggest an important role for dorsal striatal DA in the somatosensory experience of physiologically-induced stress. As such, it could provide an explanation for the absence of this effect in healthy subjects confronted with a non-physiological (i.e. psychological) stressor. Thus, the dorsal striatal DAergic response to physiological stressors may not necessarily be related to stress, but rather reflect the somatosensory qualities inherent to these stressors.

Another prominent function of DAergic activity in the dorsal striatum is related to movement[69-72]. Its sensorimotor functional subdivision in particular, but also the AST, plays an essential role in motor control[73]. Given its involvement in motor activity, the dorsal striatal DAergic stress-response might be related to the *fight-or-flight* reaction that readies the system for action when presented with a stressor. That dorsal striatal DAergic activity is not observed in HV undergoing psychological stress may then be explained by the active motor control conditions employed in these studies. Indeed, a motor task that requires movement-planning or motor-learning is not associated with additional DAergic activity in the SMST or AST when compared to motor control alone[73]. Unfortunately, none of the studies reviewed here incorporated measures related to motor activity (or motor readiness), rendering this explanation speculative. Interestingly, increasing working memory load during a motor task elicits DAergic activity in the dorsal striatum[74], emphasizing the impact of cognitive demand on this area. Thus, while dorsal striatal DAergic activity may be related to motor activity or cognitive planning, the strongest evidence thus far points to the somatosensory activity in response to physiological stressors. Future research can be essential in separating somatosensory, motor and cognitive aspects of the DAergic stress response in the dorsal striatum.

A final speculation on the discrepant results on dorsal striatal DAergic activity between stressor types is not related to function of the DA system, but instead pertains to the efficacy of stress induction of the psychological tasks compared to the physiological paradigms. Whereas hypertonic saline[75, 76] and especially 2DG[77] elicit robust increases in cortisol levels, previous studies have shown that the MIST effectively induces elevations in salivary cortisol in about 50% of all participants[78, 79], suggesting that in actuality stress is induced only in approximately half of all participants. If cortisol levels are positively correlated with DAergic activity, as suggested in three reports[52, 56, 62], high inter-individual variability in the cortisol response might indicate similar variability in DAergic activity. Subgroup analyses in "responders" or the use of a psychological stressor that increases cortisol levels more consistently may provide more stress-specific results.

The healthy ventral striatal response

Whereas the dorsal striatal DA response seems to be associated with the sensory and affective properties related to the stressor itself, DAergic activity in the ventral striatum varies with subjective expectations about the stressor. Only when controlled for pain-specific components does an increase in ventral striatal DAergic activity become apparent, which correlates with pain stress-related negative affect and fear[38]. That only one study to date reported stress-induced ventral striatal DAergic activation in HV is somewhat surprising, given consistent reports on DAergic involvement of this region in animal studies[27-30]. One explanation for the relative paucity of stress-related findings in this area is that stress-induced DAergic activity here is subject to more variation compared to other regions. The ventral striatal DAergic stress response has been associated with genetic variation in several SNPs[42, 43, 45, 46, 48], personality characteristics [51] and rearing conditions[54, 56], indeed suggesting that stress-induced DAergic activity here is susceptible to many factors. DAergic activity in the ventral striatum is typically associated with reward expectancy[80, 81]. However, governed by the findings relating ventral striatal DA to aversive stimuli as well[82], the ventral striatal DAergic stress response might subserve an evaluative function, in the case of stress assessing salience and expectations about the stressor. In line with this reasoning, Scott and colleagues[83] reported a positive relationship between DAergic activity in the ventral striatum and anticipated placebo analgesia. Firm conclusions however cannot be drawn until ventral striatal DAergic involvement in HV has been demonstrated with more consistency within and between stressors.

The healthy extrastriatal response

In line with findings from animal studies, all three independent samples of HV that investigated cortical areas reported increased DAergic activity during stress in the mPFC[57-59]. Furthermore, DAergic activity here was positively associated with subjective stress ratings and heart rate, directly relating this response to experiential and physiological measures of stress. As with the striatal response, DAergic activity in the mPFC might be valence-unspecific. Indeed, both in animals[84-87] and humans[88, 89], cortical DAergic activity has been associated with reward learning. Interestingly,

reward anticipation-induced blood oxygenation level dependent (BOLD) activity in the mPFC is positively associated with reward-related DAergic activity in the ventral striatum[90], possibly stipulating the modulatory function of cortical processes. As in reward-related functions, the prominent role of DAergic activity in the mPFC during stress may serve modulatory purposes, regulating the more instinctive limbic and ganglionic responses to stress. Animal studies examining the effects of stress in mPFC-lesioned rodents seem to affirm this hypothesis[91-93]. In humans, the task-induced mPFC BOLD response predicts efficacy of the MIST in inducing stress[78] while limbic activity is suppressed[79]. Conversely, high baseline DA D2/D3 receptor availability (e.g. low tonic DAergic activity) throughout the PFC is related to increased amygdala BOLD reactivity to unpleasant stimuli[94]. These findings strengthen speculations about the role of the mPFC and, specifically, mPFC DAergic activity in functions such as threat monitoring and evaluation of threat levels. To confirm this explanation, future studies could simultaneously investigate prefrontal and striatal DA responses to acute stress in humans.

It is noteworthy that all estimates on cortical DAergic activity reported here were obtained using DA D2/3 radiotracer [18F]fallypride. The relative paucity of DA D2/3 receptors[95, 96] and long scanning times[97] with 18F ligands renders assessments of cortical DA function susceptible to noise and movement. In order to limit some expectancy effects and noise, some of the reviewed studies have employed a one-day single plus bolus infusion[59] or single infusion design[57, 58, 60, 61], resulting in different assumptions about steady state and estimation approaches (modeling versus subtraction).

Although results on stress-related cortical DAergic reported here were relatively consistent between studies, stimulant challenge studies in combination with [18F]fallypride have produced more variable reports. While this apparent discrepancy may also be related to the inherent differences between task-related and stimulant-induced PFC DA release[98], the development of high affinity ligands such as FLB 457[99, 100] presents a necessary avenue to confirm the role of cortical DAergic activity in the stress response.

The dysregulated stress response

Results on stress-induced DAergic activity in vulnerable individuals are heterogeneous. Whereas the fibromyalgia group showed no pain stress-induced DA response, the CNBP group showed pain stress-induced DAergic activity in both the dorsal and ventral striatum, but these results were not directly associated with pain or affective measures. These preliminary results are in line with animal studies showing that repeated pain stress decreases DA function in the striatum[32, 33].

In individuals who reported low maternal bonding, and are assumed to be at risk for a broad range of psychopathology, psychological stress increased DAergic activity in the ventral striatum. This is in line with work in animals where maternal separation increases stress-induced ventral striatal DA levels[34], although not always consistently so[101]. Within the psychosis spectrum specifically results are mixed. During psychological stress, increased DAergic activity has been reported in the ventral striatum in individuals reporting physical anhedonia, but not in those reporting perceptual aberrations[54], SZ or CHR[52]. Similarly, no main effect of metabolic stress in unaffected siblings of SZ has been observed[50]. That no stress-induced increases in ventral striatal DAergic activity are observed in SZ, CHR, individuals reporting perceptual aberrations or unaffected siblings of SZ is surprising given that increased ventral striatal DA is typically observed in positive-symptom schizophrenia in general and aberrant salience attribution in particular[102, 103]. Although the association between NAcc left-right DAergic asymmetry and psychosis liability[50] stipulates a link between DAergic activity in the ventral striatum and psychotic symptomatology, conclusive evidence for increased stress-induced DAergic activity in this region is presently lacking.

In the dorsal striatum, increased DAergic activity during stress was observed in individuals reporting physical anhedonia, SZ and CHR[52, 54], but not in individuals reporting perceptual aberrations or unaffected siblings of SZ[50, 54]. These results partly affirm increased stress-related dorsal striatal DAergic activity in the psychosis spectrum. The mixed results within the striatum are unexpected considering the solid evidence for aberrant striatal DAergic functioning in psychosis[22, 104] in combination with the well-validated putative link between stress and psychosis[105, 106].

For the ventral striatum, the lack of reports on increased stress-related DAergic activity in groups reporting (sub)clinical positive psychotic symptoms may be related to abundant variability in the DAergic stress response in this region. In sum, larger sample sizes of healthy and clinically ill individuals are necessary to provide conclusive answers on the role of stress-induced DAergic activity in striatum and its role in psychosis.

In cortical areas, no main effect of stress has been reported in the psychosis spectrum when compared to HV[58, 60], but in first-degree relatives of individuals with a psychotic disorder increased subjective stress was associated with less stress-induced DAergic activity in the mPFC. Deviations in prefrontal DAergic activity may perhaps not be expected based on inconclusive findings in the existing literature on DA in psychosis[23], although recent work seems to suggest blunted amphetamine-induced DAergic activity in SZ as measured with FLB457[100]. Again, replication samples and especially the use of high-affinity D2/3 tracers may provide insight into altered stress-induced cortical DAergic activity associated with psychosis (vulnerability).

Consistent with findings showing that greater cannabis use is associated with lower DA synthesis capacity[107], a decrease in psychological stress-induced DAergic activity was reported in all functional striatal subdivisions and GP in CHR-CU[55]. On the other hand, no psychological stress-induced DAergic activity was found in CU[62] and years of cannabis use was associated with increased stress-induced DAergic activity in the LST in CU[62]. Furthermore, the increase in stress-induced DAergic activity in the dorsal striatum seems at odds with the clear decrease in CHR-CU. While it has been demonstrated that both tetrahydrocannabidol[108] and the psychosis spectrum[22, 109] impact the DA system, both may affect the DAergic striatal stress response in a different fashion. The substance abuse pathway to psychosis may be associated with different abnormalities in DAergic functioning than other pathways[110]. However, at present, the complex interrelationship between DA, psychosis, CU and stress remains to be illuminated.

In short, changes in stress-related DAergic activity have been demonstrated in a range of psychopathology spectra. These changes are not only apparent in clinical disorders but also in groups at risk of these disorders. The exact nature and extent of DAergic

functioning during acute stress seem to depend on changes in stress-sensitivity, psychopathology spectrum and, possibly, the stressor employed. Given that the evidence for altered stress-related brain DA function in (sub)clinical groups is still preliminary, it is essential that future studies further explore these DAergic changes in relation to quality and quantity of psychopathology spectrum-specific symptoms and stress-source.

Stress-related DA and other neurotransmitter systems

When interpreting the role of the DA system in acute stress processing, it is important to consider it constitutes only a part of the entire neurochemical stress response. Cortical glutamate is associated with subjective pain perception during pain stress and, compared to HV, is decreased in chronic pain patients[111-114]. Moreover, possibly through gamma-aminobutyric acid neurons, prefrontal glutamate[11, 115, 116] and prefrontal and brainstem norepinephrine[117, 118] release may modulate stress-related cortical and striatal DAergic activity. Finally, the endogenous opioid system is involved in both physical[119, 120] and psychological stress[121, 122] and administration of a μ-opioid receptor agonist affects both cortical and subcortical DAergic activity[123, 124]. Thus, while the role of the DA system in stress processing may be relevant for stress-related disorders, the ultimate goal remains to investigate how these various neurotransmitter systems operate in synchrony to orchestrate the stress response.

Summary

This review attempted to provide an overview of the current literature on DAergic activity during acute stress. Similar to animal studies, the results from this review demonstrate that both the striatum and cortex play a role in stress processing. Stress-induced dorsal striatal DAergic activity may reflect the somatosensory experience induced by the stressor, but also involvement in active avoidance behavior or cognitive aspects of stress. The experience of stress, however, seems to be more directly related to mPFC DAergic activity, serving as a threat evaluation system, and ventral striatal DAergic activity, possibly related to expectations about the stressor. In dysregulated stress-systems, preliminary results indicate a blunted striatal DAergic response in pain-

related disorders and cannabis use and an augmented striatal DAergic response in psychosis. However, the scarcity of studies, modest sample sizes and inconsistent findings prevent any firm conclusions.

Future studies with larger samples could be aimed at investigating i) the relative involvement of stress-induced dorsal striatal DAergic activity in somatosensation, movement and cognition, ii) the function of stress-induced ventral striatal DAergic activity, iii) the relation between prefrontal and striatal DAergic activity during stress, iv) direct comparison of psychological and physiological stressors in the same sample, and v) the location and function of DAergic activity in dysregulated stress systems.

Table 1: Overview of study characteristics and findings

Pain stress First author (year)	Sample (female:male)	Radiotracer (receptor)	Protocol	Comparison	Main effects for dopaminergic activity (group comparisons) Secondary findings
Scott (2006)	17 HV (7:10)	[^{11}C]raclopride (D2/D3)	1-day fixed order	ITS - HTS (rest - HTS) - (ITS - HTS)	(↑) in dorsal caudate and putamen Positive association with subjective pain ratings in dorsal caudate and putamen (↑) in contralateral NAcc Positive association with negative affect and fear ratings in NAcc
Wood (2007)	11 FM (11:0) 11 HV (11:0)	[^{11}C]raclopride (D2/D3)	2-day fixed order	ITS - HTS	No difference in FM (↑) in GP, putamen and caudate in HV Positive association with pain rating in AST, SMST and whole striatum in HV
Scott (2007)	4 HV (0:4)	[^{11}C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↑) in dorsal caudate
Mickey (2012)	54 HV (32:22)[a] 11 HTR2C SER23 carriers	[^{11}C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↑) in NAcc, caudate and putamen in whole sample (HTR2C SER23 carriers > non-SER23 carriers)
Love (2012)	55 HV (32:23)[a] 32 OXT rs4813625 C allele carriers	[^{11}C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↑) in the ventromedial caudate in whole sample (female OXT CC/CG genotype> female GG genotype and male CC/CG genotype) Negative association with emotional well-being in ventromedial caudate in women Positive association with trait anxiety scores in ventromedial caudate in men
Burghardt (2012)	50 HV (28:22)[a] 14 LEPrs12706832 GG homozygotes	[^{11}C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↑) in NAcc, caudate and putamen in whole sample (LEP GG genotype > AA and AG genotype) Positive association with circulating leptin in ventral striatum and dorsal striatum in entire sample

Peciña (2013)	52 HV (30:22)[a] 27 DRD2 rs4274224 AG heterozygotes	[11C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↓) in NAcc, caudate and putamen in whole sample (DRD2 AG genotype < AA and GG genotype)
Peciña (2014)	50 HV (29:21)[a] 36 OPRM1 A118G AA homozygotes	[11C]raclopride (D2/D3)	1-day fixed order	ITS - HTS	(↓) in NAcc in whole sample (OPRM1 AA genotype < AG and GG genotype) No association with affective state or pain ratings
Peciña (2014)	42 HV (23:19)[a] 19 FAAHPro129 homozygotes	[11C]raclopride (D2/D3)	1-day fixed order	rest - HTS	No difference in whole sample No difference between FAAH Pro129 homozygotes and Thr129 allele carriers
Peciña (2014)	49 HV (28:21)[a] 11 BDNF Met[66] allele carriers	[11C]raclopride (D2/D3)	1-day fixed order	rest - HTS	(↑) in NAcc in whole sample (BDNF Met genotype > Val/Val genotype) Positive association with total, sensory and affective pain ratings in ventral striatum Mediates effect of BDNF on pain ratings in ventral striatum
Martikainen (2015)	16 CNBP (7:9) 16 HV (7:9)	[11C]raclopride (D2/D3)	1-day fixed order	ITS - HTS	(↑) in caudate, putamen and NAcc in whole sample (CNBP < HV in caudate) Positive association with pain unpleasantness in caudate in HV

Metabolic stress

First author (year)	Sample (F:M)	Radiotracer (receptor)	Protocol	Comparison	Main effects for DAergic activity (group comparisons) Secondary findings
Adler (2000)	6 HV (0:6)	[11C]raclopride (D2/D3)	1-day fixed order	rest - 2DG	(↑) in whole striatum
Brunelin (2010)	8 SIB (3:5) 10 HV (4:6)	[11C]raclopride (D2/D3)	1-day fixed order	rest - 2DG	No difference in SIB (↑) in left vs. right NAcc and putamen in SIB (↑) in caudate and putamen in HV Positive association with psychometric psychosis liability scores in left-right NAcc in HV and SIB

Psychological stress

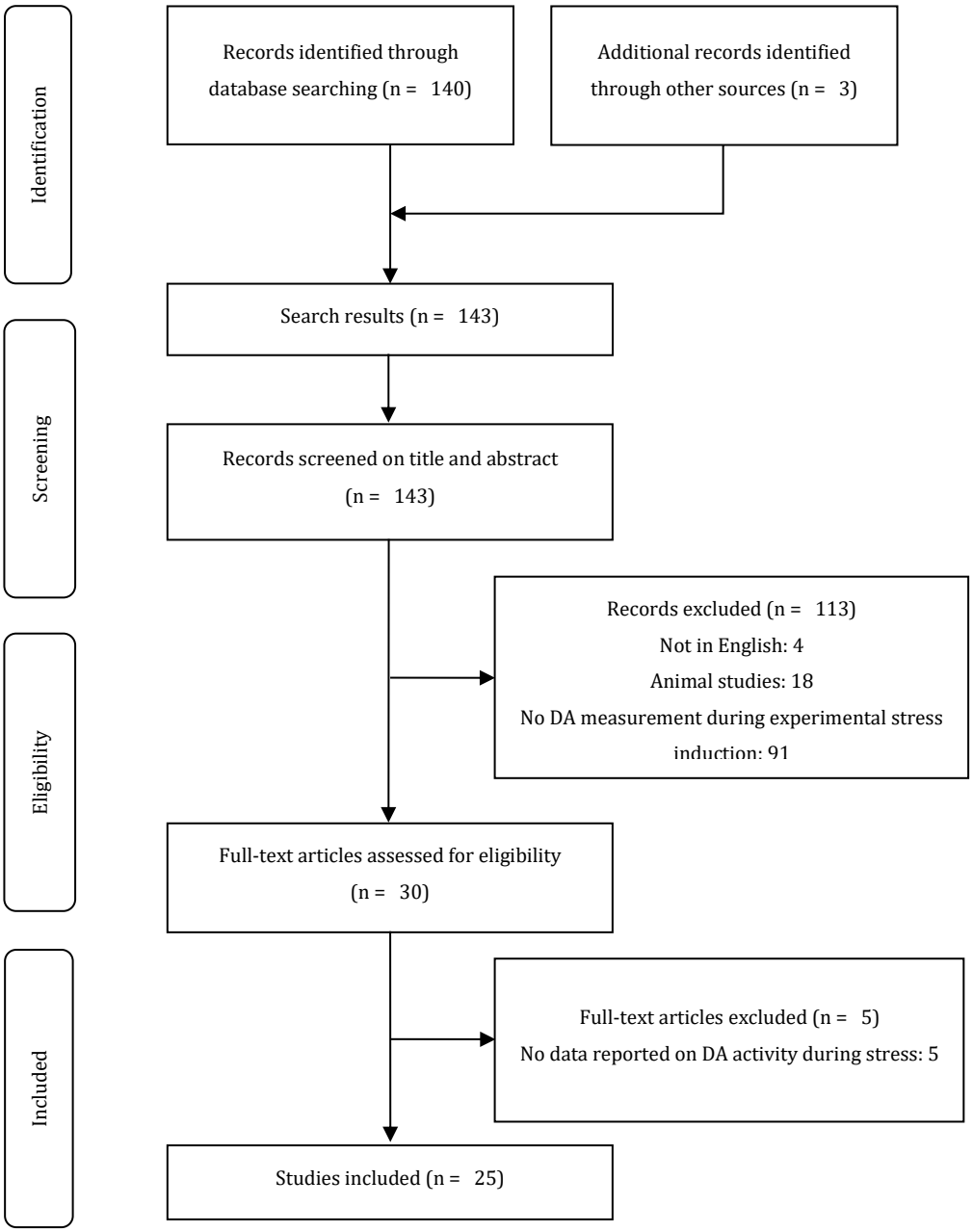
First author (year)	Sample (F:M)	Radiotracer (receptor)	Protocol	Comparison	Main effects for DAergic activity (group comparisons) Secondary findings
Pruessner (2004)	5 low MB (0:5) 5 high MB (1:4)	[^{11}C]raclopride (D2/D3)	2-day counter-balanced	rest - MIST	(↑) in bilateral ventral striatum in low MB No difference in high MB Positive association with stress-induced cortisol release in ventral striatum in whole sample
Montgomery (2006)	14 HV (5:9)	[^{11}C]raclopride (D2/D3)	1-day fixed order	CB - SUB	No difference No association with stress-induced cortisol
Soliman (2008)	9 PER-A (7:2) 7 PHY-A (6:1) 10 HV (9:1)	[^{11}C]raclopride (D2/D3)	2-day counter-balanced	SMCT - MIST	(↑) in bilateral ventral striatum, putamen and caudate in PHY-A No difference in PER-A and HV Negative association with maternal care score in whole sample No association with stress-induced cortisol
Lataster (2011)	12 HV (4:8)[b]	[^{18}F]fallypride (D2/D3)	1-day fixed order	SMCT - MIST	(↑) in ventromedial PFC Positive association with subjective stress in ventromedial PFC No association with stress-induced cortisol
Mizrahi (2012)	12 CHR (5:7)[c] 10 SZ (3:7) 12 HV (5:7)[d]	[^{11}C]-(+)-PHNO (D2/D3)	2-day fixed order	SMCT - MIST	(↑) in AST, SMST and whole striatum in CHR and SZ (CHR < SZ) No difference in HV Positive association with stress-induced cortisol in AST, SMST and whole striatum in whole sample
Suridjan (2012)	11 HV (4:7)[d]	[^{11}C]-(+)-PHNO (D2/D3)	2-day fixed order	SMCT - MIST	Negative association with angry-hostile personality trait in AST Negative association with vulnerable personality trait in LST Negative association with depressive personality trait in GP Negative association with openness to values personality trait in GP and substantia nigra
Mizrahi (2013)	13 CU (7:6) 12 HV (5:7)[d]	[^{11}C]-(+)-PHNO (D2/D3)	2-day fixed order	SMCT - MIST	No difference in CU Positive association with stress-induced cortisol release in AST in whole sample

Hernaus (2013)	26 HV/REL (11:15)[b,e] 18 COMT[158]Met carriers	[18F]fallypride (D2/D3)	1-day fixed order	SMCT - MIST	(↑) superior and inferior frontal gyrus in whole sample (COMT Met carriers < non-Met carriers)
Nagano-Saito (2013)	11 HV (0:11)	[18F]fallypride (D2/D3)	2-day counter-balanced	SMCT - MIST	(↑) in medial PFC/anterior cingulate cortex Positive association with stress-induced increase in heartrate No association with stress-induced cortisol
Lataster (2013)	14 REL (7:7)[e] 10 HV (2:8)[b]	[18F]fallypride (D2/D3)	1-day fixed order	SMCT - MIST	No difference in REL Negative association with subjective stress in ventromedial PFC in REL Negative association with subclinical psychotic symptoms in ventromedial PFC in REL
Mizrahi (2014)	12 CHR (5:7)[c] 12 CHR-CU (6:6)	[11C]-(+)-PHNO (D2/D3)	2-day fixed order	SMCT - MIST	(↓) in AST, LST, SMST and whole striatum in CHR-CU
Hernaus (2015)	12 PDNA (4:8) 12 HV (4:8)	[18F]fallypride (D2/D3)	1-day fixed order	SMCT - MIST	(↑) in medial PFC and temporal cortex in PDNA and HV Positive association with subjective stress in ventromedial PFC in whole sample

Abbreviations: HV: healthy volunteers; FM: fibromyalgia; CNBP: chronic non-neuropathic back pain; SIB: siblings of SZ patients; MB: maternal bonding; PER-A: perceptual aberrations; PHY-A: physical anhedonia; CHR: clinical high risk; SZ: schizophrenia; CU: cannabis users; REL: first-degree relatives of psychotic patients; PDNA: non-affective psychotic disorder; ITS: isotonic saline; HTS: hypertonic saline; 2DG: 2-deoxyglucose; MIST: Montreal imaging stress task; CB: counting backwards; SUB: subtraction task; SMCT: sensorimotor control task; NAcc: nucleus accumbens; GP: globus pallidus; AST: associative striatum; SMST: sensorimotor striatum; PFC: prefrontal cortex; LST: limbic striatum.

[a,b,c,d,e]: these samples refer to the same individual

Figure 1: Literature flowchart



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Chapter Six

Act in Daily Life: a Momentary Intervention Approach

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Abstract

The current article describes the Acceptance and Commitment Therapy (ACT) in Daily Life (ACT-DL) training, a new mobile Health treatment protocol for ACT. Between weekly ACT therapy sessions, patients are asked on several instances throughout the day to fill out brief questionnaires on an app about their mood, symptoms, activity, and current context, thus promoting awareness, a crucial component of ACT. The app also provides them with visual cues and exercises specifically related to the ACT sessions to help them implement the techniques previously learned in therapy into their daily lives. ACT-DL helps to apply ACT skills to diverse contexts of everyday life and to extend practice beyond the therapist's office. ACT-DL is person-tailored as patients practice with their own experiences and complaints and it increases patient empowerment. Since ACT is not symptom-specific, ACT-DL is supposed to be suited for many different target populations. Limitations and future directions are discussed.

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Introduction

In the current article, we describe a new mobile Health (mHealth) treatment protocol – ACT in daily life (ACT-DL)- based on Acceptance and Commitment Therapy (ACT)[1], helping patients develop more adaptive automatic responses to stressful situations and engage more in their personal values. ACT-DL uses a smartphone app to implement the therapeutic content into the patient's everyday life.

ACT uses cognitive and behavioral techniques to teach patients psychological flexibility (i.e., the ability to adapt one's cognitive strategies to changing conditions in the environment[2]), which in turn decreases stress and improves mental health[3]. It focuses on *acceptance* of negative thoughts and emotions instead of trying to change or control them. ACT is not symptom-specific, it can be applied to a wide range of experiences that people have. Similarly, ACT aims to teach patients skills that they can apply in new situations. Furthermore, ACT does not only help patients to handle stressful situations, it also teaches them how to engage more in the values they deem important and yet are not sufficiently reflected in their pattern of behavior – referred to as the *commitment* component[4]. Due to this broad remit, ACT has been demonstrated to be an effective treatment for many mental disorders and mental health problems[5, 6]. ACT seems to be equally effective as traditional Cognitive Behavioral Therapy (CBT) in the treatment of anxiety disorders, depression, addiction, and somatic disorders[6]. It thus seems to be a promising new approach for the treatment of mental health problems.

Most psychotherapies to date, including ACT, are applied in the therapist's office, which may contribute to the lack of success in producing consistently large effect sizes[7-9]. A promising extension to this office-based approach is the mHealth approach, which employs the use of mobile devices for the delivery of health care services and public health communication in real life[10]. Although still in its infancy, mHealth has been proven to be useful in a wide range of areas, both in physical and mental health, its methods being deployed for treatment of diabetes, asthma, weight loss, smoking, depression, and anxiety[11-16]. Using apps to introduce the therapeutic elements into the patient's everyday life, may aid in 1) focusing on the specific needs and complaints of that specific patient, thus making it person-tailored, and 2) translating the techniques

that patients have learned at their therapist's office into their everyday lives, thus increasing patient empowerment. Acquiring effective coping skills is an important step in the therapeutic process, but without the ability to apply these strategies when appropriate, they may be of little use to the patient. Unfortunately, situations that require the application of therapeutic techniques (i.e., subjectively stressful situations) often lead individuals to switch from goal-directed to habitual behavior[17]. Hence, individuals often respond by resorting to old, dysfunctional patterns as these are most familiar to them. Using newly acquired coping strategies needs to be practiced in real-life context in order to become a response that is easily accessible.

ACT in particular may benefit from an mHealth approach. ACT has its philosophical roots in *functional contextualism,* which emphasizes the relevance of the context in which a behavior is taking place and the function the behavior is serving. For example, while avoidance of a dark back alley may be adaptive, avoidance of a supermarket or public places in general (typical behavior in patients diagnosed with agoraphobia) may actually sustain mental illness. In ACT, the central question is not "Are my thoughts valid?" but "is what I am thinking useful for me in this situation?". This philosophical basis makes ACT particularly suitable for expansion to real life using an mHealth approach, putting the therapeutic techniques - quite literally - into context.

In sum, in the current article a protocol of ACT-DL is introduced, an ACT mHealth intervention that aims to increase ACT's therapeutic effectiveness through improved integration of its therapeutic techniques into the patient's everyday life.

The ACT model

In ACT, acceptance of unwanted experiences provides room for active investment in one's values. *Acceptance* is one of six components that, together with *cognitive defusion, self-as-context, contact with the present moment, values, and committed action*, comprise ACT[18]. Mastery of all six components provides an individual with the *psychological flexibility* to handle a broad range of challenging experiences. The ACT process typically starts with an exploration of the individual's unsuccessful attempts to cope with unwanted experiences (typically based on avoidance) in a process called creative hopelessness. An alternative is offered in the form of acceptance of these experiences,

taking distance of unwanted cognitions and ideas about the self, being aware about the present moment (together referred to as the acceptance core component of ACT), and investment in personal values (the commitment core component). One of the strengths of new-generation contextual psychotherapies in general, and ACT in particular, is that it trains a broad and flexible behavioral repertoire that is not symptom-specific but can be applied in almost any situation.

ACT in Daily Life

ACT in Daily Life (ACT-DL) is an ACT-based mHealth program aimed at transferring the skills and insights learned during weekly ACT sessions into the practice of daily life. In ACT-DL, patients engage in a mobile intervention that requires active exercise of ACT principles throughout the day in addition to standard ACT sessions. The program's total duration can be adapted to the patient's demands or therapist's professional appraisal (e.g., sessions can be repeated if needed). As noted earlier, in contrast to some other treatments, ACT is not aimed at symptom reduction per se, but rather applies to the full range of an individual's experiences. This approach ideally lends itself to an mHealth format based on the experience sampling method (ESM)[19, 20], a structured diary technique assessing current experiences repeatedly throughout the day. Using mobile technology, ACT-DL guides individuals in the application of ACT in the real-world and in real-time, within the scope of their current experiences and situation.

In ACT-DL, individual ACT sessions are provided under the guidance of an ACT therapist in every week of the program. An overview of the sessions' content, as well as a description of ACT-DL components and techniques, is provided below. During the sessions patients are introduced to the basic principles of ACT and provided with insights, exercises, and metaphors that help implementing ACT in their lives. ACT-DL makes use of metaphors as a reminder of its basic ideas in an intuitive format. In ACT-DL, a metaphor is presented as a visual image of an abstract situation that cues the individual to apply ACT principles to any given situation. When trying to change old behavior patterns or to achieve a lasting change, frequent practice of new behaviors is necessary. Hence, in addition to the metaphors, practical exercises are a crucial element of ACT-DL.

Following an ACT session, the patients engage on at least three consecutive days in a mobile ACT phase focusing on the components discussed in that week's session. The ACT-DL teaches patients to directly apply the newly discussed ACT components to their daily lives in the form of exercises and metaphors. The mHealth modules of ACT-DL make use of a mobile application that can be installed on a smartphone, tablet, or dedicated device. During the mobile intervention periods, patients receive each day prompts on their mobile aid at eight semi-random moments. When prompted, they are provided with a short questionnaire assessing their current mood, symptoms and activity, which guides them in the process of becoming aware of their momentary psychological state and increase their contact with the present moment. At the end of the questionnaire, patients are either presented with a visual illustration of an ACT metaphor or with a written description of an ACT exercise. In case of acceptance or defusion exercises, patients have to indicate whether or not they currently suffer from unwanted experiences. Depending on their response they receive an exercise that taps into current negative experiences or an exercise to train general ACT principles. Throughout the entire ACT-DL patients are given the opportunity to activate an ACT exercise at any time they need assistance in dealing with difficult thoughts or emotions. Furthermore, they are advised to do an extra exercise in the morning, afternoon, and evening of each day. The theme of the metaphors and exercises depends on the ACT components that are discussed during that week's session.

During the ACT session on personal values, the patients identify three values (e.g., family, career, health) which they feel are not sufficiently reflected in their daily behavior. After the next ACT session, discussing the committed action component, patients are asked to take some time in the morning to consider one of these three personal values. They are instructed to choose a value with the intention of acting in ways consistent with it throughout the day. Patients are asked to set a practical, feasible goal for that day, to guide them in their commitment to the chosen value. After every questionnaire, and once more at the end of the day, patients are asked to evaluate the extent to which they were able to live in keeping with their chosen value and if they were able to reach their goal for the day.

After all components are trained separately, the mobile intervention expands to cover the full range of ACT processes and patients learn to flexibly adopt skills and mindsets depending on the context (see Table 1 for an example of a full training program). Patients are instructed to employ learned techniques specifically in situations when they are needed (i.e., at times of distress, distressing symptoms, or challenging situations). This renders the intervention person-tailored and interactive, considering current mental state as well as contextual situation.

The following paragraphs describe each of the eight modules of ACT-DL, including the ACT component central to the module and the structure of its daily-life part. During the first session, a brief introduction to ACT and its principles and cornerstones is provided where the therapist explicitly stresses that ACT is a behavioral therapy and explains the use and importance of metaphors and exercises. The therapist furthermore provides an overview of the ACT-DL program, including the ACT-DL mobile application and the concept of the questionnaires, metaphors, and exercises within the mobile intervention. Although therapists can choose the order of the modules, some logical structure should be applied (e.g., Cognitive Defusion should precede the Self as Context module and the Values module logically precedes the Committed Action module). The last paragraph of this section describes how ACT-DL can be applied flexibly and tailored to each unique situation.

Creative Hopelessness Module

Creative hopelessness is a process of understanding that despite all frantic efforts to avoid negative experiences, the suffering remains (note that the fact that the individuals sought help for their complaints indicates the ineffectiveness of these efforts). Importantly, no alternative to avoidance is offered during the session, typically leaving the individual with a sense of hopelessness. This ultimately creates room for change and hope, which is necessary before an alternative strategy can be offered.

During the week following this session, on three consecutive days patients engage in the daily-life part this session, using the ACT-DL mobile app module: creative hopelessness. This module contains two different ACT Metaphors and four ACT Exercises with the theme “creative hopelessness” (see Table 2 for examples of ACT-DL

Metaphors and Exercises). The metaphors and exercises help the patients in their daily lives to recognize their avoidance behavior and to experience the costs (and relative lack of benefits) they come with.

In addition to each module in the mobile intervention, ACT-DL contains a questionnaire and four exercises of the "contact with the present moment" component. The questionnaires help the patients to become aware of the present moment by assessing their current experiences. Awareness of current thoughts and feelings is a necessity in the process of integrating the ACT skills and insights in daily life, and hence these skills are practiced from the first session. In the "creative hopelessness" module, the questionnaires and exercises will help the patients gain consciousness about their avoidant coping strategies in the process of creative hopelessness.

Acceptance Module

In this session, acceptance is offered as the alternative to control and avoidance. This session focuses on acceptance of unpleasant emotions or sensations and learning to "just notice" them, instead of trying to make them disappear. Patients practice acceptance through exposure to their pain. ACT assumes that pain is an inevitable part of life and that suffering is a result of ineffective coping with pain (i.e., avoidance). Pain, here, does not necessarily refer to nociception, but instead to any unwanted sensation or emotion. Suffering, then, refers to the negative consequences of avoidance behaviors, such as social isolation as a consequence of ceasing to engage in pleasant social activities because of social anxiety.

In the acceptance module, patients are provided with two ACT metaphors and seven ACT exercises centered on the "acceptance" component. Three of these exercises are aimed at current unwanted emotions and sensations; four are general acceptance exercises. During three days of the week following the session, they learn to face their own pain without attempting to control it in order to diminish the unnecessary suffering. Throughout the day, ACT metaphors remind them of the newly learned coping strategies to stop fighting pain. Practical exercises help them to put the theory into practice and experience their unwanted emotions and sensations without trying to change them. Again, this module is paralleled by ACT exercises and questionnaires of

the contact with the present moment component. This helps the "acceptance" exercises, as they crucially rely on awareness about the pain.

Cognitive Defusion Module

With regard to unwanted thoughts, cognitive defusion is offered as a possibility to take some distance from thoughts. ACT is built on the premise that people have a tendency to respond to their thoughts in a fused manner, treating them as if they were facts. If patients respond to their negative or judgmental thoughts as if they were facts, and base their behavioral choices on such thoughts, they may end up engaging in behaviors that are self-limiting or self-destructive. To defuse from one's thoughts is a skill that can only be mastered through practice, and patients are guided in this process by exercises that focus on observation of, and distancing from their thoughts.

This week's mobile intervention module contains two metaphors of the "cognitive defusion" component. In addition, the module contains seven exercises focused on cognitive defusion, three of which are aimed at current unwanted thoughts and four of which are general defusion exercises. "Cognitive defusion" is a core ACT skill that requires substantial exercise. Once patients of the ACT-DL program are able to detach from their thoughts, they can transfer these techniques to thoughts about the self as well and let go of their self-image, which is the topic of the "self as context" module.

Self as Context Module

The ACT session of this module discusses the "self as context" component. Here, the distancing from unpleasant thoughts (as learned during the cognitive defusion session), is generalized to include believes about the self as well. ACT distinguishes between the 'thinking self' and the 'observing self.' Whereas the first is the part of the self that produces thoughts, memories and convictions that form the self-image, the latter can be seen as the inner observer, the part of the self that observes the thinking self. This distinction is crucial for understanding that thoughts and feelings are something that we **have**- not that we **are**. From an ACT perspective, the fusion between self-image and thoughts or feelings is referred to as the 'conceptualized self' and limits behavioral flexibility. As patients experience that their self-image takes different forms in different

contexts they learn to realize that the self is not a rigid entity and that ultimately the observing self is the only characteristic of the self that persists over time. Like the ACT session, the daily life module of this week centers on the "self as context" component and contains two metaphors with this theme. The module further consists of four "self as context" exercises which guide the patients throughout the day in the process of understanding this relatively abstract component and living with a flexible self-image.

Contact with the Present Moment Module

As patients of the ACT-DL program practice with the "contact with the present moment" component throughout the other modules, they are familiar with the concept when they start this session. As the name suggests, the "contact with the present moment" component teaches patients to focus less on the past and future, and more on the here and now. As people worry about the future or ruminate on the past, the present passes by unnoticed. As such, the "contact with the present moment" is also about awareness about the environment (both internal and external) instead of lingering in thoughts. Possibly even more than other components, "contact with the present moment" exercises need practice, which is why a considerable part of this session is dedicated to practical exercise.

Practicing continues during the daily life module in the week following this session, where two "contact with the present moment" metaphors remind patients to be aware of the current moment and the same four exercises that they have been practicing with thus far guide them in the process.

Values Module

In contrast with the previous modules, this module aims to help people live a life guided by values, rather than uncomfortable experiences. A first step in doing so is to become aware of what matters most to the individual. During this session, patients are invited to think about their personal values. Values are those principles that matter most to a person, which serve as a direction in life, as a guide for our behavior. Exploration of personal values is necessary to invest in them, which is the aim of the next ACT component: "committed action".

The ACT-DL module of this session contains two metaphors of the "values" component. Furthermore, in addition to the four "contact with the present moment" exercises, during three days following this session, patients are provided with four exercises of the "values" component. These exercises aid them in further exploring which values are important to them.

Committed Action Module

Putting theory into practice, the "committed action" session is dedicated to the formulation of meaningful, realistic, concrete goals that are in accord with the personal values identified during the "values" session. Setting concrete goals helps the patients to translate the abstract idea of a value into practical actions to carry out. Patients learn that knowing what is important to them is an important first step, but in itself does not influence their lives; committed action is necessary.

The "committed action" daily life module contains two new metaphors and four new exercises that aim to help patients to set goals and reach them taking one step at the time. In addition, patients will still be able to opt for "contact with the present moment" exercises whenever they wish and will be presented with "contact with the present moment" questionnaires throughout the day. The final additions to this module are the morning and evening questionnaires, which remind the patients of their chosen values and let them think about actions to invest in them.

Psychological Flexibility Module

The last step in ACT pertains to the integration of all components by means of psychological flexibility, providing the patients with a variety of skills to adapt to every situation. The central theme of the last ACT session is learning to apply ACT skills in a flexible manner to any given situation, depending on the demands of the present moment. This concept is compared to learning to dance, where separate elements, such as different movements, keeping balance, and following the rhythm, represent ACT skills. Only after practicing all skills in isolation an individual is able to harmoniously combine them to a cohesive pattern. Exercises that require switching between different

ACT skills during the session provide the patients with an opportunity to practice with psychological flexibility.

During this last week of the therapy patients are provided with a module that brings all previous components together. This module contains one metaphor for each of the components acceptance, cognitive defusion, values, and committed action and all acceptance, cognitive defusion, values, committed action, and contact with the present moment exercises. In addition, it contains morning and evening questionnaires (which remind them to commit to a valued action every day) and "contact with the present moment" questionnaires. Thus, during the final week of ACT-DL the patients are guided in the flexible application of all skills they learned throughout the therapy.

The end of the ACT-DL program does not imply that patients should stop using the daily life protocol. The period of the last daily life module may be prolonged for as long as patients wish. As has been emphasized before, ACT skills need sufficient practice before they become intuitively integrated in everyday life. The daily life protocol aids this integration to the point where the patients feel that they adopted all skills and are able to apply them naturally in daily life.

ACT-DL as a flexible treatment

As presented here, ACT-DL adds an mHealth protocol to a standard ACT therapy. However, for various reasons (e.g., symptomatology, personality characteristics, practicalities, etc.) ACT-DL may be adjusted to match the diverse needs of the patients. First of all, ACT is a flexible treatment that can be fully adapted to the patient's needs and therapist's preferences. Not only can a therapist decide on the order of the modules, they can also opt to spend an extra week on the same module, or skip a module altogether. Another option is to add a psychoeducation session at the start of the therapy. Especially when patients experience excessive fear or confusion about their symptoms, starting off with a psychoeducation session aimed at normalization of the symptoms may create conditions where patients are more open for treatment in general. Another possibility is to shorten the therapy when this is desirable, or when one is limited to a preset number of sessions. For example, "cognitive defusion" and the "self as context" may be discussed in one session, as may values and committed action;

the contact with the present moment module may be left out as this component runs through all daily life modules in the form of exercises. Finally, the ACT-DL protocol can also be applied in group sessions.

Discussion

In the current article we describe the new mHealth approach ACT-DL, designed to facilitate the translation of therapeutic techniques learned during in-person ACT sessions into the patient's daily life. Following each ACT session, patients use a mobile phone application in order to train the newly acquired techniques in different contexts of their daily lives. Through self-monitoring on the one hand, which helps to increase patients' awareness of their current experiences, and the provision of visual cues and brief exercises on the other hand, patients receive direct support in those moments and environments where they need help the most[21].

The approach described in the current protocol, i.e. the adoption of ESM or self-monitoring, differs from other mHealth approaches to ACT. While mHealth has been implemented in ACT trainings before[22-25], no former mHealth ACT protocol has integrated ESM into a face-to-face ACT training program. Earlier approaches to the combination of ACT and mHealth used text-messaging and/or audio-files as a substitute for guided face-to-face therapy sessions[22, 24, 25] and required the patients to self-initiate use of the provided electronic tools[23-25]. On the one hand, ESM supports habit formation in different contexts. On the other hand, guided, personal ACT training builds on a framework that emphasizes the importance of context in our behavior and which has been proven to be effective for a wide array of psychological obstacles[5, 6, 8, 9, 26, 27]. The combination of both may particularly aid in developing healthy and consistent coping behavior in real life and an overall increased quality of life.

The current protocol provides patients with a certain number of 'reminders' in addition to the possibility to self-initiate coping and other experiential exercises in order to counteract the potential difficulties patients may experience if required to self-initiate new coping strategies in their everyday lives. These reminders increase the likelihood that exercises are carried out at different times of day and in different environments. Moreover, the use of ESM in itself governs the acquisition of self-insight and awareness

of one's emotions, behavior, physical, and social environment[28, 29], hence a core-component of ACT. It is therefore a suitable extension for this type of therapy.

An initial version of ACT-DL introduced in the current article has already been tested on its feasibility and acceptability among psychiatric patients in a feasibility study[30]. One hundred sixty-one in-patients with varying DSM-IV diagnoses (both on axis I and axis II, with the exception of psychotic disorder) participated in the trial. Overall, patients evaluated the training favorably and experienced the addition of the mHealth component as a useful training component, promoting the use of ACT in daily life. Moreover, patients indicated that they would recommend the use of ACT-DL to others. Based on findings of this first feasibility study the current protocol was developed further and is currently being implemented in a randomized clinical trial (trial number: NTR4252), testing its effectiveness in individuals in the prodromal and early stage of psychosis.

Next to the potential to improve effectiveness of ACT, the current protocol may have some limitations. First and foremost, patients might need to adjust to the number of prompts and their potentially disruptive nature. ESM implies that patients are prompted with several beeps per day, requiring them to interrupt their daily routine on multiple occasions each day. This procedure might be experienced as challenging. However, patient reports from other ESM studies by our group have shown that many individuals grow fond of the device and find it a valuable tool in their treatment process[31]. Another potential limitation is that execution of some of the ACT-DL exercises, such as mindfulness exercises, in the presence of others might lead to an unpleasant degree of self-awareness. However, since the ACT-DL exercises were designed to be carried out in varying life situations, usually the presence of others would not hinder execution of those exercises. Moreover, only regular engagement in the exercises within varying environments will establish a routine in the application of the newly acquired ACT skills. If patients practice these skills in only one environment (i.e., an environment where it is easy to practice), generalization of these skills to different contexts will be much less likely to occur. Hence, it is assumed that this initial burden will eventually turn into a valuable procedure.

Advancements in technology imply advancements in mHealth, and the current protocol holds potential that has not yet been exhausted. One possibility to further improve the current ACT-DL protocol is to build on the answers patients provide via the ESM questionnaires, i.e., to use momentary indications of mood and symptoms to subsequently feed back exercises adjusted to these indications[21]. For instance, whenever a patient indicates they are ruminating, a mindfulness exercise that specifically tackles rumination would be suggested at the end of the questionnaire. This adjusted feedback mechanism based on patients' current needs, a feature that has already successfully been implemented into other mHealth protocols[32], would imply an even greater degree of personalizing treatment.

The present paper introduces an innovative approach to improve translation of ACT techniques into the patient's daily life. Utilizing the inherent properties of ESM in an mHealth approach, the ACT-DL protocol aims at helping patients to a faster habit formation that is not context-dependent, substituting former, unhealthy coping strategies with adaptive ones and supporting patients in pursuing their personal values. If this protocol proves to fulfil this aim, it will be made available for clinical use in the future.

Table 1: Example of an ACT-DL training

	Week							
	1	2	3	4	5	6	7	8
ACT Session	Creative Hopelessness	Acceptance	Defusion	Self as Context	Contact with the Present Moment	Values	Committed Action	Psychological Flexibility
Beep Questionnaire	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment	Contact with the Present Moment
Metaphors	Creative Hopelessness	Acceptance	Defusion	Self as Context	Contact with the Present Moment	Values	Committed Action	Psychological Flexibility
Exercises	Creative Hopelessness Contact with the Present Moment	Contact with the Present Moment Acceptance	Contact with the Present Moment Acceptance Defusion	Contact with the Present Moment Acceptance Defusion Self as Context	Contact with the Present Moment Acceptance Defusion Self as Context	Contact with the Present Moment Acceptance Defusion Self as Context Values	Contact with the Present Moment Acceptance Defusion Self as Context Values Committed Action	Contact with the Present Moment Acceptance Defusion Self as Context Values Committed Action
Morning/Evening Questionnaire							Committed Action	Committed Action

Note: ACT sessions: One session per week; Beep Questionnaire: Eight beeps per day, on at least three consecutive days per week following a session.; Metaphors: Four times per day following a beep questionnaire, on at least three consecutive days per week following a session.; Exercises: Four times per day following a beep questionnaire, on at least three consecutive days per week following a session.; Morning/Evening Questionnaire: Once per day, on at least three consecutive days per week following a session in week 6-8.

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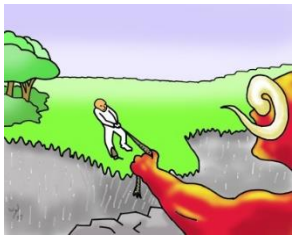
Appendix

Table 2: Examples of ACT-DL metaphors and exercises

	Metaphors	Exercises
	**CREATIVE HOPELESSNESS - Boomerang** Avoiding a negative emotion is like throwing a boomerang. You'll get rid of it for a moment, only to return twice as strong! This doesn't get you further.	**CREATIVE HOPELESSNESS - Avoid, flight fight** Think about the last two hours. Did you do something to *avoid* a negative feeling? Did you do something to *lose* a negative feeling? Did you do something to *exchange* a negative feeling for a positive feeling?
	**ACCEPTANCE - Tug of War** Your struggle with your emotions is like a tug of war between you and a big monster: however hard you pull, you cannot win this contest. Alternatively, you can let go of the rope, just like you can let go of your negative emotions. Now you invest the energy you spent in the struggle with your emotions in something that really matters.	**ACCEPTANCE - Opening up** You are having negative feelings again. Try to open up to them, to let them in. What do you feel? What does this do with you? Try to keep with this feeling for a little while.
	**DEFUSION - Waterfall** Your thoughts are like a waterfall, and endless, unstoppable stream pouring down on you. What happens if you take a step backwards? You'll find yourself behind the waterfall. You can observe it, but it can't drag you along anymore. Now you can decide which thoughts to pick, and which to let pass.	**CONTACT WITH THE PRESENT MOMENT - Senses** … stop Take a deep breath. Aim your senses on your environment. What do you see? What do you hear? What do you smell? What do you feel? … and continue your day.
	**VALUES - Compass** A compass can be used to guide us on our journey if we don't know which way to go. Let your values be your inner compass, guiding you to that what matters most.	**COMMITTED ACTION - Personal values** Morning 8:00 In which of your 3 values are you going to invest today? Think about 3 things you can do invest in this value today. Noon 12:00 Were you able to invest in your value? Early afternoon 18:00 Were you able to invest in your value? Late afternoon 22:00 Were you able to invest in your value?

Chapter Seven

Discussion

The aim of this thesis was threefold: i) to critically evaluate methods that have been used to measure daily-life stress sensitivity, ii) to review the mechanism of stress sensitization in psychosis across stress systems, and iii) to consider treatment options for psychosis that target stress coping styles.

Measuring Stress Sensitivity in Daily Life

Experience sampling research has produced several ways to measure the subjective stress response. **Chapter one** discussed some of these options, and attempted to assess their validity using the "known group" method, associating these measures with an abundance of clinically relevant concepts. Being able to validly assess stress in an individual's daily life is of critical importance to psychiatric research. It circumvents the recall bias typical stress questionnaires suffer from, and offers high ecological validity in return. However, compared to measuring the subjective experience of distress in a controlled environment, ESM stress assessment faces several problems. Below I address its three main issues and attempt to articulate acceptable solutions.

Assessment of the Stressor

First, as stress is not experimentally induced in daily life, to be able to compose a measure of stress reactivity, additional identification of the stressor is necessary. ESM stress assessment solves this problem by incorporating items on stressfulness of the current situation, or of recent events, to gain information on what caused the subjective distress. However, it is important to keep in mind that these reports are subjective appraisals, not objective observations. The difficulties with this approach become apparent when considering the circularity of the stressor – stress response relationship (that a stressor is only a stressor if it elicits a stress response). Reports of a current stressful situation, or past stressful event, reflect an individual's experience of distress in that situation. To assess stress reactivity to this situation, then, means to assess the effect of the situational experience of distress on the momentary experience of distress, which may rather reflect affective congruence than reactivity.

There may be no ultimate solution to solve the difficulties accompanying stressor assessment, but two main approaches could be used to improve current ESM stressor

assessment: i) to omit stressor assessment or ii) to search for a more objective measure. To omit stressor assessment means that stress reactivity cannot be measured. This may seem radical, but in many cases, it may not be necessary to identify the cause of distress. Depending on the research question, measuring the extent of the stress response in either frequency, magnitude, or duration, may be enough to differentiate between groups, to identify risk factors, or to investigate chronic stress in daily life. The second option, to use a more objective measure, has been opted for by researchers providing study participants with a set of events that may occur in daily life. The listed items include events that are possibly stressful, such as *"I was under time pressure"* or *"I had an argument with others."* Although one could still argue that responses to these items, to some extent, require and involve cognitive appraisal of the situation, this option suffers less from circularity as having an argument or being under time pressure are potentially, but not necessarily, stressful situations. This is similar to experimental stress tasks, where giving a public speech or solving math problems under time pressure may be stressful to some individuals (and under some circumstances) but not to all. In addition, this list need not be exhaustive, but should cover several potentially stressful situations the study participants are likely to encounter in daily life. Another possibility to more objectively assess the presence of a stressor is provided by the developments in passive remote monitoring technology. As mobile devices offer opportunities to track location, movement, presence of others, sounds, and vision, researchers are provided with a unique opportunity to have a look into people's lives. Advances in wearable technology can help in providing objective determination of potentially stressful situations (e.g. crowds, loud arguments) and thus contribute to solving this problem in the future.

Directionality

Second, as both stressor and stress response are often measured at the same moment, inferences on directionality are precluded. This is most apparent for assessment of momentary stressors (i.e. current stressful situations). Aside from the presumed effect of contextual appraisal on mood, current affect likewise colors the appraisal of the context[1], further blurring the lines between, in this case, stressor and stress response.

There is arguably much overlap between both concepts operationalized as such and treating them as two distinct variables with unidirectional effects of one on the other seems unjustified. Assessment of recent stressful situations suffers somewhat less from this problem, as here the presumption is that the stressful situation occurred sometime before the beep, implying chronological order. Hence, statements on directionality may be more justifiable, although even here no conclusive inferences can be made.

A possible and perhaps necessary solution here would be to incorporate time lags in the statistical analyses, operationalizing stress reactivity as the effect of a current stressful situation at t0 on the experienced stressfulness at t1. Although this approach cannot fully exclude the possibility that persistent feelings of distress may have influenced the appraisal of a situation (perhaps even caused the stressful situation), or a third variable caused both, it uses chronology to make inferences about the direction of the effects. Still, however, some stress systems may have returned to baseline by the time of t1, limiting the applicability of this approach.

Transience

A final problem pertains to the methodological approach of capturing a transient situation.

Although not uncommon, daily hassles occur rather infrequently and are often short-lived. As a result, standard ESM sampling rates are likely insufficient to capture these stressors in the moment. Moreover, if a beep is to coincide with a stressful situation, chances are that situational demands prohibit one from responding to it. Event-contingent sampling could be better able to capture these moments, but may suffer from measurement reactivity[2], where overt focus on stressors facilitates behavioral change. The same difficulties can be argued for capturing the stress response, although the experience of distress tends to outlast many typical daily hassles.

An obvious solution here is to abandon in-the-moment stressor assessment, and only use retrospective assessment of recent stressful situations (i.e. since the last beep). Although it circumvents the issue of capturing short-lived stressors to some extent, it comes with recall bias and, akin to momentary stressors, is subject to current mood. This last point seems inherent to subjective measurements, however, and may

therefore not have a satisfactory solution. Increasing the sampling rate is also not desirable due to the increased burden for the participant. Looking for options that do not rely on sampling moments, passive remote monitoring may again offer a solution. Using continuous monitoring to detect instances of increased physiological stress and potentially stressful situations can detect situations that standard ESM protocols fail to pick-up. Further developments in the communication between wearables and ESM software may allow for changes in physiology indicative of a stress response to trigger a beep, assessing the situation and the subjective stress experience.

Proposed Measures

Measuring stress in daily life comes with several challenges, and although there may be no ideal solutions to these problems, the ideas proposed here can contribute to more reliable and valid assessment of daily-life stressors. The first decision a researcher has to make is if answering the research question requires assessment of stress reactivity, or if measuring the (subjective) stress response can suffice. In the latter case, subjective distress can be measured using a single item (e.g. *"I feel stressed"*) or a composite of several items (e.g. *"I feel nervous/relaxed(reversed)/ anxious"*). Importantly, thus far studies have often combined all negative affect measures, including low arousal items. As a reflection of the fight-or-flight response, the subjective stress response should arguably incorporate only items on both negative valence and high-arousal, although a direct comparison of the two has not been made and it thus remains to see whether exclusion of the low-arousal items improves the measure's usefulness.

If assessment of the reactivity to a stressor is deemed necessary to answer the research question, it is best to avoid assessing both presence of a current stressor and stress response at the same time. Retrospective inventorying (i.e. since the last beep) of the occurrence of potentially stressful situations may offer a method of stressor assessment that suffers less from circularity than asking participants to appraise the unpleasantness of a situation, and is able to capture situations that occur in between assessment moments. Yet, it is important to keep in mind that, depending on the sampling frequency, the time-window between the stressor and the beep may be too large to pick-up the acute stress response. Lastly, recent and future advances in

wearable technology provide for continuous measurement that does not depend on subjective appraisal of the situation, and may provide further solutions to deal with the difficulties that accompany subjective stress assessment in daily life. An interplay between wearable technology and ESM software may be able to trigger beeps upon a sudden increase in physiological arousal, and thus allow for a momentary integration of subjective reports and physiology.

Stress Sensitivity in Psychosis

Increased stress sensitivity has been proposed a mechanism putting vulnerable individuals at risk of developing psychotic symptoms[3, 4]. **Chapters 3, 4, and 5** of this thesis have investigated affective, cortisol, and dopaminergic stress sensitivity in psychotic and other psychopathology, and found only partial proof for this account. In the next paragraphs, I will briefly review the evidence for increased stress reactivity in psychosis across stress systems, bringing together the findings on different stress systems based on the coherence/compensation model[5].

The Subjective Experience

Increased affective reactivity to daily stressors has been observed in samples across the psychosis continuum[6-12], with most pronounced increases in individuals at high clinical risk for developing psychosis[10, 12, 13], and affective reactivity to daily-life stressors has been found to predict persistence of psychotic symptoms[14], demonstrating the clinical relevance of this measure. A recent review on experimental stress, however, found no evidence for sensitization of subjective distress in psychosis[15]. Indeed, all of the studies using samples of individuals with psychosis reviewed in **chapter five** reported no differences in experienced stressfulness or anxiety induced by a psychosocial stress task[16-20], revealing a large gap between ESM findings and results of experimental studies. Several studies attempting to relate reactivity to a lab stressor with daily life reactivity found no convincing associations in endocrine[21, 22], or cardiovascular measures[23-26]. The only study to report unambiguous associations of cortisol reactivity also noted significantly different temporal affect patterns between a laboratory task and a naturalistic public speech event[27]. These discrepancies seem to indicate that daily

life and experimental stress reactivity reflect different temporal processes. For instance, whereas experimental stress induction typically has a very sudden onset and termination, daily hassles (e.g. being stuck in traffic) may have a more gradual course, with a more ambiguous onset. Moreover, since, as described in the previous section, ESM assessments are unlikely to immediately follow stressor onset, they may fail to capture the acute stress response, which is typically what is reported in studies on experimental stress. A finding that may shed further light on this issue is that in the study presented in **chapter three**, the strongest ESM predictor for both onset and persistence of symptoms indicative for psychopathology was overall negative affect. Furthermore, three independent samples reported higher overall negative affect levels as measured with ESM in individuals at ultra-high risk for psychosis compared to controls[10, 12, 13]. These findings seem to suggest that, at least in the early stages of illness development, it may not be overall increased reactivity to acute stress, but rather the prolonged feeling of (possibly symptom-related) distress that signals an individual's vulnerability.

Cortisol

In line with meta-analyses[28, 29], the study described in **chapter four** indicated blunting of the cortisol stress response in psychosis. However, higher overall cortisol levels, although often reported in psychosis[30, 31], were not observed in this sample. Taking a closer look, increased basal cortisol is mainly found in individuals at clinical high risk for psychosis[32] and in patients in an acute phase of the illness[30], suggesting basal levels increase in more stressful phases. Cortisol reactivity to psychosocial stressors seems to be increased in both chronic patients[29] and high-risk individuals[33]. Like the subjective experience, the cortisol alterations in psychosis seem to depend on illness stage, with increased basal levels especially in the at-risk stage and the early psychotic phases, and decreasing cortisol reactivity to stressors over the course of illness development.

The Autonomic Nervous System

Although not directly investigated in this thesis, another important branch of the stress system is the sympathetic nervous system. Indeed, there is evidence that the overall

sympathetic nervous system is augmented in psychosis[15, 34, 35], possibly suppressing HPA-axis reactivity. However, there is no convincing evidence for altered sympathetic stress reactivity in psychosis[15]. The sympathetic nervous system thus shows a pattern of a generally increased baseline and seemingly unaltered reactivity.

The Coherence/Compensation Model

Bringing the subjective, autonomic, and HPA stress responses together, Andrews, Ali, and Pruessner[5] put forward the coherence/compensation model. According to this model, the subjective experience of stress triggers a response of both the HPA axis and the sympathetic nervous system, which have a compensatory relationship[5]. Although the (peripheral) effects of HPA axis activation are delayed compared to those of the sympathetic nervous system, basal cortisol levels have a regulating effect on sympathetic activity. At a second stage, however, cortisol reaches its peak and inhibits both the sympathetic response and the subjective experience, returning them to baseline[5].

Compiling the evidence of this thesis provides for speculation on the alterations to this model within the psychosis continuum. In at-risk individuals, continuous subjective experience of stress (i.e. increased overall negative affect), chronic high levels of cortisol[36] and increased overall sympathetic activity (possibly stimulated by a decreased vagal tone)[37, 38] may attenuate HPA axis activation in response to a stressor, the effects of which do not become evident until the second stage of the stress response. As a result, there are no evident differences in stress response in the first stage of the model. In the second stage, however, an attenuated cortisol response (**chapter four**) may impair autonomic recovery to baseline. This is in line with the findings of a review on the autonomic nervous system in psychosis, posing that a decreased vagal tone fuels sympathetic dominance and impairs recovery[37]. Being closely related to the sympathetic response, subjective experience also remains increased.

Considering this framework, the discrepancies in affective reactivity between individuals on the psychosis spectrum and healthy volunteers as measured in response to experimental versus daily-life stressors, may be explained as a result of different timeframes. Whereas in experimental settings the measurements may predominantly

occur in the first stage, in daily life most assessments will fall in the recovery stage of the stress response, since stressor onset will rarely coincide with the ambulatory assessment signal (that is, as long as they are not one and the same). If the difference between psychosis patients and healthy volunteers lies predominantly in the second stage of the response, increases in subjective experience and sympathetic activity are not expected to differ during stage one. Furthermore, the several ESM accounts reporting increased affective reactivity in psychosis may reflect difficulties in recovery (i.e. prolonged higher levels of stress), rather than a higher initial response to acute stress.

However, several inconsistent findings preclude strong hypotheses based on the coherence/compensation model. For one, associations between the endocrine and affective stress responses are found only in a minority of studies[39]. In fact, one study found that suppressing both the HPA-axis and sympathetic nervous system did not have any influence on subjective stress reports[40], suggesting that the biological stress response may not be as closely associated to the subjective experience as expected. How these systems integrate, and how they differ in psychosis, are issues that need to be addressed in future studies. Also, it has to be noted that altered stress reactivity is not unique to psychosis. For instance, findings from this thesis and previous literature provide evidence for altered stress responsivity in depression and anxiety disorders as well[29, 41, 42]. How these differences relate to those found in psychosis, and what they signal, is to be further understood.

Treatment of Psychosis

Acknowledging the importance of stress in the developmental course of psychosis, it makes sense to see if there are opportunities for stress-targeting interventions. Aiming to interfere with the autonomic stress response, Clamor and colleagues[43] studied the effects of a training based on heartrate variability biofeedback in individuals reporting subclinical psychotic symptoms. Those participants adhering to the training protocol showed increased heart rate variability and reported higher experienced control and less paranoia following experimentally induced stress compared to an active control group[43]. Similar improvements were achieved on measures of stress tolerance, mood,

and anxiety in an uncontrolled study in youth at high clinical risk for psychosis[44]. These results are promising, although effects are still modest. A potentially valuable addition may be, to study the effects of such trainings in daily life, using newly developed passive remote monitoring technology. As decreased vagal tone and increased basal stress levels may underlie altered stress reactivity, however, perhaps larger effects can be achieved by targeting coping with ongoing stressors, such as negative thoughts or feelings.

The relative success of new wave cognitive behavioral therapies as a treatment for psychosis[45], and Acceptance and Commitment Therapy (ACT) in particular[46-52], further strengthens the idea that targeting stress coping strategies might be a fruitful endeavor.

Chapter six describes the protocol of ACT in Daily Life; an mHealth training based on ACT. The mHealth approach is key to intervening with old, maladaptive habits, and the training and putting into practice of new coping strategies in daily life. mHealth is a rapidly growing field, and several studies so far have been conducted in psychosis patients, proving it a potentially invaluable tool in bringing treatment to patients' homes[53]. ACT in Daily Life aims to bring about behavioral change by offering users a multitude of new skills to cope with stressors and behave in accordance with their personal values, and does so in the environment of everyday life. The efficacy of ACT in Daily Life has thus far been tested in three independent scientific studies. An initial pilot study has indicated its feasibility in a sample of mixed psychopathology[54]. Two ongoing studies are testing its effectiveness in large samples of preclinical depressive and psychotic symptoms (SMARTSCAN project, Maastricht University, The Netherlands) and individuals with an at-risk mental state or first-episode psychosis (INTERACT project, KU Leuven, Belgium). Results of these studies will shed light on ACT in Daily Life's efficacy in improving overall functioning and wellbeing through stress reduction.

Future Directions and Concluding Remarks

The results and ideas formulated in thesis contribute to a better understanding of stress sensitivity in psychosis. More importantly, however, it uncovers directions for future research. The indications that differences between healthy volunteers and individuals higher on the psychosis spectrum may not be detectable during the first stage of the

stress response call for new strategies in daily life assessment of stress reactivity. Therefore, it would be interesting if ambulatory stress assessment would investigate the prolonged effects of acute stress, as well as overall increased stressfulness, in relation to development, persistence, and improvement of psychotic symptoms. One way of operationalizing recovery could be to quantify the amount of time it takes for the increase in subjective distress following a stressful situation to normalize. If risk for psychosis is indeed marked by impaired recovery, this should produce a measure that is able to differentiate between groups along the psychosis continuum, and predict onset and persistence of psychotic symptoms. For this purpose, longitudinal accounts are pivotal.

Simultaneously, there is a need to combine passive remote monitoring with other stress measures in ESM. To understand the full stress response means to investigate each system involved and their dynamic interplay, in interaction with the environment. Thanks to the developments in wearable technology, ambulatory assessment studies investigating autonomic nervous system activity continuously are now emerging. Research combining these techniques with ambulatory cortisol and subjective stress measurements, however, is still scarce. Future studies must investigate how the ambulatory autonomic, endocrine, and subjective stress response cohere. To better understand the complexity of the stress response, the first aim should be to study these systems in a healthy population. A methodological study incorporating several measures of subjective distress, as well as continuous collection of physiological data, is a necessary first step. Importantly, direct comparison with experimentally induced stress (and recovery) is crucial to understand how these two processes relate. Continuous monitoring of physiological responses enables for the identification of every instance of increased autonomic arousal; subsequent assessment of subjective experience can inform us about their nature. Moreover, it allows for investigation of the role of decreased vagal tone, operationalized as increased heart rate variability, in alteration of the acute stress response and its recovery. If the delayed recovery indeed accurately signals risk for emerging psychotic symptoms, remains to be investigated.

Stress assessment in daily life faces several challenges, which perhaps cannot all be overcome. At the same time, it provides unique opportunities to study stress and stress

reactivity in daily life. Its relevance for identification of risk, mechanistic understanding of symptom development, and selection of targets for interventions highlight the importance this line of research has for psychosis and many other pathologies. Next steps must be made to gain better insight in the interplay between this complex system and its environment. Only then, can we timely identify and interfere with the debilitating effects of a system that is so vital for our survival.

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Chapter Eight

Valorization

The global impact of mental illness on society and the lives of individuals has been greatly underestimated during the last decades1. Worldwide, lifetime prevalence rates for mental illness varies between 12% and 47%2. Although the lifetime prevalence for psychotic disorders are estimated at a much lower 2.3-3.5%3, its societal and personal impact are out of proportion. Individuals diagnosed with a psychotic disorder are often confronted with stigmatization, social isolation or exclusion, as well as increased chances of being unemployed, homeless, living in supportive home environments, and receiving long-term treatment. However, advances in treatment methods, as well as the shift in timing to earlier stages of illness development, seem promising. Research on risk factors and mechanisms is therefore vital in the understanding of the developmental course of psychosis, and ultimately to develop adequate early intervention strategies. The current thesis adds to this.

The work printed in this thesis describes scientific studies and reviews on stress reactivity in psychosis and other disorder-spectra. As such, it broadens our knowledge on the role of stress in the emergence of early psychotic symptoms. With regard to reactivity to stressful daily events, stronger affective responses were not necessarily associated with worse outcome. This highlights the notion that stress is, at its core, an adaptive, healthy process, and a greater stress response is not indicative for vulnerability. Hence, attenuation of this response should not be a target for treatment strategies, especially since an attenuated cortisol response is associated with psychosis, as was shown in this thesis. Only under circumstances where the response is disproportionally large, as in the case of minor hassles, or when the effects linger, can we speak about a dysfunctional response that may indicate a vulnerability to develop mental illness. Higher overall negative affect, indicative of the prolonged experience of stress, was the strongest daily-life predictor of the onset and persistence of symptoms indicative of psychopathology in adolescents and young adults. A possibility is that negative affect remains high after the occurrence of unpleasant events due to problems with recovery. Instead of focussing on the magnitude of the response, investigating the duration may provide a more valid, and therefore more accurate, estimate of the risk. Being able to optimize risk assessment is of crucial importance for early intervention

strategies, and this thesis, contributing to the understanding of disease development and progression, provides a piece of that puzzle.

Treatment of serious mental illness often involves medication or traditional cognitive behavioural therapy that targets specific symptoms. However, both approaches have their downsides, as medication has limited long-term effects with high chances of relapse upon discontinuation, and symptoms may change over time, or not represent the main source of distress (think about problems related to social and societal functioning). This thesis emphasizes the positive effects of acceptance and commitment therapy (ACT) or ACT-based treatment approaches for psychosis. The unspecific nature of ACT may be exceptionally well suited for clinical pictures in which sources of stress are not restricted to the symptomatology. In this thesis, the protocol of ACT in Daily Life is presented; an mHealth add-on to ACT in which individuals learn to cope with any given daily stressor. Ecological momentary interventions are well suited to bring the intervention in the individual's daily life. Random beeps force the user to take a minute to reflect on his or her current context, mood, and behaviour. Depending on the momentary situation, the user is provided with a tailored exercise or reminder of an adequate coping strategy. New developments in wearable technology offer the addition of continuous assessment of physiological measures, which can be used to detect sudden increases in arousal indicative for acute stress. Such treatment approaches may bring us one step closer to immediate intervention, at moments where it is needed most.

Ultimately, however, the goal is not to treat, but to prevent. As exposure to early-life stressors may sensitize stress reactivity in vulnerable individuals, early interventions are the only answer to timely interfere with the developing course of stress-related pathology. One possibility lies in school programs that are aimed at stress coping. A meta-analysis on interventions targeting stress management in primary and secondary schools shows large positive effects on stress symptoms and coping, although there was significant heterogeneity in study quality4.

Altogether, the work in this thesis has contributed to our understanding of the role of stress in the development of psychosis and other disorders, and has proposed new intervention and prevention avenues that promote mental health.

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Epilogue

Summary

This thesis contains work on stress sensitivity in psychosis. Although the stress response is adaptive in nature, it is involved in the developmental course of a broad range of somatic and mental illnesses.

Chapter one provides a general introduction to the concept stress and the role it plays in the development of psychosis. Psychosis is considered a mental illness that is characterized by loss of touch with reality. However, psychotic symptoms may vary considerably in terms of expression and intensity, forming a continuum. Exposure to stressors may sensitize those who have a genetic vulnerability, and put an individual at risk for developing psychosis and other paychopathology. The remainder of this thesis looks into the concept of stress sensitivity and its link to mental illness, with a main focus on psychosis.

Before we can study stress sensitivity in daily life, we need a valid way to do so. **Chapter two** describes methods of stress assessment in daily life and attempts to validate these using the "known group" method. This method is based on the knowledge about known group characteristics. ESM stress assessment was indeed able to distinguish between groups that are assumed to have higher stress reactivity and control groups. Furthermore, they are associated with biological measures, clinically relevant concepts, and factors that may explain the mechanism underlying increased stress reactivity. Yet, each method has its particular disadvantages and careful consideration is required when assessing ambulatory stress reactivity.

In **chapter three**, an original study is described that investigates the predictive value of increased affective stress reactivity for symptoms indicative of psychopathology. Increased stress sensitivity is thought to be a risk factor for a broad range of psychopathology, though the link between increased affective reactivity to daily stressors has hardly been investigated. The results show that only increased affective responses to minor hassles are associated with an increase in symptoms, one year later. As the stress response is a generally adaptive system, reacting with an increased in negative affect to daily stressors may actually reflect healthy behaviour. A similar response to the smallest of daily hassles, however, may reflect abnormal affective reactivity. However, the strongest predictor was overall negative affect, indicating that prolonged feelings of distress may constitutee the most acurate indicator of worsening mental health. These results build on the existing knowledge on the role of stress in the development of psychopathology and should be build-upon in future research.

Chapter four is a study on cortisol, a major stress hormone, in psychosis. As previous research showed psychosis to be associated with increased affective responsiveness to daily hassles, we were interested to see if we could find biological alterations as well. The results show that there are no differences in overall levels of cortisol between psychosis patients and their first-degree relatives or healthy control subjects. However,

the cortisol response to daily stressors was blunted in both patient groups, showing that psychosis is associated with impaired HPA functioning. Patients who were taking antipsychotic medication did, however, not differ in their cortisol response from patients not currently taking antipsychotics, which suggests that this effect is not related to medication use. These findings point towards an impaired biological stress system that is apparent in everyday life.

Striatal dopamine, the most consistent biomarker for psychosis, has also been associated with stress. **Chapter five** presents a systematic review of the literature on dopamine release in the brain during stress. Although there is a shortage of studies investigating stress-induced dopamine release, patients with psychosis indeed seem to have more dopaminergic activity during stress in the striatum than healthy volunteers. Differences between stressor types may be accountable for differences in dopaminergic responses observed in the striatum. It is important that future studies try to replicate these findings and investigate where these differences come from.

Chapter six describes ACT in Daily Life – a treatment protocol that aids individuals in coping with daily stressors, based on Acceptance and Commitment Therapy. The implementation of skills and insights that are topic of any psychotherapeutic session in daily life remains a challenge. Ecological momentary interventions constitute a promising approach, in that they offer support in this process. The protocol described here uses the ground principles of Acceptance and Commitment Therapy – accepting negative thoughts and feelings that cannot be changed, and investing in one's values – and reminds the individual of these principles via a smartphone app. Guided exercises help applying these principles in the moments where they are needed most: everyday life. Large randomized controlled trials must investigate the efficacy of this approach in the future.

Finally, **chapter seven** brings the findings of all previous chapters together in a general discussion on the three main themes of this thesis: assessment, mechanism, and intervention. Daily-life stress assessment is crucial for psychiatric research, but to date there is no consensus on how to do so. In this discussion, methods of ambulatory stress assessment are critically evaluated and alternatives proposed. It also brings together results on different systems of the stress response, and attempts to integrate these findings based on the coherence/compensation model. Finally, intervention strategies are discussed that target stress reactivity, as well as considerations on future research.

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Epilogue

Curriculum Vitae

Thomas Vaessen was born on September 17 in 1982 in Nijmegen, the Netherlands. After graduating from the Karel de Grote College in Nijmegen, he received his HAVO diploma at the Regionaal Opleidingen Centrum in the same city. In 2006, he graduated from the one-year bachelor program in Applied Psychology at the Fontys Hogeschool in Eindhoven, and later that year he started his bachelor's in Psychology at Maastricht University. There, he graduated cum laude in 2009, after which he followed the two-year master program in Clinical and Cognifite Neuroscience at the same university, including a half-year internship at the University of Oxford. After graduating in 2011, Thomas worked in the clinical field as a psychologist for the RIAGG in Maastricht. In 2013 he started working as a PhD candidate at the department of Psychiatry and Neuropsychology of Maastricht University on a project on stress sensitivity in psychosis with Inez Myin-Germeys. Since 2015 he is also enrolled in the doctoral training program of the KU Leuven as part of a joint doctorate degree.

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List of Publications

Published

Vaessen, T., Hernaus, D., Myin-Germeys, I., & van Amelsvoort, T. (2015). The dopaminergic response to acute stress in health and psychopathology: A systematic review. *Neurosci Biobehav Rev*, 56, 241-251.

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Vaessen, T., Kasanova, Z., Hernaus, D., Lataster, J., Collip, D., van Nierop, M., Myin-Germeys, I. (pending revisions). Cortisol Reactivity to Daily-Life Stressors in Psychosis. *Psychoneuroendocrinology*.

Myin-Germeys, I., **Vaessen, T**., van der Gaag, M., Kasanova, Z. (in press). Hoe ontstaat een psychose? In M. van der Gaag & T. Staring (Eds.), *Handboek Psychose*. Boom, Amsterdam.

Vaessen, T.*, Steinhart, H.*, Batink, T., Klippel, A., van Nierop, M., Reininghaus, U., Myin-Germeys, I. (in preparation). ACT in Daily Life: A Momentary Intervention Approach.

Reininghaus, U., **Vaessen, T**.*, Klippel, A.*, Steinhart, H.*, van Nierop, M., Viechtbauer, W., Batink, T., Kasanova, Z., van Aubel, E., Quee, P., Demunter, H., van Winkel, R., Marcelis, M., van Amelsvoort, T., van der Gaag, M., de Haan, L., Myin-Germeys, I. (in preparation). Efficacy of Acceptance and Committment Therapy in Daily Life (ACT-DL): study protocol for a multi-centerrandomized controlled trial.

* Authors contributed equally