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REVIEW ARTICLE

The dynamic nature of depression: a new micro-level perspective of mental disorder that meets current challenges

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The examination of moment-to-moment, 'micro-level' patterns of experience and behaviour using experience sampling methodology has contributed to our understanding of the 'macro-level' development of full-blown symptoms and disorders. This paper argues that the micro-level perspective can be used to identify the smallest building blocks underlying the onset and course of mental ill-health. Psychopathology may be the result of the continuous dynamic interplay between micro-level moment-to-moment experiences and behavioural patterns over time. Reinforcing loops between momentary states may alter the course of mental health towards either a more or less healthy state. An example with observed data, from a population of individuals with depressive symptoms, supports the validity of a dynamic network model of psychopathology and shows that together and over time, this continuous interplay between momentary states may result in the cluster of symptoms we call major depressive disorder. This approach may help conceptualize the nature of mental disorders, and generate individualized insights useful for diagnosis and treatment in psychiatry.

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Introduction

Major depressive disorder (MDD) is a common mental disorder that affects about 15% of the population worldwide. It makes a substantial impact on the quality of life (Mathers & Loncar, 2006) with considerable costs to society due to healthcare consumption and decreased work productivity (Donohue & Pincus, 2007). Despite significant scientific advances, societal burden associated with MDD has not decreased. One explanation for the lack of impact of scientific research on treatment improvement is that the exact nature of mental disorders such as MDD remains elusive. As long as we do not understand the essence of mental disorders, it is hard to find their underlying mechanisms (Kendler *et al.* 2011). One possible way forward is to increase knowledge on how symptoms evolve at the level of the individual in daily life; elucidation of mechanisms at the level of real-world everyday life experience and on individual-specific rather than group-based mechanisms may benefit the generation of clinically useful information (Myin-Germeys *et al.* 2009; Wichers *et al.* 2011*a*, *b*). This review will discuss a novel approach that may help to resolve current challenges and that may contribute to new insights into the dynamic nature of mental disorders and personalized real-life mechanisms. This approach integrates recently described philosophical and methodological views on mental disorders (Kendler *et al.* 2011; Cramer *et al.* 2012*a*; Borsboom & Cramer, 2013) with a micro-level experiential perspective, building on research using momentary assessment technology (Wichers *et al.* 2009*a*, *b*; Kramer *et al.* 2013).

Challenges in the field of psychiatry

As mentioned above, an important first challenge facing psychiatry is the lack of conceptual clarity as to the nature of mental disorders (Kendler *et al.* 2011; Kendler, 2012). MDD is defined in the current Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) as a syndrome arising from a cluster of several co-occurring symptoms. However, in the search for causes and mechanisms, MDD has often been treated as if the symptoms of depression reflect a single underlying construct. For example, many attempts have been made to find specific genes

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contributing to MDD, suggesting that genes could be matched to the expression of this single underlying 'essence' of MDD as a whole. Notwithstanding significant recent progress in our understanding of the human genome, genome-wide association studies (GWAS) have not been successful in identifying genes that explain a significant proportion of the incidence of mental disorders (Ripke *et al.* 2013). Reality seems more complex in that genotypes underlying mental ill-health may not map as cleanly onto phenotypes as observed for somatic conditions (Kendler, 2005). As causal pathways to the development of symptoms may be unique for each patient with a mental disorder, the study of individual-specific patterns of onset and outcome is essential for psychiatry. Therefore, the question arises as to what degree the scientific search for universal causes and mechanisms can be reconciled with the existence of unique individual pathways to the emergence of psychopathology. Novel views on the nature of mental disorders may be required to elucidate this issue, and improve the scientific search for solutions.

A second challenge is to improve the clinical impact of scientific developments in the field. The last decades have seen significant progress in the elucidation of possible mechanisms underlying mental disorders, such as alterations in the stress, reward or salience systems and their interactions (Kapur *et al.* 2005; Lemos *et al.* 2012; Greening *et al.* 2013). Animal studies have suggested possible molecular mechanisms, human imaging studies potential brain circuitries, and molecular genetic studies potential genetic variants associated with these systems. But where do we go from here? Despite these new insights, the societal burden of MDD and other mental disorders has not decreased. Also, new antidepressants that have entered the market in the past decades have not further improved treatment efficacy. A stronger clinical impact resulting from modern neurobiological insights may require translation to knowledge with direct clinical relevance. For most of the new mechanistic insights it is unknown how they relate to ecologically valid knowledge in terms of real-life experience and behaviour. Real-life experiential and behavioural patterns, however, are close to the endpoint of translational research, since they may provide concrete and identifiable real-life targets for intervention. Recent advances in technology such as smart phones and mobile applications for the first time allow for routine assessment of experiential and behavioural patterns in the flow of daily life.

Third, as explained above, individual-specific causes and symptoms are a core characteristic of the field of psychiatry. Therefore, more than in other areas, the challenge in psychiatry is to translate group findings to knowledge that is relevant to the individual patient. To date, with the exception of a few studies (Borckardt *et al.* 2008; Tschacher & Ramseyer, 2009; Hoenders *et al.* 2012; Oorschot *et al.* 2012; Rosmalen *et al.* 2012), scant attention has been given to this issue. However, in order to force scientific and clinical progress, personalized insights in mechanisms underlying the emergence or persistence of symptoms are urgently required.

In short, psychiatry is in want of a novel approach which can (i) elucidate the nature of mental disorders and solve the issue of how universal causes relate to individual-specific symptom clusters, (ii) reveal insights in mechanisms as they play out in real life (close to the translational endpoint) and (iii) produce knowledge that is relevant to the individual patient. In this article, I will first discuss some recent and relevant developments in the field, and then propose a new approach towards unravelling the mechanisms of mental disorders. This approach integrates a new micro-level perspective of the development of mood disorders with recently proposed network views on psychopathology (Kendler *et al.* 2011; Cramer *et al.* 2012*a*; Borsboom & Cramer, 2013). In addition, examples based on real data are presented to support the validity of the approach, and to highlight the implications of this approach for our understanding of mood disorders.

Relevance of examining mental states at the micro-level of experience

To date, science has mostly adopted a macro-level perspective in examining the mechanisms of psychopathology. Implicitly, it has long been assumed that mental disorders – such as depressive symptomatology – represent discrete entities that can be rated as present or absent. Research, therefore, has largely focused on macro-scale cross-sectional differences and longitudinal changes in the presence *versus* absence of episodes of MDD with the aim of finding precise causative factors responsible for the expression of the disorder. Many studies and meta-analyses have been conducted trying to identify a combination of factors, such as certain genetic variants combined with early-life traumatic situations or major life events, which predict the occurrence of a full-blown state of depression (Zimmermann *et al.* 2011; Fisher *et al.* 2012; Wong *et al.* 2012; Brown *et al.* 2013; Wilkinson *et al.* 2013). Indeed, this approach has successfully identified general risk factors, some of which undoubtedly are related to the development of MDD. The question is whether this approach will bring us further to examining why these factors are related to MDD and how and where exactly we should intervene to prevent MDD.

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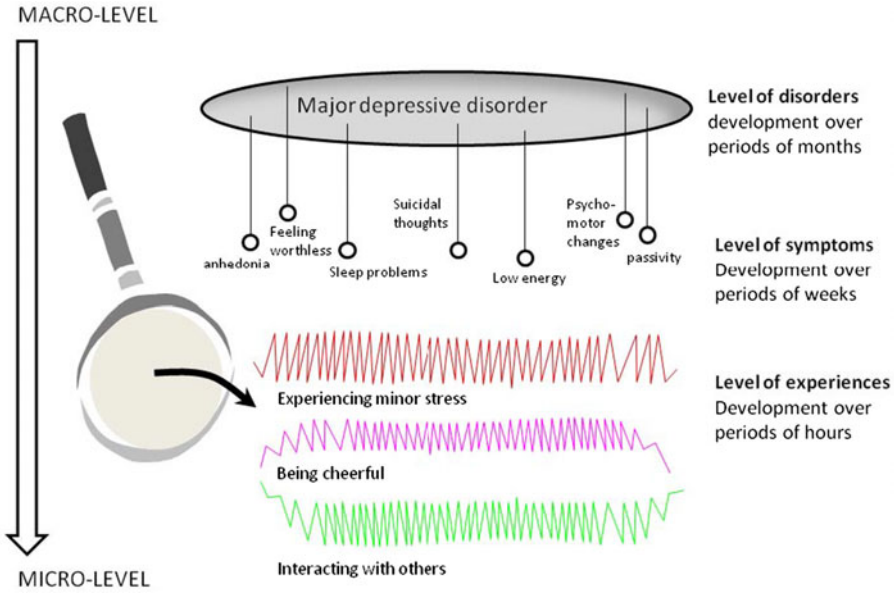

Fig. 1. Illustration of various levels at which research examines the aetiology of psychopathology. These levels – varying from macro-level research (level of disorders) to micro-level research (level of experiences during the day) – complement each other. Micro-level research may further assist in finding the smallest building blocks that contribute to the course of mental (ill-) health. This level of detail may reveal concrete and manageable pieces of real-life experience and behaviour that are easy to target and show the deeper and detailed structure of psychopathology.

Evidence suggests that depression is actually better conceptualized as a dimensional construct rather than as a discrete diagnostic entity (Kendler & Gardner, 1998; Judd *et al.* 2002; Hankin *et al.* 2005; Slade, 2007). We can therefore assume that aetiological factors operate at the level of bringing about dimensional changes. This suggests that in order to find the essence of MDD, a focus on smaller units of variation is required, replacing the focus on presence or absence of disorder. Many studies take into account the dimensional perspective by focusing at aetiological factors related to changes in symptoms instead of changes in fulfilling diagnostic criteria only. However, even smaller building blocks may underlie symptom formation, requiring psychopathologists to zoom in even further (Fig. 1).

It is proposed that the smallest building blocks underlying psychopathology can be identified at the level of momentary experiences in the flow of daily life. Recent studies have shown that zooming in to the micro-level of experience generates insights that could not have been detected with research at the traditional symptom-based or disorder-based macro-level of psychopathology. For example, macro-level gene–environment interaction studies suggest that genetic variation in the brain-derived neurotrophic factor (*BDNF*) gene is associated with MDD (Pae *et al.* 2012; Quinn *et al.* 2012). Micro-level research at the level of daily life mental state experience, however, may contribute mechanistic knowledge as to why this genetic variation may relate to MDD, and what mechanism of risk may be involved. Thus, variation in the *BDNF* gene was shown to be associated with subtle alterations in the response to minor frequently occurring stressors in the flow of daily life (Wichers *et al.* 2008*b*). Each time when a minor daily life stressor presented itself, Met carriers of the *BDNF* $Val^{66}Met$ genotype experienced more negative affect than Val carriers. Cumulatively, such repeated exposure to increased levels of negative affect may make an impact on the risk of mental ill-health. It has been shown several times that increased negative affective reactivity to daily life stressors predicts future psychopathology, amongst others depressive symptoms and MDD (Schneiders *et al.* 2006; Wichers *et al.* 2007, 2009*a*). The above findings in combination thus may explain why *BDNF* genetic variation may be involved in MDD.

Similarly, sleep problems have been associated with MDD in many studies. A recent micro-level study in a general-population sample revealed that the underlying mechanisms of risk may be related to the fact that lower sleep quality makes a negative impact on experience of positive affect the next day (Hasler *et al.* 2012; De Wild-Hartmann *et al.* 2013). Furthermore, lower sleep quality at baseline predicted follow-up depressive symptoms (De Wild-Hartmann *et al.* 2013). Positive affect is widely known to have an impact on attentional function and behaviour (Fredrickson & Branigan, 2005; Fredrickson *et al.* 2008; Garland *et al.* 2010). It facilitates social contact,

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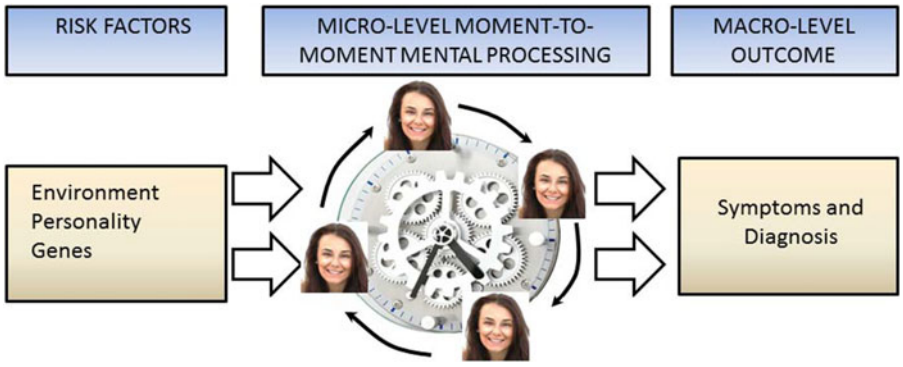

Fig. 2. Illustration of the suggestion that alterations in moment-to-moment ongoing patterns of experiences and behaviour during our daily lives form the pathway by which risk factors for psychopathology make an impact on the outcome of psychopathology. This suggestion is supported by recent studies.

exploration, motivation for activities, etc., resulting in further increases in positive affective experience. Lower levels of positive affect may alter these reinforcing behavioural patterns and, in turn, provide the individual with fewer opportunities to experience positive affect. A vicious cycle may thus ensue which eventually puts individuals at increased risk for MDD (De Wild-Hartmann *et al.* 2013). Similarly, Kramer *et al.* (2013) showed how momentary dynamic patterns of affect explained why risk for depression may relate to psychotic experiences and psychosis. The authors showed that micro-level negative affect triggered short-lived paranoid experiences at subsequent moments during the day. Furthermore, the authors showed that stronger associations between momentary negative affect and on momentary paranoia predicted the development of psychotic symptoms over subsequent months (Kramer *et al.* 2013).

Other micro-level dynamic patterns have also been found to predict the onset and course of mental ill-health. For example, there is strong evidence that the way in which individuals respond to stressful or rewarding daily contexts predicts the development of later depressive symptoms (Wichers *et al.* 2009*a*; Geschwind *et al.* 2010). Furthermore, other characteristics such as variability in momentary mental states or how long mental states persist over time appear informative for the risk for future depressive symptoms (Wichers *et al.* 2010; Kuppens *et al.* 2012; Thompson *et al.* 2012).

Not only are momentary patterns of mental states informative with regard to the course of mental health, evidence is accumulating that major risk factors for mental disorders, such as early adversity, recent negative life events, genes or personality traits, alter these momentary mental states patterns (Wichers *et al.* 2008*a*, *b*; Jacobs *et al.* 2011; Lardinois *et al.* 2011). Low birth weight and childhood adversity, for example, are associated with increased negative affective responses to everyday minor stressors (Wichers *et al.* 2009*b*), and childhood adversity was found to modify the impact of negative affect on paranoia (Kramer *et al.* 2013). Thus, subtle alterations in momentary mental states may constitute important mediators of risk factors that make an impact on mental health outcomes (Fig. 2).

In short, research has shown that known macro-level risk factors for depression – genetic variations but also early adverse environments, personality or sleep – indeed act on micro-level dynamic patterns of affect and responses to daily life situations. Furthermore, research has shown that these micro-level experiences predict the outcome of MDD. Together, the data suggest that risk factors may bring about mental disorders by conferring vulnerability to maladaptive micro-level affective patterns (see Fig. 2). Cumulatively, these very subtle and small differences between individuals in affect and their interplay with daily life context may eventually explain macro-scale individual differences in the course of MDD. Just as biologists zoom in with a microscope to get insight into the smallest building blocks of life, in psychiatry it may be productive to zoom in to the level of micro-level experience in order to develop mechanistic knowledge.

On the importance of dynamics between momentary mental states

While the way in which people experience everyday life and their resulting dynamic pattern of momentary mental states may contribute mechanistically to the development of psychopathology, the next question is how exactly such micro-level moment-to-moment processing may result in a cluster of symptoms that defines a mental disorder like MDD. Several research groups have recently described the notion that a cluster of symptoms that we define as a particular mental disorder in fact may not represent a latent liability from

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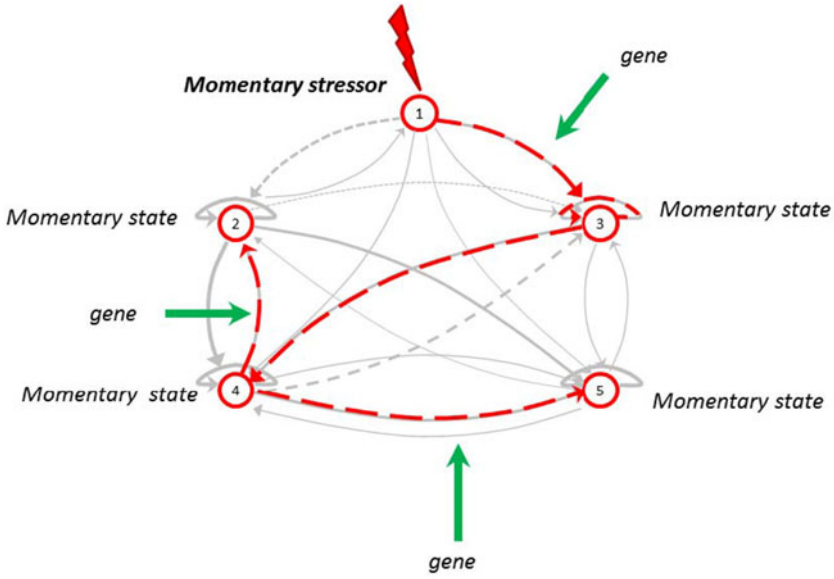

Fig. 3. Example of a network illustrating how momentary states may trigger the activation of other momentary states and how stressors and genes may act upon this network of effects. A momentary stressor (1) may trigger activation of another momentary state (3; e.g. negative affect) at the next moment. In turn, this momentary state (3) may again trigger the occurrence of other momentary states. In addition, it may also activate itself, illustrated by the arrow starting at state 3 and pointing to state 3 (autoregression coefficient). Genetic variation may drive part of the individual differences in connection strengths.

which all symptoms come into existence together in an independent way. Much more likely is a scenario where a cluster of symptoms arises because symptoms trigger each other, thus forming a circuitry of causal relationships (Borsboom *et al.* 2011; Kendler *et al.* 2011; Cramer *et al.* 2012*a*, *b*). In the case of MDD, an example following this principle would be that sleep loss may trigger anhedonia, which leads to increased passivity, which induces rumination, etc. Together, this symptom interplay may potentially result in a syndrome that fulfils the (broad) criteria of MDD. In extreme cases – such as in individuals with mental disorders – symptom interplay may give rise to a vicious circle of experiences from which an individual cannot easily escape anymore (Garland *et al.* 2010; Borsboom & Cramer, 2013). Such interconnections between symptoms can be visualized as a network in which nodes (symptoms) are connected by arrows representing the impact of the one symptom on the other (Fig. 3). This view suggests that if we would open the black box of what we call a disorder then this network structure of interconnections between symptoms is what we would find. However, as argued before, rather than at symptom level, mechanisms probably play out at the micro-level of experience – the level of continuous and ongoing dynamics between experiences, feelings and resulting behavioural actions. Clinical symptoms do not arise out of nowhere. Rather, they represent the endpoint of the long-term impact of very small subtle moment-to-moment dynamics and the vicious circles that were strengthened in this continuous interplay. We can assume, for example, a hypothetical continuous interplay between the extent to which people engage in social interaction and positive affect. When positive affect is low, less social interaction may ensue at first. In turn, less social interaction would result in less positive affect. Cumulatively, this dynamic interplay would result in a downward spiral (Garland *et al.* 2010) and end in the clinical expression of anhedonia and social isolation. Thus, building on recent ideas arguing that mental disorders actually reflect clusters of interconnected symptoms, it is argued here that zooming in on the structure of dynamic interconnections between momentary mental states may show us the basic building blocks at the smallest level of detail responsible for the development of a disorder (Fig. 3).

A network visualization hereof also enables us to understand better the impact of environmental stress and genes on psychopathology. Stressors would be hypothesized to activate a node in the network (Cramer *et al.* 2012*a*), for example, negative affect (Wichers *et al.* 2007). In the network, it would depend on the nature of the interconnections what happens if a stressor activates a node, which may result in activation of other nodes and, eventually, a vicious circle, which may drag the individual further and further into a cycle of negative experiences. For example, in one

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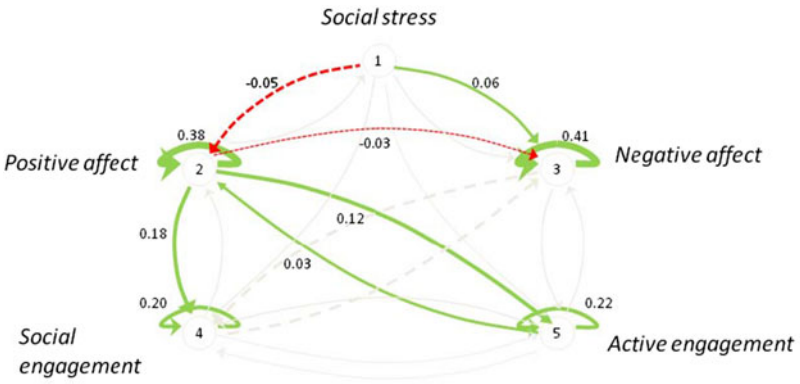

Fig. 4. Real data example of the network perspective applied to dynamic effects between micro-level experiences in the flow of daily life. The arrows indicate the time-lagged effects [moment(t – 1) → moment(t)] between momentary experiences of social stress, affect and behaviour in a sample of individuals with residual depressive symptoms. The arrows that start at the same circle as where they end reflect autoregressive coefficients of the particular variable. Only significant effects are shown. Social stress was hypothesized as an inducer of effects only. Effects from other variables on social stress were therefore not tested. The numbers represent the sizes of effects (the β-coefficients in the regression analyses).

individual, bidirectional negative interconnections between stress-induced negative affect and positive affect may drag the person into a progressively negative mood state. Another individual, however, may have a different pattern of interconnections and smaller connection strengths from stress to other nodes, allowing the impact of a similar stressor to 'die out'. Additionally, it can be imagined that genetic variation makes an impact on connection strengths within the momentary mental state network, as previous studies have shown that genetic variants moderate the associations (i) between stress and negative affect and (ii) between experience of pleasant activities and positive affect (Wichers *et al.* 2008*a*, *b*).

There is credence for the notion that the dynamic interplay between mental states over micro-periods of time in daily life may have relevance to long-term clinical outcome. Time-lagged associations between momentary negative affect and self-esteem (Thewissen *et al.* 2008) and paranoia (Kramer *et al.* 2013) have been reported. Likewise, dynamic associations over time were found for positive affect at one moment and negative affect (Wichers *et al.* 2012*a*), sleep (De Wild-Hartmann *et al.* 2013) and physical activity (Mata *et al.* 2012; Wichers *et al.* 2012*b*) at another. These moment-to-moment dynamics additionally were informative with regard to the course of macro-level symptoms and diagnoses. Furthermore, behaviour not only resulted in alterations in affect at subsequent moments, but also the other way around (T. Lataster *et al.* unpublished observations). And, as previously mentioned, there is evidence that persistence of mental states over time (also called 'inertia') predicts the long-term course of symptoms (Koval *et al.* 2012; P. Höhn *et al.* unpublished observations).

However, to date these micro-level effects have mostly been examined separately and not been brought together in a single conceptual framework, representing a complex network of dynamic causal interrelationships as proposed above. The only study in which micro-level experience sampling methodology (ESM) data were combined with a network perspective (Bringmann *et al.* 2013) showed the feasibility of such an approach. A network perspective is necessary to show how (reinforcing) interacting effects between momentary states over time evolve in a dynamic system underlying vulnerability to stressors and vicious circles of negative experiences. Thus, a dynamic perspective, expanded to dynamic associations between multiple mental, contextual and behavioural states, may be ideal in the further exploration of the question to what degree dynamic circuitries between these states may create the vicious circles of causal relationships that we call a mental disorder.

Examples of micro-level dynamic networks of momentary states based on real data

To further illustrate this approach with real data, dynamic multilevel time-lagged associations between multiple momentary states were examined in data of individuals with residual symptoms of depression (Geschwind *et al.* 2011). We selected a contextual state (social stressor), experiential states (negative and positive affect) and behavioural states (active and social engagement), given that (i) social stress is an important risk factor and a potential inducer of MDD, and (ii) symptoms of MDD occur in the domain of affective experiences and behaviour. Fig. 4 shows the combined results of significant time-lagged associations between these states expressed in a network in

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which nodes represent the states and the arrows the time-lagged impact of one state on the other. Measurements were obtained using ESM and were on average 90 min apart (10 per day) and collected over a period of 6 days. Associations between states were assessed only for the first time lag [(t−1) → (t)]. The social stressor was measured using the participant's appraisal of current company on a scale from 'like very much' to 'dislike very much'. Affective states were obtained by performing a factor analysis on the available affect adjectives and by using the outcome thereof to construct the variables negative and positive affect. The behavioural measures that were included were (i) current appraisal of degree of activity and (ii) current appraisal of social interactivity since there is scientific support for the idea that active behavioural patterns and engagement with the world around us play an essential role in mental health (Fredrickson *et al.* 2008; Garland *et al.* 2010; Kanter *et al.* 2012). Analyses were exploratory – not based on theory – comprising all possible interrelationships between the variables. Only one exception was made for the variable 'social stress' which was hypothesized as an inducer of effects only. Furthermore, negative affect and positive affect were always corrected for each other in the analyses. Also, social interactivity was always corrected for social stress. Autoregressive effects were always included [for example, if positive affect is the outcome variable at (t) then the effect of positive affect at ($t-1$) was included in the regression model]. All analyses allowed for random intercepts and slopes.

What results is a circuitry of interrelationships between contextual, experiential and behavioural states. In this sample, some associations are unidirectional and others appear to be reinforcing loops. Since the observed dynamics are repetitive and occur on a momentary basis, the effect of vicious circles may accumulate over time – if not counteracted – and may eventually have clinical impact. It can easily be envisaged from the results in Fig. 4 that if social stress is increased in a dynamic circuitry with these characteristics in terms of types and strengths of interrelationships, a vicious circle may ensue in which more negative affect, less positive affect and less active involvement in daily life cumulatively may contribute to outcomes of social isolation, low activity levels, anhedonia and low mood. This supports the idea that the connection strengths between momentary experiential and behavioural states may determine vulnerability to the development of depressive symptoms and that this vulnerability does not result from linear prediction between two variables but from a complex and continuous dynamic interplay between multiple factors that can be visualized in the form of a network. This network also shows why positive affect may eventually prevent depressive symptoms. Positive affect is a very central node in this network. Strengthening the experience of positive affect would restore healthy activity in the other nodes, resulting in less negative affect, more daily life activity and increased social engagement, guiding the continuous interplay between these daily experiences in a more favourable future direction. Subsequent experimental modification of positive affective experience in this population indeed resulted in reduced depressive symptoms (Geschwind *et al.* 2011), supporting the validity of a dynamic micro-level perspective in psychiatry.

The advantage of momentary assessment techniques such as ESM, in which multiple momentary assessments are obtained for each individual, is that analyses can be personalized (Oorschot *et al.* 2012; Rosmalen *et al.* 2012). In other words, we can examine how network dynamics look like for a particular individual. In the near future, it will be possible to routinely examine individual-specific mechanisms and to generate clinically relevant knowledge. The hope is that individual network analyses may be used to gain insight into individual vulnerabilities and the specific locations in the network where intervention is necessary to get the dynamic system back into an equilibrium of stable mood. Fig. 5 shows examples of two separate individuals with very different underlying network structures. These analyses were performed in the same way as the group-based analyses, but now using the data of a single individual. The first individual (Fig. 5*a*) shows a strong negative affective response to daily social stressors, which could potentially be the result of sensitization to a significant early stress exposure (Wichers *et al.* 2009*b*). The acquired negative affect also tends to linger over time. In this network structure, negative affect triggers increased social engagement. In this case, this may reflect the search for social support from friends or a partner. This, in turn, decreases negative affect and increases positive affect. Social engagement is central in this network and helps the individual to neutralize the impact of social stress. Fig. 5*b* shows the network of another individual who responds to social stress with decreases in positive affect and activity levels. This individual also shows persistence in levels of positive affect over time. This may be a disadvantage in the context of lower positive affect following social stress, since it would inhibit quick recovery to levels of positive affect experienced before moments of social stress. The reduced activity levels in turn trigger increases in negative affect. In this network structure, negative affect might be neutralized by being more actively engaged. However, it may be more difficult to restore levels of positive affect as no other arrows than those from social stress seem

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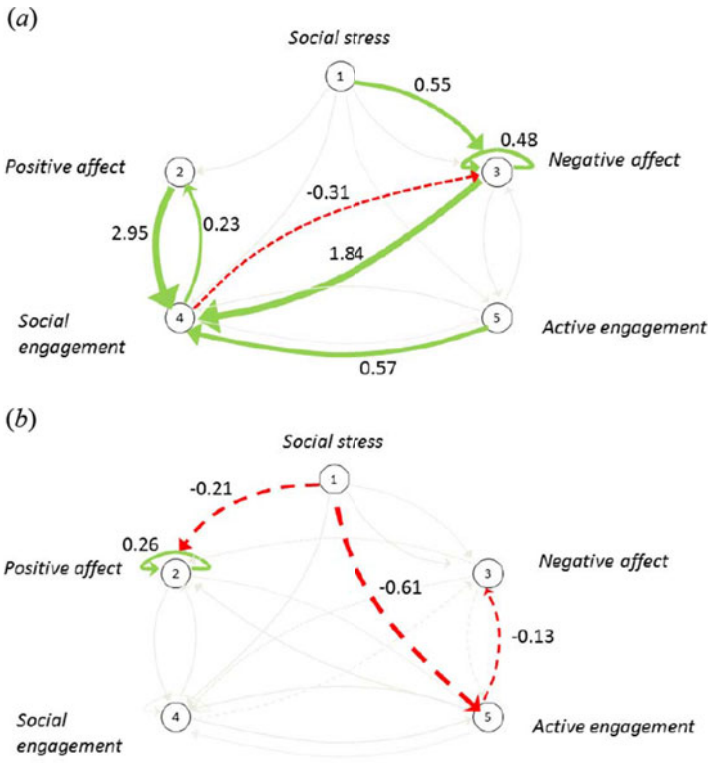

Fig. 5. Hypothetical networks of two different individuals. β-Coefficients of time-lagged effects with $p<0.2$ are depicted. (*a*) Network of one individual who responds strongly to social stress with increases in negative affect. This negative affect also tends to linger over time. According to this network structure, the individual responds to this by increasing social engagement (which may reflect social support from friends or a partner). This in turn decreases negative affect and increases positive affect. (*b*) Network of another individual who responds to social stress with decreases in positive affect and activity levels. This individual shows autocorrelation in levels of positive affect that may inhibit quick recovery to previous levels of positive affect following social stress. The reduced activity levels in turn may trigger increases in negative affect. According to this network structure, negative affect might be remedied by being more actively engaged.

to make an impact on positive affect. Therefore, it could be hypothesized that this individual is more resistant to recovery. This is in fact also what we observed. While the first individual showed strong reductions in depression scores in response to subsequent treatment, the second individual did not. These individual-specific networks may thus actually represent the underlying structure of the individual's psychopathology at the smallest level of detail. If this is true, then it may reveal important information on individual vulnerability and resilience.

A new approach to enrich psychiatric practice

As mentioned in the Introduction, a number of challenges impede the translation of scientific endeavours to clinical practice in psychiatry. The proposed dynamic micro-level view may contribute to refining our understanding of the development and maintenance of mood disorders.

First, it may clarify the conceptual nature of mood disorders. The dynamic micro-level perspective may explain how the continuous interplay between everyday situations (such as stressors), momentary mental states and behavioural responses to mental states may actually constitute the smallest building blocks of what eventually – in those who end up into a vicious circle of negative experiences – may become an MDD. It is this moment-to-moment level of detail which may contain information on mechanisms which, given the continuous ongoing interplay between daily states and experiences, may have clinical impact and long-term consequences. In addition to combining contextual factors, affect and behaviour in a single network, this approach allows a more fine-grained examination of individual affective states (such as paranoia, anxiety, sadness, cheerfulness, contentment, etc). This may help to build more specific models of affective (dys)functioning.

The micro-level network model illustrates what pre-existing vulnerability may look like in this context. The network structure between momentary states and experiences is complex and dynamic and may vary between individuals and over time. How individuals

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respond to, for example, momentary social stress may crucially depend on this underlying dynamic structure. The connection strengths and directions of effects between states and experiences may determine how quickly nodes of the network can be turned on and how activity of these nodes propagates through the network. It is the combination and the complex interplay between all these effects that constitute an individual's current vulnerability.

This dynamic view on the development of depressive symptoms explains how different causes may eventually yield similar clusters of symptoms. Causes may make an impact on different places in the dynamic network structure. Certain genes or previous stressors may result in stronger or weaker interconnections between particular nodes in a different way in each individual. However, in the end these differences could result in similar reinforcing loops of states and experiences. Second, it also explains why similar causes for individuals do not necessarily result in similar outcomes. Differences in connection strengths between the nodes in the network determine the final impact of a stressor, for example. Thus, the same stressor eventually may have different impacts across different persons.

It can be hypothesized that the underlying vulnerability structure in terms of strengths and direction of interconnections in the network may additionally be modified over time by epigenetic processes, life events (stress sensitization), therapy or other important life experiences, which further illustrates the complexity of psychiatry.

A second challenge in psychiatry is the gap between experimental findings and their relevance to real-life experiences and processes. Apart from the fact that it is aetiologically relevant to examine mental states at the micro-level of experience, the other advantage of the ESM network model is that momentary assessment techniques collect real-world measures of real-life experiences and behaviour. These measurements thus have a high level of ecological validity. Mechanisms discovered in these studies are expressed in real-life experiential and behavioural patterns. Therefore, the results may pinpoint concrete patterns in the lives of patients in need of intervention.

Third, in order to aid progress in psychiatry, personalized mechanistic knowledge is required in addition to group-level knowledge on mechanisms. Attention for the necessity of individual-specific insights is growing and is expected to enrich approaches in psychiatric research. A dynamic micro-level approach allows for the examination of mechanisms both at the group and individual level. Since many prospective observations are collected separately for each individual over time, individual-specific analyses can be performed, resulting in individual-specific knowledge on real-life dynamic patterns of affect and behaviour. For each individual, this may yield knowledge on the nature of underlying vulnerability such as the specific locations in the network that cause or maintain unfavourable patterns of affect or behaviour. Consequently, such knowledge also provides insights in identifying the network connections that need alteration for a particular individual in order to maximize the probability of recovery. In other words, this development may provide knowledge that is of direct use in clinical settings.

Technology has only recently advanced to a level where it has become feasible to integrate momentary assessment techniques not only in science but also in clinical practice. New PDAs (personal digital assistants or handheld devices), web applications and mobile phone applications allow for easy collection of moment-to-moment experiences and behaviour in real life (Wichers *et al.* 2011*b*). Additionally, the recent emergence of this new technology is indispensable for the direct storage of potentially large amounts of data. This makes it possible to translate collected data directly into informative individual network graphs that can be presented to patients and their clinicians. This novel development takes into account the dynamic complexity that is embedded in the subject matter of psychiatry, is close to the translation endpoint and – combined with the available technological advances – may enhance and improve the diagnosis, monitoring and treatment of mental disorders.

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