Network complexity modelling of psychopathology to encompass symptoms, genetic and environmental influences

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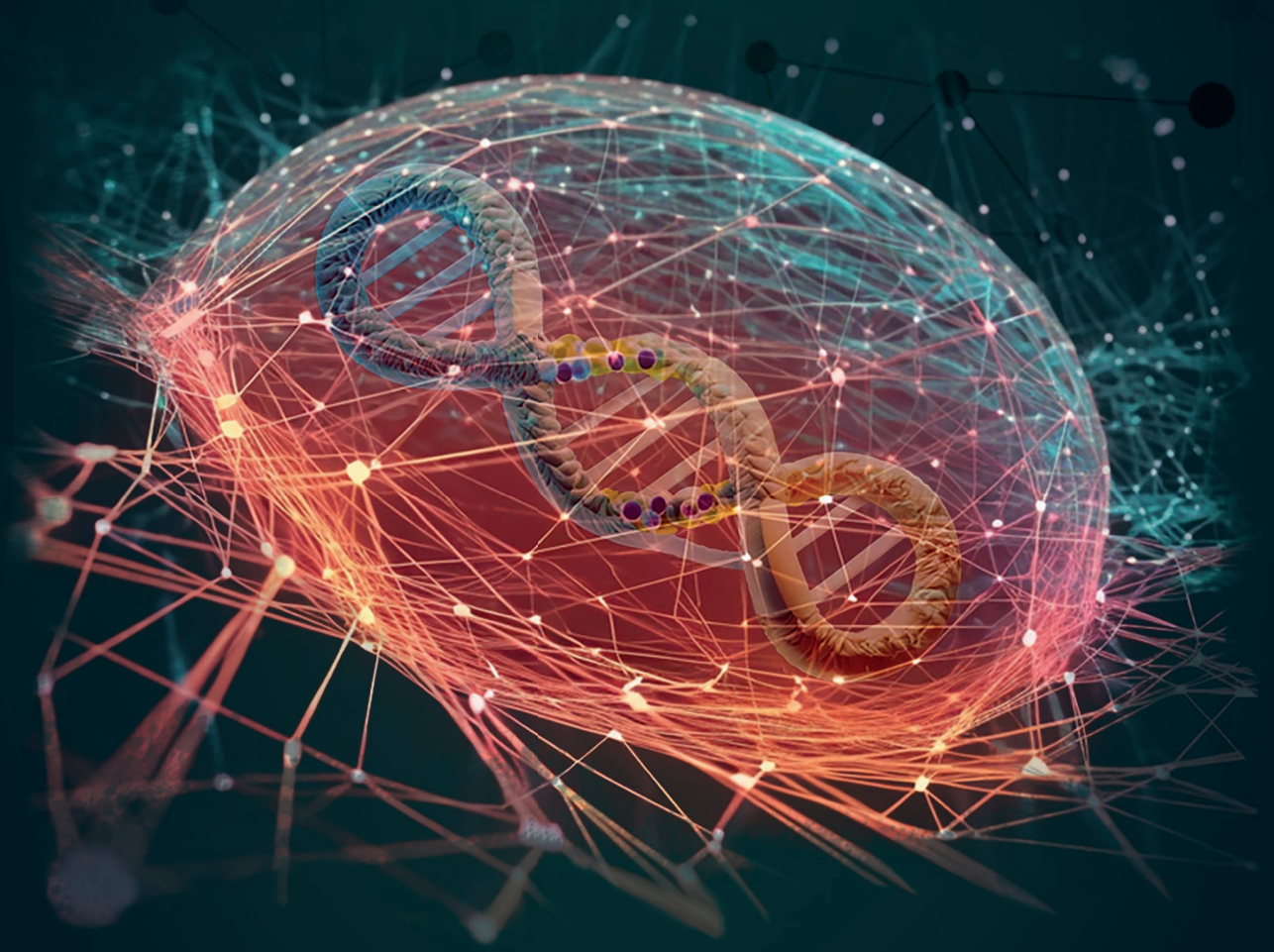

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Introduction

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Introduction

With the specified aim of concentrating the research focus on common themes within psychiatry, an expert review identified 15 research questions worthy of prioritising. Among them was the more precise identification and delineation of the role of symptoms in psychiatry and the development of computational assays for symptom-guided reassembly of psychiatric nosology[1,2]. Furthermore, multicausality of various conditions is now a largely accepted fact within the field, highlighting the complexity of this issue[3]. Despite this, the current standard of practice still conforms to the conception of mental disorders as categories based on statistical differentiation between symptoms that cluster together, ignoring the link between them and to the possible causes. These associations and complexities are, however, becoming better understood and modelized through the research of authors such as Vinogradov et al. proposing an associationist model of the symptom dimensions of paranoia, or such as Odgers et al., showing that acute phase transitions can be modelled as part of a dynamic system[4, 5]. Furthermore, risk factors are not specific to psychiatric categories. Childhood trauma (CT) has been linked in replicated findings to both affective and psychotic disorders[6]. The same is true of genetic polymorphisms, which increasingly challenges the previously accepted Kraepelinian dichotomy between affective and psychotic disorders[7].

More importantly, traditionally treatments are based on trial and error and are not able to bring full recovery in most instances. Between 60 and 80% of patients do not recover after a first episode of psychosis[8], 80 to 91,9% of patients with schizophrenia do not achieve recovery[9] and 30% do not experience remission from a first episode of major depressive disorder. In other words, if the classical model of conceptualising mental disorders had been valid, treatment would arguably have been more successful.

A fully described representation of psychopathology was recently proposed, consisting of a complex, mutually reinforced network of causal mechanisms that include genes, environment, and symptoms themselves[10-13]. In the last decade, many research studies have been conducted to elucidate this model, focusing on how symptoms impact on one another and on themselves in dynamic networks, or circuits, challenging existing methodologies and their limitations. Few, if any, studies to date tested empirically the integration of biological, environmental, and symptom components in non-clinical cohorts, representative of the general population. With this dissertation, we intend to empirically test various models of integration of these elements in the etiopathogenesis of mental disorders, with a later emphasis on psychotic emergence.

In this chapter, we first unpack the relationship between symptoms and etiological factors, as currently understood. Next, we exhibit the role of affective dysregulation in affective and psychotic disorders etiopathogenesis, and lastly, we present how etiological factors, and the network model can be integrated to understand the emergence of psychopathology.

1.1 Symptoms are related both mutually and with etiological factors.

Symptoms impact on one another in a causal fashion. The symptoms of mental disorders might intuitively be seen as related in some way. Negative views about oneself and the world cannot be considered separately from the depressive mood. The same applies to lack of appetite and weight reduction. Patients seek medical attention because they experience certain symptoms. Even treatment, whether it be pharmacotherapy or psychotherapy, is symptom focused. However, the use of symptoms in classification systems is currently not that straightforward. Symptoms are presented as individual items or criteria, which has simplified the diagnostic process in daily psychiatric practice to establishing a certain number of criteria that meet the threshold for a condition, at which point a diagnosis is given as set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM), or the International Classification of Diseases (ICD). The condition is then treated accordingly[11, 14]. By contrast, the cognitive and behavioural psychotherapy model uses the complaints that motivated a person to seek help as a starting point. The complaints are explored, and phenomenological links drawn between the complaints and what reinforces them. These are usually other symptoms or context factors or even familial or biographical anamnesis. A final conceptualization is drawn from that work and specific interventions are implemented that will change the components of the constellation to influence the entire system and ultimately treat the original complaint[15].

Additionally, symptoms overflow category borders as observed in clinical practice and repeatedly documented in the comorbidity literature[16, 17]. The next step was then aimed at proving the validity of this intuitive link between symptoms and, more importantly, unravelling its true nature. Previous authors have therefore investigated the nature of the connection between symptoms both on a theoretical, methodological, and empirical level, and from different perspectives, throughout the spectrum of mental disorders.

1.1.1 Modelling at the theoretical level

The question arises, how is this relationship modelled at the theoretical level? Based on the most prominent body of literature, we could distinguish between two main models that stand in contrast to one another and consider the connection between symptoms with or without etiological factors. The first is the *latent variable model*. According to this model, while symptoms are considered observable variables, there are unobserved factors, otherwise called latent variables, that predict symptoms and

explain their clustering[18]. In the personality research literature, a 5-factor model can be fitted to personality data. Factor scores would be based on summations of sub-scores, that is extraversion given to the weighted sum score of the items corresponding to it. This factor score would be considered as an estimate of the extraversion level[19]. Likewise, depressive mood, anhedonia, insomnia, lack of appetite, hopelessness, trouble concentrating, loss of energy, and motor retardation are observable through external evaluation or introspection. The diagnostic category 'depressive episode' would be a latent common cause that creates the association between the observed variables[20]. But a disorder cannot be a cause, as it is merely a theoretical construct. In empirical studies following this theory, symptoms described above would be included as sum scores[18, 20-23]. Consistent with this theory, observable variables are also assumed to be independent[18]. Which is not possible in the reality of the experience of symptoms, for example a depressive mood cannot be independent from negative thoughts.

The second theoretical model is the *network approach*, that considers all variables as observable and acts as mutually predictive on each other. The latter is more phenomenologically compatible with the experience of the individual, whereas the former can be viewed as non-ecologically valid[24]. On the other hand, while symptoms (or mental states, as discussed in the next section) can be argued to act as building blocks of any conceptualisation, it is important to denote their non-exclusivity. Biological, social, and environmental factors should also be included in the network model (see corresponding section).

Parallel to the two models cited above, other approaches have been followed, namely the endophenotype approach that has been expounded to help link mental disorders to their genetic roots[25]. According to its underlying logic, disease-specific phenotypes should be the downstream manifestation of a narrower genotype than the entire disease-related genotype[25]. Or other theories postulated such as connectionist-inspired ones[23, 26]. In a suggested connectionist-inspired network of depression, input nodes reflected aetiological variables, an intermediate layer represented symptomatic and pathophysiological outcomes, and the output node represented the onset of depression or of comorbidity. According to this model, the onset of depression rely solely on the interactions between the various endpoints[26].

1.1.2 Symptoms versus mental states

Following the latent variable model, the variables studied are mostly sum scores of questionnaires that otherwise dull the role of individual symptoms. Psychopathology networks, on the other hand, chose in some known previous works to implement items of the DSM or ICD, for the sake of standardisation of analysis and comparability of eventual future studies[20]. Alternatively, researchers have settled on momentary mental states (MMS), especially when tackling the area of experience sampling method (ESM) based networks. Those would be displayed as nodes in a network graphical representation of the

data (Figure 1 in Chapter 2). They constitute feelings, cognitions, and behaviours of daily life on a finer-grained time scale and are argued to be the building blocks of symptoms, that is symptoms of depressed mood is the summation of feeling down (i.e. MMS), that persists over time and is therefore less reactive to positive events, that otherwise (in the case of a healthy state) would make the person switch to feeling joyful (i.e. MMS). This means, that not only the MMS are building blocks of symptoms[27], but the latter also have a clinical and pathological denotation. Therefore, a convincing case can be made for the use of MMS in the field of mechanistic research or in the research concerning complex dynamical systems[28], and even more accurately if the research is based on a non-clinical population or one with sub-threshold of psychopathology.

In the network literature, the terms 'symptoms' and 'MMS' are frequently employed interchangeably[29-31]. To maintain consistency and clarity throughout this chapter, we will henceforth utilize the term 'symptom,' with the understanding that 'MMS' is implicitly subsumed when the context pertains to temporal networks literature.

1.1.3 Modelling at the methodological level: Network analysis

As the network research has been stepping from the theoretical background towards a data-driven investigation of the causal system within and/or between mental diseases, multiple statistical methods have been utilised. Initially network studies were based on cross-sectional data. When inferred from cross-sectional observational data, we can distinguish between four major types of networks, depending on the type of the estimation method producing the relationship between the variables (in other terms, the edges between the nodes)[13, 32]. Edges representing zero-order associations (estimated using e.g., Pearson correlation method) are called association networks. When these associations are conditionally independent (e.g., partial correlations) they are called pairwise Markov random field networks (PMRFN) or concentration networks (see below), when the associations are estimated using the Bayesian method, they are referred to as directed acyclic graphs (DAG) [32]. Lastly, when they are derived from the application of a specific algorithm on regression R2 factors they are called relative importance networks[33].

(1) Association networks are commonly computed as zero-order correlations between pairs of items. In this type of symptom network, edges represent statistical correlations between reported items, that represent the nodes. The network is typically weighted and undirected (i.e., no arrows at the tips of edges, and with edges graphically representing the corresponding correlation value e.g., in the form of varying edge thickness). As a result, clusters of symptoms may form and appear as several distinct networks, meaning that the correlations between symptoms belonging to the same cluster appear to be stronger than the correlations between symptoms belonging to different clusters[13]. This type of network analysis is primarily used in explorative studies as a hypothesis generating tool. Thevalue for inferring

causality is weak as the relationship between symptoms may have many explanations[13]. A symptom may cause another symptom, for example fatigue may result from depression-related insomnia. Alternatively, a third symptom might link the other two, or a third variable is responsible for both symptoms[13]. For that reason, both methodologies described below came to complete and give more indication about causality to the association between the variables of interest.

(2) In concentration networks we distinguish depending on the nature of the variables or nodes between: (a) The Gaussian Graphical Model (GGM), also called partial correlation network, that is suitable for continuous variables (e.g., intensity of a given symptom on a 5-point Likert scale). It is based on the extraction of partial correlation coefficients from the data, which is a correlation between two given symptoms after controlling on all the other symptoms, and which will give the thickness or strength of each undirected edge or arrow. It is supposed to bring us closer to causality by eliminating the pairwise connections in the networks that are solely due to a third node. GGMs can be estimated using the qgraph package[34]. (b) Ising models more suitable for binary variables (presence/absence of symptoms) using the IsingFit package[35,36, 37]. (c) For data that include both ordinal and binary variables (presence vs absence of an exposure, and symptoms quotation on a scale), networks can be estimated with the use of Mixed Graphical Models (MGM) that are designed for mixed data[38]. The lack of directed edges, and therefore the lack of indications regarding causality direction, is one of the fundamental limitations of concentration networks. This is what the following two network types, Bayesian networks and relative importance networks, try to overcome.

(3) Bayesian networks are graphical depictions of the probabilistic relationships (edges) between variables of interest (nodes), estimated using the Bayesian method[39]. In the produced directed acyclic graph (DAG), every edge terminates with an arrow, denoting that one node probably predicts the next node[32]. They are useful for extracting causal knowledge from psychological data[40]. This method can be used to predict the emergence of a disorder or the consequences of an intervention[41].

(4) Networks of relative importance are based on the proportion of variance (e.g., R2) one item explains in another item after controlling for all other items. The relative importance of networks can be estimated using the relaimpo package [33].

While above mentioned network methodologies are promising, temporal under sampling is likely to occur with traditional assessments that take place once (in cross-sectional procedures), or over periods of years, months, or weeks (in cohort studies). Additionally, time precedency is an important factor in causality[40]. In that sense parallel efforts in the network literature were directed to finer-grained time series-based networks. Mutual interaction of symptoms have been studied using novel, longitudinal, within-person tracking methodology [42], that capture the moment-to-moment dynamics of symptoms

impacting on each other in the flow of daily life [31, 43]. The ESM incites individuals to document their affective states (e.g., feeling cheerful, fearful, energetic, down or relaxed), anomalous experiences (e.g., feeling suspicious, hearing voices, losing control), and context (e.g., minor stressful events, activity, company) after incentives (i.e., beeps or signals emitted via a watch or some device) occurring at unpredictable moments throughout the day[27]. Participants' responses to items in the questionnaire are adjectives qualifying the mental state in the moment of the beep, referred to as MMS. The intensive repeated measurements over time permit the within-person analysis of temporal associations, provides more elements for causality, and reveals dynamic mechanisms that are neglected in cross-sectional, between-subject designs [42, 44].

In the ESM literature, symptoms – or more broadly, mental states – were revealed to interact in dynamic relationships[31]. For example, insomnia may lead to a depressed mood the day after [45], a depressed mood may predict paranoia, and hallucinatory experiences may give rise to delusional ideation the next moment [42, 46]. These associations can typically be represented in a network of MMS impacting on one another, where the momentarily assessed mental states are represented by a node and associations between MMS are typically represented by a directed edge denoted by an arrow [12, 13]. Associations are typically estimated using vector autoregression (VAR), which is basically the use of a repression model on variables that are assessed over time to predict a change in their state. In a standard VAR model, used in the context of an ESM based temporal network of MMS, a current MMS at time point t is regressed on its lagged values, at time $t - 1$ (autoregressive effect) and the lagged values of each of the other emotions (cross-lagged effects)[47].

Despite this advancement in the psychopathology network analysis, one of the limitations of the temporal network method is that the majority of standard models used to infer network models estimated using VAR, assume stationarity. This means that the mean and variance of each variable values at all time points must remain constant over time[48]. A violation of this assumption may present false estimations of the regression coefficients. However, data suggest that most time series in psychology are non-stationary, and thus VAR regression utilising non-stationary time series may provide spurious results[49]. If we take affect dynamic research as an example, assuming stationarity is rather difficult to meet, a changing variance over time can be an inherent feature of emotional dynamic regarding a healthy state but especially in mental disorders (see the section on affective dysregulation). Therefore, one possible solution to the problem of spurious findings related to stationarity is to test for it and then adjust it in the analysis by incorporating a random slope of time.

1.1.4 Network analysis: Centrality measures

Once the network has been estimated from the data using one of the methods described above, other measures derived from the graph theory allow us to calculate centrality measures. Centrality analyses

allow for the identification of nodes that are more 'central' than others in the network. Given their centrality, they are able, when triggered, to create a 'domino effect' and activate the remainder of the other nodes to which they are connected[13]. Three well-known centrality indices are usually calculated: node strength, closeness centrality and betweenness centrality [34, 50]. The *node strength* or *strength* is the sum of the absolute value of the weighted connections (both inward and outward) of specific nodes, thus indexing the extent to which this node is connected in the network. *Closeness centrality* refers to the inverse total of the shortest distances (or shortest paths) connecting a specific node to all others, with these distances calculated as the sum of the inverse partial correlation (or regression) coefficients. This metric assesses the potential influence of a particular node on all other nodes by considering all outgoing connections (greater closeness indicates more impact) [50]. *Betweenness centrality* on the other hand, represents the frequency with which a node appears on the shortest paths between any two other nodes. A node with elevated betweenness centrality is situated on numerous shortest paths. Consequently, a node with elevated betweenness centrality signifies a substantial number of connections between nodes relying on that specific node, which enhances its ability to control interactions within the network. For a comprehensive analysis of these centrality measures, we encourage you to consult Chapter 3[13, 50].

The newly introduced measure of predictability in the network perspective[51] can provide information about how much of the variance of a given node can be explained by its connections. For example, if a depressed mood has strong connections with guilt or loneliness and with insomnia, it does not give us a clear idea about the role each connection plays, or how much of the variance is explained by all the connections.

1.1.5 Empirical studies of symptoms interactions

Table 1.1 shows a selection of search results using the keywords 'symptoms', 'association', 'relationship', 'network' and 'psychiatric', using PubMed and different Boolean combinations, in studies that included participants from 18 to 65 years old, but excluding studies on dementia. A total of 4,860 research papers were identified and filtered down to include only studies exploring a predictive association or a conditional dependency between individual symptoms. Using these criteria, 57 studies were identified, compared, and listed in table 1.1.

We differentiate between two main types of research, namely studies using the network approach and those who do not. In identifying research articles that use the network approach, we follow the lead of a recent theoretical review that posits as such any study that considers the phenomena under investigation as consisting of components interacting with each other and giving rise to emergent properties[52], such as the ESM study that found that negative symptoms result in the interaction between momentary emotions through over-regulation[53]. This characteristic of complex systems, whose whole is more than the sum of

its parts, is called the emergence[54]. This is to be distinguished from using explicitly the network methodology, that resort to the concepts of statistical and graphical models as detailed in the previous section. Thus, in table 1.1, the studies following the network approach do not necessarily use network methods but some of them use complex dynamical system methodologies instead.

Among studies identified focusing on affective and anxiety disorders while not using the network approach [55], a research estimated the association between two factors of ruminations, brooding and reflection, with negative affectivity in relation with each of the two categories, depression and anxiety (table 1.1). Pearson correlation showed that all the four components load significant associations with each other. Negative affect (NA) association with depression was dependent on both rumination factors. Noteworthy was the finding that although anxiety correlates with ruminations and with NA separately, this does depend on the latter but not through ruminations[55]. These results are suggestive of a mechanistic role of an important cognitive symptom in depression. However, this study used sum scores as outcomes and thus keeps many mechanistic questions open, for example if NA are involved differentially in relation with ruminations, or with what symptom of depression rumination is correlated to, knowing that rumination and NA belong to depression itself. Another research study examined rumination and worry using them both as outcomes in relation to the presence of a DSM diagnosis of depression or anxiety disorders and found ruminations and worry to be transdiagnostic[56]. In sum, although both studies showed a link between affective and cognitive domains, using the latent variable approach prevented shading the light on fine grained mechanisms.

Adding to this, in a meta-analysis of 66 longitudinal studies about the link between anxiety and depression, all categories of anxiety disorders predicted all types of later depression and vice versa with the same strength, yet social anxiety disorder and specific phobia were more predicted by depression than vice versa[57]. The authors posit that the effect of depression on the later development of an anxiety disorder may be due to behavioural inhibition and social rejection experienced by individuals with depression, that are known predictors of social phobia[57]. We can add to these hypotheses, the possibility that a learned dysfunctional emotional regulation during the depressive episode would allow for a vulnerability to anxiety disorders. Yet investigating this aspect would need studies to use adapted tools for studying emotion regulation (see corresponding section below).

In the same category of studies using the latent variable approach, a longitudinal investigation of the relationship between sleep disturbances and later depressive symptoms in a representative sample of the UK general population, cross-sectional correlation was significant but not the longitudinal one, bidirectionally, while controlling for all other factors[58]. While one could interpret these results in favour of the exclusion of insomnia as an important risk factor for the development of a depressive episode, one could argue against it, in a closer temporal scope, considering the strong cross-sectional correlation

between the two. Indeed, insomnia might increase the risk for other individual depressive symptoms through the mediation of other symptoms like ruminations. This could have been obscured in the cited study using sum scores of depression scales. Taken together, studies not using the network approach support the presence of predictive associations between symptoms but remain limited in providing direct indications about mechanisms that involve these associations for the emergence or maintenance of a mental disorder.

In contrast to the studies mentioned above, the network approach allowed findings giving specific indications about mechanisms of comorbidity between affective and anxiety disorders. A cross-sectional network research examined the symptom structure of depression and symptoms of general anxiety disorder (GAD) regardless of meeting the cut-off for a diagnosis category and found irritability and depressed mood to bridge anxiety to depressive symptoms[59]. Bridging symptoms being determined statistically by calculating the absolute node's strength using the edges that link each node to clusters of nodes other than its own (i.e., inter-community edges but not intra-community edges, or what Blanken et al. (2018) refer to as 'communicating symptoms')[60]. In the same vein, in a psychiatric sample of 1029 individuals, depressed mood, worry, feeling nervous and guilt were found to bridge GAD and depressive symptoms[61]. This was in line with findings from a network analysis of the association between depression with anxious distress, and mixed depression demonstrating agitation or inner tension and state of nervous excitement bridging anxiety, depression, and mixed depression[62]. Regarding research on suicide, entrapment, emotional pain, and ruminations were proposed to maintain other symptoms of the suicidal crisis[63]. Similarly, psychomotor agitation or retardation and valuelessness were suggested to have a direct regulation role on suicidal thoughts[59].

Collectively viewed, studies from the network perspective are more prone to generate mechanistic hypotheses about maintaining factors of affective disorders and about the mechanism of comorbidity, for example the above-mentioned irritability and its corollary inner tension were found in two network studies to be a probable cause of comorbidity between affective and anxious disorders. Furthermore, lending credence to the network method's superiority, a research compared the prediction power of multilevel regression model to discrete Bayesian networks revealing the superiority of the latter in predicting dementia from a disturbed olfactory identification[41].

In studies of psychosis, symptoms that are considered intrinsically psychotic (hallucinations, delusions, disorganised thoughts, negative symptoms) were studied in their mutual interaction. Negative symptoms were found to be in great prevalence in the general population (20-22%), yet they exhibit an increased risk for later schizophrenia and, to a lesser extent to non-psychotic disorders, only when associated with psychotic experiences (OR 13.0 (CI 2.1–79.4)) [64]. Subject to the fact that they might share common risk factors like cannabis use, that was overrepresented in that population, and that can cause negative

symptoms, for example flattening of affect and amotivational syndrome. In another work, thought processes and depersonalization were analysed in relation to absorption and hallucinations. The metacognitive item 'uncontrollability and danger' was linked to hallucinations only in acute phases and both the absorption and depersonalisation were positively correlated with the metacognitive components[65]. However, no mediation role of any of the variables was examined letting the question open about the mechanism that would have been more unravelled using the network methodology.

Not only symptoms interact with each other, but symptomatic constructs have been shown to have an inner structure, that might also have mutual influences between its parts. This was recently investigated concerning paranoia assessed in a representative sample of the UK general population. Interestingly, the 4-factor structure of paranoia was supported using both the latent variable and the network analysis approach in a similar way [66].

Alongside psychotic symptoms, so-called ancillary symptoms, are experiences that are not inherent to psychosis, that is depression, anxiety, worry, low self-esteem, dissociation, insomnia, and nightmares, yet highly prevalent in the population with psychosis. Traditionally considered as simple epiphenomenon, recent research has been analysing their role in psychosis with closer attention. Findings from an ESM study for unravelling the relations between psychosis symptoms and affective states indicate an increased regulatory tendency of emotions dynamic (return time to baseline after deflection) associated with the severity of negative symptoms[53]. In this study, ESM allowed to capture affect variability in real life with an accuracy that is less possible with cross-sectional methodology, which only captures a snapshot of individuals' experiences at a single point in time, and provide inappropriate summary indices for capturing dynamic processes, by using variance and standard deviation[67]. A standard deviation is not sensitive to time since it does not account for instantaneous changes in impact[67]. The table below describes the difference in research question formulations between both types of study.

TABLE 1.1 SUMMARIES OF NETWORK AND NON-NETWORK STUDIES ACROSS THE PSYCHOPATHOLOGY SPECTRUM

Disorders	Studies not using the network model	Studies using the network model
Major depression	Negative affectivity, depression, and anxiety: Does rumination mediate the links?[55]. The relationship between worry, rumination, and comorbidity: Evidence for repetitive negative thinking as a transdiagnostic construct [56].	Network structure of depression and anxiety symptoms [59]. Network analysis of depression and anxiety symptom relationships in a psychiatric sample[61].

	Anxiety and depression as bidirectional risk factors for one another: A meta-analysis of longitudinal studies[57]. Sleep disturbances and depressive symptoms: an investigation of their longitudinal association in a representative sample of the UK general population[58]. The relationship between cognitive distortion, depressive symptoms, and social adaptation: A survey in Japan[68].	The relationship between depression with anxious distress DSM-5 specifier and mixed depression: a network analysis[62]. Suicide crisis syndrome[63]. Exploring the emotional dynamics of sub clinically depressed individuals with and without anhedonia: An experience sampling study[69]. Network analysis of depressive symptoms in Hong Kong residents during the COVID-19 pandemic [70].
Psychotic disorders	The association between negative symptoms, psychotic experiences, and later schizophrenia: a population-based longitudinal study[64]**.** Relationship of metacognition, absorption, and depersonalization in patients with auditory hallucinations[65]. Linear and non-linear associations of symptom dimensions and cognitive function in first-onset psychosis[71]. Untangling the complex relationships between symptoms of schizophrenia and emotion dynamics in daily life: Findings from an experience sampling pilot study [53]. Anhedonia and positive, negative, and general psychopathology in patients with schizophrenia[72]. Anxiety symptoms in first episode psychosis[73]. Appraisals, psychotic symptoms and affect in daily life[74]. Movement disorders and psychopathology under predominantly atypical antipsychotic treatment in	A symptom network structure of the psychosis spectrum[79]. Social cognition, neurocognition, psychopathology, social skills, functional capacity, and functional outcomes[80]. A network of psychopathological, cognitive, and motor symptoms in schizophrenia spectrum disorders[81]. Disentangling the symptoms of schizophrenia: Network analysis in acute phase patients and in patients with predominant negative symptoms[82]. The network structure of paranoia in the general population[66]. A network analysis of post-traumatic stress and psychosis symptoms[83].

	adolescent patients with schizophrenia[75]. Attenuated positive psychotic symptoms and social anxiety: Along a psychotic continuum or different constructs?[76] The association between social phobia, social anxiety cognitions and paranoid symptoms[77]. Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives[78].	
Somatic Symptoms	How self-reported hot flashes may relate to affect, cognitive performance, and sleep[84]. Relationship of intensity and special characteristics of migraine to depressive and anxious features[85].	Somatic symptom disorder[86]. Mapping network connectivity among symptoms of depression and pain in Wuhan residents during the late-stage of the COVID-19 pandemic[87].
Dementia	Non-cognitive psychopathological symptoms associated with incident mild cognitive impairment and dementia, Alzheimer's type[88].	A network approach on the relation between apathy and depression symptoms with dementia and functional disability[89]. Can dementia be predicted using olfactory identification test in the elderly? A Bayesian network analysis[41].
Bipolar disorder (BD)	Relationship between dysfunctional beliefs, self-esteem, extreme appraisals, and symptoms of mania and depression over time in bipolar disorder[90].	Adolescents at high risk for BD[91] Network structure of manic symptoms[92] Symptom networks in acute depression across bipolar and major depressive disorders: A network analysis on a large, international, observational study[93].
Anxiety disorders	Association between obsession, compulsion, depression and insight in obsessive-compulsive disorder: a meta-analysis[94].	Network models of post-traumatic stress disorder (PTSD): A meta-analysis[97].

	The relationship between PTSD and depressive symptoms among children after a natural disaster: A 2-year longitudinal study[95]. Intolerance of uncertainty, worry, and rumination in major depressive disorder and generalized anxiety disorder[96].	Symptom structure of PTSD and co-morbid depressive symptoms - a network analysis of combat veteran patients[98]. Severe PTSD, somatic symptoms, and dissociation in the aftermath of trauma[99]. Acute and chronic posttraumatic stress symptoms in the emergence of posttraumatic stress disorder: A network analysis[100]. Dysfunctional posttraumatic cognitions, posttraumatic stress and depression in children and adolescents exposed to trauma: a network analysis[101]. Symptom network connectivity in adolescents with comorbid major depressive disorder and social phobia[102].
attention-deficit/ hyperactivity disorder (ADHD)	A psycho-genetic study of associations between the symptoms of binge eating disorder and those of attention deficit (hyperactivity) disorder[103].	Network structure of physical, cognitive, and emotional symptoms at preseason baseline in student athletes with ADHD [104].
Substance abuse and dependence, and other addictions	Longitudinal associations between alcohol problems and depressive symptoms: early adolescence through early adulthood[105] Anhedonia and substance-related symptoms in detoxified substance-dependent subjects: a correlation study[106].	Symptom networks in patients with substance use disorders[107]. Network analysis of substance abuse and dependence symptoms[108]. A network analysis of internet gaming disorder symptoms[109]. Network analyses of internet gaming disorder symptoms and their links with different types of motivation[110].
Eating Disorders	The relationship between alexithymia and intolerance of uncertainty in anorexia nervosa[111].	Network analysis of specific psychopathology and psychiatric symptoms in patients with eating disorders[112].
Autism		Network of rumination and depression symptoms[113].

		Autistic symptoms and social functioning in psychosis: A network approach[114].

1.1.6 Link between etiological factors and symptoms

The network approach to study the nature of psychopathology has been extended to examine biological mechanisms underlying the interplay between genes, environment, and symptoms, assisting in the search for novel treatments[10, 13, 115]. It has been hypothesised that genes and the environment may act as risk factors for developing mental disorders by making the structure of a MMS network 'risky'[116]. For example, the environment may affect the strength of the network connections so that a central symptom initiates a cascade of changes in other symptoms, eventually giving rise to a full-blown mental disorder[13,31,117,118].

If psychopathology is a complex system of interrelated components including symptoms, the question arises how to modelise, and therefore better understand, the effect of etiological factors on symptoms in this complex system. Studies following the network approach have used etiological factors as nodes. An example of that is the use of the network analysis for estimating the link between inflammatory markers and depressive symptoms, where only 'sleep problems' and 'energy levels' were significantly associated with CRP levels after adjusting for confounding factors[119]. Regarding the influence of genes and the environment many attempts were driven by data, while using the network model, for unravelling the path between the clinical and the etiological domain. In this direction, a study estimated a GGM network based on cross-sectional data of CT and a negative lifestyle in first episode psychosis, but have not led to conclusive results[120]. Another network study using MGM, that is based on partial correlations and cross-sectional data, suggested a mediative, yet only indirect role, of cognitive biases and depressive symptoms in the association between traumatic life events and psychotic experiences[121]. Findings from another network analysis showed symptoms of general psychopathology in the shortest path between CT and psychosis, with anxiety symptoms as a primary connective component [122]. The findings also pointed to several other connective pathways, for example through poor impulse control and motor retardation[122].

On the genetic part, polygenic risk score of schizophrenia (PRS) has been the most closely linked to positive psychotic symptoms, particularly the symptoms, namely ideas of conspiracy and paranoia[123]. Furthermore, a node-specific predictive betweenness test, which investigated items that are more often located on the path between two other items, one of which is always the PRS, showed paranoia and hopelessness as intermediate factors[123].

Other authors argue that it is more suitable to conceptualise etiological factors as 'external field' factors, a notion borrowed from physics[20]. In physics, an external field refers to a physical quantity, such as a force or potential, that acts on a system from outside of the system itself. This concept was suggested to be used in the study of networks, as external fields can impinge on the network and affect its behaviour

or structure. For example, in the study of electric circuits, an external field might be a voltage or current applied to the network from an external source[124]. In the study of social networks, external fields might include external events or influences that affect the relationships or interactions within the social network. By identifying and studying these external fields, researchers can gain a better understanding of the factors that shape a network and its behaviour. As application in psychopathology research, one could argue to modelise them as predictor variables, external to the network itself[20,125]. In our work we attempt to use a similar logic, by applying the network model on time series data with great ecological validity (i.e., ESM) and attempting to link them to genes and the environment, but not using them outside of the network or as nodes, but rather by using them as stratification conditions, since they are more constant and therefore much less variable than affective mental states (AMS).

1.2 Role of affective dysregulation

1.2.1 Affective dynamics definition

The word 'affect' is derived from the Latin *affectus* and denotes the receptive quality of being influenced or affected by something[126]. In clinical psychiatry 'affect' is defined as 'a pattern of observable behaviours that is the expression of a subjectively experienced feeling state (emotion)'[14](p. 763). But restricting 'affect' to what can be seen in this manner excludes the majority of what qualifies as 'affect' in contemporary affective research[126].

In this dissertation, we adopt the current definition used in constructivist theory of affective states, led by Russell and Barett, also described as core affect and characterised by valence and arousal[126]. Affect dynamics refers to the temporal fluctuations of affective states. Its study involves the examination of the patterns, regularities, and principles governing these temporal fluctuations, physiological arousal, and behaviour, as well as the underlying processes and consequences of these fluctuations[67,127]. Affect dynamics is characterised by three features: Instability, inertia, and emotional differentiation. Instability involves how emotions can fluctuate over time. Inertia is the resistance to emotional change and is characterized by the predictability of one's current emotional state based on their previous emotional states, while emotional differentiation is the capacity to make nuanced distinctions among different emotional states as they are experienced, crucial for effective affective regulation[67,127]. This definition is supported by Trull 2015, who asserts that affective dynamics should be measured using time-intensive methods such as ESM[67].

1.2.2 Affective dynamics study methods

Affective fluctuations have increasingly garnered research interest in the last few decades, particularly in relation to their role in the development and/or detection of mental disorders[28]. Accurate assessment of emotional dynamics is therefore necessary for studying and understanding these processes[67]. Hence, researchers should accurately record the time of affective fluctuations, which is best allowed by the use technology such as e-diaries and cell phones[67]. The assessments can be event-contingent, random, or both[27]. It is also important for assessments to be matched to the emotional processes being studied[128].

Since it is not always clear what processes are at work, researchers should sample affect as often as possible without overburdening individuals[129]. The ESM is the most used methodology for achieving this goal, as it allows individuals to report their mental states (e.g., feeling cheerful, fearful, energetic, down or relax), anomalous experience (e.g., indicating subthreshold psychosis like feeling suspicious, loss of control), and context (e.g., minor stressful events, activity, company), at various unpredictable moments over an extended period[130]. This approach is considered ecologically valid because it reflects the natural fluctuations of affective states in real-world settings. By prompting individuals to report on their experience's multiple times a day for several days, the ESM provides a rich and detailed picture of emotional dynamics.

Furthermore, the within-subject designs with repeated measurements over time allows for getting better along with issues of causality and reveal dynamic processes of mutually impacting affective states that are obscured in cross-sectional, between-subject designs. However, even with a proper sampling methodology, there is no guarantee of an accurate representation of emotional dynamics. Therefore, researchers must also use appropriate analytical approaches that consider the dynamic nature of affective processes[67].

1.2.3 Affective dysregulation

Affective dysregulation, refers to the impaired ability to manage emotions. It is refered to as affective instability or mood instability, and is commonly known in the clinical context as a characteristic of borderline personality disorder, but it is not exclusively specific to this disorder. It is defined as a predisposition to rapid and marked mood changes and extreme sensitivity to events that would produce less intense responses in other individuals[131]. Other aspects of affective dysregulation involve emotional inflexibility or enhanced inertia[67]. Some studies have highlighted the role of affective dysregulation in the interaction of anxiety, depression, and low self-esteem, which may result in maladaptive appraisal patterns of events[132].

Moreover, affective dysregulation has been hypothesised as an early, unspecific phenotype of emerging psychopathology. More particularly, significant interest among researchers and clinicians has been directed toward the close relationship between affective dysregulation and psychosis in recent years. In fact, epidemiological studies on psychopathology have consistently found that the earliest expression of psychosis typically arises within a transdiagnostic mix of symptoms, particularly related to depression[133], and that affective dysregulation is strongly associated with the prevalence and incidence of subthreshold expression of psychotic phenomena in the general population[134, 135]. This relationship is evident even before the onset of the first psychotic episode[134, 135]. Around 30% of broadly defined psychotic disorders are also affective in nature[136]. This suggests that affective processes may play a crucial role in the causation of psychosis, as predicted by network models of psychosis [116], in which genetic and environmental factors have been included as variables[118, 122, 123]. Moreover, mood and anxiety

disorders co-occur frequently with psychosis, both within individuals and families, and share substantial genetic and pharmacological similarities[137]. Around 20% of people with a major depression (major depressive episode according to DSM IV criteria) have psychotic symptoms [138] and in patients with bipolar disorder the rate may be as high as 70% [139]. As such, the study of non-psychotic common mental disorders with a degree of psychosis admixture and their early treatment has become increasingly important to prevent worse outcomes. In this dissertation, we will explore how affective dysregulation might mediate between genetic predispositions, environmental exposure, and psychopathology.

1.3 Networks as an integrative tool

As stated in the previous sections, and proven in countless recent findings [27, 141], the network model of symptoms, and their building blocks or MMS, connecting in causal relationships with each other, yields more mechanistically relevant conclusions, in major illness across the spectrum of psychopathology. Furthermore, the network analysis takes a neutral stance on the question of whether latent variables are the underlying common causes of syndromes, and it also permits the existence of causal interactions between symptoms in order to account for symptom clusters[13, 32, 140]. More recently, some authors have suggested the inclusion of non-symptoms in the network, corroborated by recent findings such as the highly suggested mediator effect of attention features such as increased attentiveness in the link between social avoidance and fear in a network study[141, 142]. The same authors suggested the need to choose nodes with within-person variance on an individual scale, contrasting cognitive factors such as self-beliefs and information processing bias for threat-related material, or biological factors, to gender that vary at a between-person scale, or to neurotransmitter receptor density that vary at the level of the brain region[141].

On the other hand, taking into account the suggested mediator role of affective dysregulation in the etiopathogeneses of a wide range of psychiatric disorders, a number of ESM studies used intensive time series data, to investigate the effect of genetic and environmental factors on NA and positive affect (PA), two constructs created by aggregating responses on items about AMS (e.g., cheerful, enthusiastic, satisfied and energetic for PA)[29]. It has been reported that 41% of the association between PA and NA is attributable to genetic factors[143, 144]. This makes it plausible to hypothesize that not only the sum scores, but also the connections between the individual items may be influenced by genetic factors. In addition, given the fact that psychopathology is comorbid and transdiagnostic, and that genetic liability to psychopathology is shared, to a large degree, between the different mental disorders, the impact of genes on network models may be studied productively using a measure of genetic vulnerability to general psychopathology[145]. AMS, in the ESM paradigm, have also been associated with childhood adversity[146]. A recent study investigating the persistence of momentary experience of psychosis from one moment to the next in the ESM paradigm, showed that momentary persistence was familial and moderated by CT[29]. Until the beginning of works in this dissertation (see next section), no study has

integrated genetic and environmental factors as stratification variables in the network approach of individual AMS.

1.4 Networks in the Context of Complex Systems

Networks can also be viewed within the context of complex dynamical systems, offering novel frameworks to better comprehend mechanisms of mental disorders[28, 147]. Complex systems are defined by the presence of a multitude of interacting subunits within a system, which demonstrate elaborate collective behaviour and give rise to emergent properties that cannot be solely reduced to their constituent elements[54]. These emergent properties can be universal or multiply realizable, with various configurations or factors capable of producing identical outcomes, also known in the context of psychopathology as equifinality[148 147]. Key features of complex systems also include sensitivity to initial conditions, meaning that minimal differences in the system's initial state can lead to significant outcomes over time, making their evolution challenging to predict[148], and self-organization through feedback between micro and macro levels of organization, robustness, and path-dependence[148]. Certain complex systems also display criticality, where minor inputs result in significant state changes when reaching a critical point. A high degree of connectivity or correlations between components of a system provides an indication about its criticality[148]. And a complex system is called dynamic if it evolves over time[54]. Mental health disorders share these characteristics, justifying their examination through the lens of complex dynamical systems concepts and methods[147].

Networks have been used across various disciplines in complexity science to capture the interactions between systems subunits[54, 147]. In mental health research, previous time-intensive network analysis on real ESM data has shown strong connectivity between depression symptoms before a relapse as a possible indicator of a phase transition and therefore of criticality[149, 150]. However, this finding still requires replication. In addition, recent advances in mental health research have yielded promising results through the application of complexity models utilizing differential equations mainly on simulated data, with a particular emphasis on the rate of change of mental disorders viewed as complex dynamical systems (e.g. panic disorders during psychotherapy)[151 152]. While we will not employ these techniques typically used for complex dynamical systems in the present thesis, we still are going to use the complexity framework and terminology to better understand our findings. Our focus will be on employing advanced, yet conventional, statistical methods to maintain the comparability of our results. By examining mental health disorders through diverse approaches such as networks, we aim to explore the multiple layers within the causal system of psychopathology, while ensuring our methods remain harmonious with existing research yet retain a sense of originality.

1.5 Studies in this dissertation

The primary objective of this dissertation is to explore possible mechanisms and processes that underlie the emergence of psychopathology. Our aim is to elucidate the connections between mental states or symptoms and etiological factors, including genetic and environmental influences, with an emphasis on their contribution to the development of psychopathology, specifically focusing on the onset of psychosis. Consequently, four papers have been published, which will be presented in the subsequent chapters. In the paragraphs to follow, we will briefly delve into the rationale behind each paper.

Since a previous network analysis replicated clusters of paranoia established in the same data set using latent variable techniques[66], the hypothesis that other variables, such as genetic and environmental factors, must have an influence on symptoms to have them organized in clusters arose. As an attempt to test empirically the combination of those factors with the network of interaction between mental states and given the big body of empirical research stating affect dysregulation as a core mediating factor for the emergence of psychosis, we then undertook the task of investigating the link between raw exposure factors (genes and environment) and the mediating factor (affect dynamic). In Chapters 2 and 3, we aim to investigate the extent to which both genetic and environmental factors contribute to the connections between moment-to-moment mental states impacting on each other in a network, using time-intensive intra-individual data. For that sake, we studied the differences in network connectivity and structure between categories of CT and genetic liability to psychopathology, focusing on six affective mental states: 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated' and 'down'. For the sake of scientific validity, we replicated the same methodology in a larger gender-mixed general population twin sample (Chapter 3).

In Chapter 4, we examine the question of psychopathology emergence, but this time by setting the choice on specific psychotic symptoms in their association with affective dysregulation embodied in the cluster of nonpsychotic disorders, and in relation to etiological risk factors including genes and environment. This was conducted using the longitudinal hazard risk analysis of data from a representative cohort study with 10 years follow-up.

In Chapter 5, we present the network model applied on one-year follow-up ESM data of a single patient to study lagged associations between symptoms in relation to illness severity and pharmacological treatment.

Chapter 6 provides a general discussion of the mechanisms involved in the development of psychopathology. Here, we expand on several themes addressed in this dissertation and explore the rise of fresh approaches for study and treatment of psychiatric diseases, as foreseen in future directions for psychopathology research.

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Chapter 2

Genetic and Environmental Influences on the Affective Regulation Network: A Prospective Experience Sampling Analysis

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Keywords: affective mental states, emotions, network, time-series, genetic, psychopathology, early environment, childhood trauma.

Abstract

Background:

The study of networks of affective mental states that play a role in psychopathology may help model the influence of genetic and environmental risks. The aim of the present paper was to examine networks of affective mental states (AMS: 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated' and 'down') over time, stratified by genetic liability for psychopathology and exposure to environment risk, using momentary assessment technology.

Methods:

Momentary AMS, collected using the experience sampling method (ESM) as well as childhood trauma and genetic liability (based on the level of shared genes and psychopathology in the co-twin) were collected in a population-based sample of female-female twin pairs and sisters (585 individuals). Networks were generated using multilevel time-lagged regression analysis, and regression coefficients were compared across three strata of childhood trauma severity and three strata of genetic liability using permutation testing. Regression coefficients were presented as network connections.

Results:

Visual inspection of network graphs revealed some suggestive changes in the networks with more exposure to either childhood trauma or genetic liability (i.e. stronger reinforcing loops between the three negative AMS anxious, insecure, and down both under higher early environmental, and under higher genetic liability exposure, stronger negative association between AMS of different valences: i.e. between 'anxious' at t-1 and 'relaxed' at t, 'relaxed' at t-1 and 'down' at t, under intermediate genetic liability exposure when compared to both networks under low and high genetic liability). Yet, statistical evaluation of differences across exposure strata was inconclusive.

Conclusions:

Although suggestive of a difference in the emotional dynamic, there was no conclusive evidence that genetic and environmental factors may impact ESM network models of individual AMS.

Introduction

Traditionally, mental disorders are conceived as categories based on statistical differentiation between symptoms that cluster together, ignoring the underlying causes. Vinogradov and colleagues [1] proposed an associationist model of the symptom dimension of paranoia and suggested that the origins of psychopathology may lie in a network of mental states giving rise to acute phase transitions. Odgers and colleagues showed that these transitions can be modelled as part of a dynamic system; symptoms can be described as ”amplifying” when they become more intense with time, “damped” when intensity decreases until going back to the normal state or “stable” when intensity does not change [2]. In a recent essay by Kendler and colleagues, mechanisms of psychiatric symptoms were discussed, suggesting they may be productively viewed as ‘a complex, mutually reinforcing network of causal mechanisms’ including genes, environment, and symptoms themselves [3].

The network theory of mental disorders has gained traction as a novel conceptualization of psychopathology, where symptoms — not latent classes underlying symptoms — are studied as active elements interacting with each other in a symptom network. As an example, in a clinically relevant hypothetical scenario, if an individual suffers from sleep loss, this will lead to fatigue, which in turn may give rise to anxiety that may ultimately produce a feedback loop between anxiety and sleep loss, constantly activating all these symptom nodes in the network to develop into a mental-ill state, such as anxiety disorder [4-6]. The network approach to psychopathology has become one of the most trending data-driven research fields, producing impactful research output using cross-sectional symptom data, and recently has moved forward including associations over time.

In addition, networks can be generated using AMS in healthy subjects rather than symptoms of a mental illness. In the network research, these momentary assessed AMS were also called emotions interchangeably. For example, the AMS down is part of the same continuum as the symptom depressed, but severity is far less. Therefore, besides symptom networks, AMS networks are of interest to get insight in the interplay between emotions over time [7]. More importantly, the strength of those networks may differ depending on the presence of risk factors, as is the case with risk factors and psychopathology in patient populations [8].

The experience sampling method (ESM) prompts individuals to record their AMS (e.g., feeling cheerful, fearful, energetic, down, or relaxed), anomalous experiences (e.g., feeling suspicious, hearing voices, losing control), and context (e.g., minor stressful events, activity, company) after prompts (i.e., beeps or signals emitted via a watch or some device) occurring at unpredictable moments throughout the day [9]. Participants’ responses to items in the questionnaire are adjectives qualifying the state of mind or symptoms in the moment of the beep, referred to as momentary mental states. The within-subject design with repeated measurements over time allows for the analysis of temporal associations, and has the potential to reveal dynamic mechanisms of mutually impacting mental states that are neglected in cross-sectional, between-subject designs [8, 10].

Numerous studies using this methodology have demonstrated that AMS interact in dynamic relationships [11]. For example, insomnia may lead to changes in both positive affect (PA) and negative affect (NA) the next day [6] and psychotic symptoms as assessed with ESM is associated with clinical severity in patients with psychotic disorder [12, 13]. These interactions result in a network of AMS impacting on each other, where the momentarily assessed mental state is represented by a node and the predictive association over time, between an AMS at the previous time point *t-1 (time lag)* and an AMS at the current time point *t,* are represented by a directed arrow. The arrow or edge is also weighted, with the B coefficient expressing the effect size of the predictive associations. For example, an arrow from 'relaxed' to 'cheerful' weighted at 0.08 would mean that 'relaxed' at $t-1$ predicts 'cheerful' at t with a B coefficient of 0.08 [4, 14, 15].

The network approach to study the nature of psychopathology may be extended to examine biological mechanisms underlying the interplay between symptoms, assisting in the search for novel treatments [14, 16, 17]. It has been hypothesized that genes and environment may act as risk factors for the development of mental disorders by making the structure of an AMS network 'risky'; a similar mechanism can be hypothesized for genetic liability [18, 19]. For example, genes and environments may affect the strength of the connections (edges) so that a central symptom initiates a cascade of changes in other symptoms, eventually giving rise to a full-blown mental disorder [11, 14, 20, 21]. Using intensive time series data, many ESM studies have investigated the effect of genetic and environmental factors on two constructs created by aggregating responses on AMS items: NA and PA (e.g., cheerful, enthusiastic, satisfied, and energetic for PA)[22]. A previous study that used structural equation modelling to assess the extent to which genetic and environmental factors contribute to the variability in daily life of those two constructs, showed that 41% of the association between PA and NA is attributable to genetic factors [23, 24]. Thus, it can be hypothesized that not only the sum scores, but also the connections between the individual items may be influenced by genetic factors. In addition, given the fact that psychopathology is comorbid and transdiagnostic, and that genetic liability to psychopathology is shared, to a large degree, between the different mental disorders, the impact of genes on network models may be studied productively using a measure of genetic vulnerability to general psychopathology [25].

Next to genetic factors, various environmental factors have been associated with psychopathology [18]. One of the most studied is childhood trauma [12, 26]. It is hypothesized that similar to genetic liability, childhood trauma can play a role in networks of AMS in the general population. However, to our knowledge, no previous study using time-intensive intra-individual data has investigated the extent to which both genetic and environmental factors contribute to the connections between moment-to-moment mental states impacting on each other in a network. The present study aimed to investigate the differences in network connectivity and structure between categories of childhood trauma and genetic

liability to psychopathology, focussing on six AMS: 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated' and 'down'.

Methods

Participants

The study sample was derived from the East Flanders Prospective Twin Study register [27]. The EFPTS is a population-based register, prospectively recording all multiple births in Flanders, Belgium, since 1964 [27]. The initial sample consisted of 621 female siblings (twin pairs and 45 sisters) [28]. The study was approved by the ethics committee of Maastricht University Medical Centre and all participants provided written informed consent. The current analyses are not overlapping with previous work in this sample.

Measurements

Experience Sampling Method (ESM)

Participants received a wristwatch and a set of self-assessment booklets, one for each day. The wristwatch was programmed to emit a beep at random moments in each of ten 90-minute time blocks between 7.30 am and 10.30 pm on five consecutive days. The semi-random beep design prevents participants from anticipatory behaviours. The procedure has a high self-reported adherence as shown in a previous study [28]. After each beep, participants were asked to complete the self-assessment booklet within 15 minutes. The items collected by ESM consist of around 40 variables indexing thoughts, current context (activity, social context, location), appraisals of the current situation, and affect. The time at which participants indicated they completed the report was compared to the time of the beep, in order to verify whether the participants had completed the form within 15 minutes (participants were not able to check beep times retrospectively). All reports completed more than 15 min after the signal were excluded from the analysis as earlier work has shown that outside this interval, reports are less reliable and, therefore, less valid . Participants with less than 17 valid reports (out of 50, i.e., 33%) were excluded. AMS at each beep were rated by participants on 7-point Likert scales ranging from 1 ='not at all' to 7 = 'very'. Before starting the main analyses, a subsample of 6 AMS was selected from all available AMS, using two criteria (1) representativeness with respect to valence and arousal (2) variability within subjects.

First, all AMS were labelled as positive or negative (valence) according to a factor analysis of all AMS performed previously, taking into account the multilevel nature of the current sample [30]. Accordingly, the items 'content', 'cheerful', and 'relaxed' were described as positive AMS, while the items 'guilty', 'lonely', 'down', and 'insecure' were indexed as negative AMS. In contrast, the item 'irritated' loaded strongly on both valences [30]. This first distinction allowed us to further select variables from the entire affective spectrum.

Second, since in general population studies, many NA items have floor effects, so that the normality assumption is violated in analyses, to keep models analysable and interpretable, items with strongest floor effects were avoided. Variability was checked, for each of the AMS items described above, by including the current and lagged AMS in an autoregressive model. Subsequently, the proportion of participants with horizontal slopes was calculated per AMS item. A horizontal slope points to floor effects, demonstrating a restriction of range, which can result in a type II error [31].

Finally, we selected AMS with a maximum within-person time-lagged variability, and that represent each quadrant of the four affective domains defined by valence (based on the factor analysis described above) and arousal [32]. This choice ensured calculation of associations with genetic and environmental variables across the entire spectrum of affective states. This resulted in the selection of the following AMS: 'cheerful' (positive valence, high arousal), 'relaxed' (positive valence, low arousal), 'irritated' (loading in both the negative and the PA dimensions, high arousal), 'down' (negative valence, low arousal), 'insecure' and 'anxious' (negative valence, high arousal).

Childhood Trauma

Childhood trauma was assessed using the Childhood Trauma Questionnaire short form (CTQ-SF), which is a 25 item version of the Childhood Trauma Questionnaire including items on physical, sexual, and emotional abuse, and physical and emotional neglect, scored on a 5- Likert scale (e.g. 'I was maltreated', 'I was beaten often', 'I was abused', 'There was not enough food' and 'I was neglected') [33, 34]. The CTQ-SF is widely used and validated in various languages, including Dutch [34, 35]. At the request

of the Flemish Twin Register, the four most explicit items concerning sexual and physical abuse were omitted. If necessary, items were reversed before generating the sum score. The continuous variable 'childhood trauma' reflected the mean score of the 25 CTQ-items. To visualise the effect of childhood trauma on the network, the childhood trauma variable was recoded into 3 categories of severity. Tertials were used as cut-off points because the CTQ sum score has no official cut-off points and these cut-off points warrant enough subjects per category.

Symptom Checklist -90-R

The Symptom Checklist-90-R (SCL-90-R), a reliable and valid self-report instrument for screening a range of symptoms occurring in the past week, was used to index the overall severity of psychopathology [36]. The SCL-90-R consists of nine subscales (Somatization, Obsessive-compulsive, Interpersonal-sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid Ideation and Psychoticism), covering the entire range of psychopathology. The SCL-90-R was assessed twice within an interval of 6 months. First, scores were averaged per participant. Subsequently, SCL-90-R was dichotomised using the 75th percentile cut off point in order to define genetic liability of the co-twin (see below).

Genetic liability to psychopathology

Genetic liability to psychopathology was determined based on the SCL-90, value (i.e., 'low' or 'high' psychopathology) in the co-twin and zygosity status, consistent with previous work [19, 25, 36, 37]. This procedure resulted in three classes of 'genetic liability': participants with co-twins having a low level of psychopathology (the reference category); participants with a dizygotic (DZ) co-twin with a high level of psychopathology (intermediate level of genetic liability for psychopathology) and participants having a monozygotic (MZ) co-twin with a high level of psychopathology (highest level of genetic liability for psychopathology).

Statistical analysis

All analyses were performed using Stata version 13.0 [38]. To take into consideration the hierarchical structure of the data, multilevel (mixed-effects) linear regression models were fitted using the XTMIXED procedure in Stata, considering that level-one units (multiple observations per individual) clustered into level-two units (level of individual twins), that were nested within level-three units (twin pairs).

Associations between t-1 AMS and current AMS

Time-lagged variables were used as predictors in the multilevel models [15]. Cheerful at time t was predicted by (i) 'cheerful', (ii) 'relaxed', (iii) 'irritated', (iv) 'insecure', (v) 'anxious' and (vi) 'down' at t-1 (lag 1). All lagged variables were person mean centred to disentangle within- subject from between subject effects [39]. The same analysis was performed for each of the other AMS at time point t (dependent variable) in six separate models. Thus, the six AMS variables at t were predicted by all the six AMS variables at t-1. All lagged AMS variables were entered simultaneously in the model, as to assess their independent effects. One example of a regression model is:

$$\text{Cheerful}_{ijk} = (B0+e_{ijk}) + B1 * \text{lag cheerful}_{ijk} + B2 * \text{lag insecure}_{ijk} + B3 * \text{lag relaxed}_{ijk} + B4 * \text{lag anxious}_{ijk} + B5 * \text{lag irritated}_{ijk} + B6 * \text{lag down}_{ijk} + (B7+u_{7ijk}) * \text{time}_{ijk}$$

Where time is the beep number over days (1-50), the subscript *i* stands for the assessment level, *j* for individuals, *k* for twin pairs and $u7_{ijk}$ for the random slope of time (see below). As seen above, the B coefficients (B2-B6) are obtained using linear regression analysis. Because the data includes multiple assessments per person and includes twins, we used a regression analysis that can give valid results despite the multilevel structure. The obtained regression coefficients can be interpreted the same way as in regular linear regression analysis. In terms of network analysis, those B coefficients are then used as weights for the time lagged associations between an AMS at a current time point and the AMS at the next time point. The higher the value of the regression coefficient or weights (in term of network language) the higher the chance the two AMS are associated over time and the value of it gives the quantification of the association.

As the time between lagged and current moment has to be contiguous, and all beep moments were in the waking period of the day,*t-1* AMS variables excluded the last beep moment of a day as a lag of the first beep moment the next day. Analyses were performed across 3 strata of childhood trauma as well as across 3 strata of genetic vulnerability.

Random slope of time

A time variable (i.e., beep number, counting from 1 to 50) was included in all regression models since a lagged coefficient can be interpreted as an autocorrelation coefficient only if, conditional on all other fixed effects in the model, no systematic trend is present in the data. Because any trend that may be present could differ across participants, a random slope for *time* was added to the models at the individual level, representing the standard procedure for analysis in network research [39].

Permutation testing

Mixed-effects models should ideally include random slopes for all time-varying predictor variables (and use fully unstructured covariance matrices for the random effects) [40]. This procedure allows for standard errors and thus p-values to be correctly estimated. However, this approach is not feasible in the present context, due to the large number of predictor variables and hence the large number of parameters that would need to be estimated (attempts to fit such models result in convergence problems). Therefore, a single random slope for *time* was included in the model (see above), and to obtain valid p-values, permutation tests examined the statistical significance of observed B coefficients.

Permutation testing is developed to obtain the distribution of regression coefficients under the null hypothesis. Subsequently, the observed regression coefficient obtained from the real analysis is placed on this normal distribution, to obtain a valid p-value. For this, data in which there is no association (the null hypothesis assumption) were analysed. E.g., for the first set of permutations, whose aim is to test the significance of each association between two AMS, i.e., each observable regression coefficient (see below), the dependent variable was removed from the data and shuffled in a random order and merged to the original data, while keeping the multilevel structure. The regression coefficients are calculated repeatedly for 1000 times using that data to draw a normal, under the null hypothesis, distribution. The percentage of permuted regression coefficients that is to the more extreme end of this distribution than the observed regression coefficient gives the p-value (2-sided). The p-value is considered significant at the threshold of 0.0162 after Simes correction (0.0002 for between-groups comparison) (see below). Two different types of permutation tests were performed. The first type was used to obtain valid p-values for each regression coefficient (edge weight). The second type was performed to compare regression coefficients across different strata of genetic vulnerability and childhood trauma.

For the first set of permutations, the value of the outcome variable (e.g., ‘cheerful’ at *t*) was removed from each record of the original data file and reassigned to the same participant in random order in a

copy of the original data set. Because assessments were shuffled within participants, the level of clustering within the data described above was unchanged. Refitting the model based on the permuted data then provides estimates of the model coefficients under the null hypothesis of no association. By repeating this process, a 1000 time, a distribution of the regression coefficients under the null hypothesis was generated. Then, the observed coefficients were compared with the respective regression coefficient under the null hypothesis distribution to obtain p-values (i.e., the proportion of times that the coefficient in the permuted data was as large as or larger than the observed coefficient; multiplied by two to obtain a two-sided p-value). Given 2 x 3 x 6 x 6 tests for statistical significance, Simes correction for multiple testing was applied [41]. Graphs derived from the analyses are shown both before and after Simes correction for multiple testing. While main results are the Simes corrected slopes, presentation of the figures with uncorrected slopes prevents conclusions being directly drawn on differences that are merely the result of differences in power related to sample size in subgroups during the calculation of the Simes correction.

In the second set of permutations, the values of the childhood trauma variable were randomly assigned to the participants in another copy of the original data set. Again, regression coefficients in the original data were compared with regression coefficients under the null hypothesis of no difference in regression coefficients between the childhood trauma strata. With this procedure, all regression coefficients of the 36 connections (edges) in the network were tested for differences between the childhood trauma strata, regardless of the level of significance obtained with the first type of permutation testing. This same procedure was repeated for the different strata of genetic liability. Again, Simes correction for multiple testing was applied.

The construction of AMS networks

The regression coefficients (B1-B6) obtained from the equation in section 2.3.1 were represented in a graph to express the bidirectional time lagged associations between each set of two AMS.

A complete set of analyses in one stratum yielded 36 unstandardized regression coefficients (B). These coefficients were represented in a graph using the following procedure:

A 6-by-6 matrix with the regression coefficients (B) was constructed. The connection thus denotes the extent to which the AMS variable (e.g., cheerful) at time point t-1 predicts another AMS variable (e.g., relaxed; → $B_{cheerful\text{-}relaxed}$) at time point t, while controlling for all other variables. The elements on the diagonal are the autoregressive effects (self-loops, e.g., $B_{cheerful\text{-}cheerful}$). This procedure was applied in the 3 strata of childhood trauma and the 3 strata of genetic liability, separately (in total 6 graphs).

Visualization of networks was obtained using R (qgraph package) [42].

Assessment of the network structure: Centrality indices

Besides quantitative assessment of the connections in the network, another important set of parameters for assessing the influence of genetic and environmental factors on the characteristics of the network are the node centrality indices. Centrality analyses allow for the identification of AMS that are more 'central' than others in the network. Given their centrality, they are able, when triggered, to create a 'domino effect' and activate the other AMS [14]. Three well-known centrality indices were calculated, allowing for a descriptive comparison across the three genetic liability and the three trauma strata: node strength, closeness centrality and betweenness centrality [42, 43]. The *node strength or strength* is the sum of the absolute value of the weighted connections (both inward and outward) of a specific AMS, thus indexing the extent to which this AMS is connected in the network. Self-loops (e.g. regression weight between e.g. down at t-1 and down at t) are counted twice as to fulfil the definition of the Strength taking into account the fact that self-loops are good indicators of emotions inertia, previously described as an indicator of increased vulnerability and decreased psychological flexibility [44, 45]. *Closeness centrality* is defined as the inverse sum of the shortest distances to all other nodes, where the shortest distances are the sum of the inverse of the regression coefficients. It measures the potential impact of a specific node on each of the included AMS (higher closeness means more impact) [43]. *Betweenness centrality* of a node is the number of shortest paths between any two other nodes that pass through that particular node. A node with high betweenness centrality lies on many shortest paths. Thus, a node with a high betweenness centrality means that there is a high number of connections between AMS that depend on that specific AMS, thus increasing its capacity to regulate interactions in the network. More detailed information on these centrality indices can be found elsewhere [14, 43]. All indices, except node strength, were computed using qgraph in R [42, 46]. Node strength centrality was calculated using the function graph strength in the igraph package in R [46].

Results

Sample Characteristics

Of the initial study population of 621 individuals, 610 completed the ESM procedure and returned the questionnaires. Twenty-five participants were excluded because of too few valid assessments, leaving a sample of 585 individuals (328 monozygotic twins, 208 dizygotic twins and 45 sisters); the 45 sisters were excluded from the genetic liability analysis (n=540). Participants were aged between 18 and 61 years (mean age 27.7 years; SD 7.9). The larger part of the sample (63.5%) had a college or university degree, 35% had completed secondary education, and 2% had completed primary education only. The majority was in a relationship (75%), and most of the participants were employed (95%).

The average childhood trauma score was 1.66 (SD 0.58), and the average SCL-90-R score was 1.37 (SD 0.33). Mean levels of AMS were as follows: Cheerful 4.63 (1.40); insecure 1.41 (SD 1.02); relaxed 4.77 (SD 1.44); anxious 1.23 (SD 0.76); irritated 1.58 (SD 1.28); down 1.36 (SD 0.96). Table 2.1 presents the sample characteristics and AMS levels stratified by childhood trauma and genetic liability.

TABLE 2.1 | Descriptives stratified by childhood trauma and genetic liability.

	Low CT	Medium CT	High CT
N (subject level)	190	193	192
Mean age	26.2 (*SD* = 7.07)	26.4 (*SD* = 7.57)	30.7 (*SD* = 8.29)
Range	18–46	18–58	18–61
Mean Trauma Score	1.19 (*SD* = 0.11)	1.51 (*SD* = 0.09)	2.29 (*SD* = 0.58)
n (assessment level)	6992	7072	6786
Cheerful (mean)	4.81 (*SD* = 0.88)	4.68 (*SD* = 0.81)	4.39 (*SD* = 0.83)
Insecure (mean)	1.29 (*SD* = 0.43)	1.43 (*SD* = 0.56)	1.51 (*SD* = 0.67)
Relaxed (mean)	4.96 (*SD* = 0.83)	4.84 (*SD* = 0.81)	4.51 (*SD* = 0.76)
Anxious (mean)	1.14 (*SD* = 0.24)	1.24 (*SD* = 0.37)	1.30 (*SD* = 0.48)
Irritated (mean)	1.38 (*SD* = 0.47)	1.55 (*SD* = 0.60)	1.81 (*SD* = 0.73)
Down (mean)	1.20 (*SD* = 0.37)	1.38 (*SD* = 0.50)	1.51 (*SD* = 0.65)
	Low liability	High liability in DZ	High liability in MZ
N (subject level)	390	54	77
Mean age	27.2 (SD = 7.16)	27.99 (SD = 8.72)	26.11 (SD = 7.24)
Range	18–46	18–46	18–44
Mean Scl-90 total score in the co-twin	1.22 (SD = 0.13)	1.85 (SD = 0.35)	1.83 (SD = 0.32)
n (assessment level)	14342	1873	2897
Cheerful (mean)	4.70 (SD = 0.84)	4.35(SD = 0.90)	4.49 (SD = 0.87)
Insecure (mean)	1.34 (SD = 0.46)	1.66 (SD = 0.77)	1.54 (SD = 0.68)
Relaxed (mean)	4.85 (SD = 0.77)	4.54 (SD = 0.86)	4.61 (SD = 0.96)
Anxious (mean)	1.19 (SD = 0.32)	1.33(SD = 0.40)	1.33 (SD = 0.53)
Irritated (mean)	1.52 (SD = 0.59)	1.81 (SD = 0.77)	1.72 (SD = 0.69)
Down (mean)	1.29 (SD = 0.45)	1.47 (SD = 0.66)	1.59 (SD = 0.70)

SD, Standard deviation; DZ, Dizygotic twins; MZ, Monozygotic twins; Scl-90, Symptoms

Environmental effects in the affective regulation network

Figure 2.1 depicts the dynamic network structure corrected for multiple testing between the six AMS in each of the three childhood trauma exposure groups. When applying Simes correction for multiple testing, alpha was 0.0162. Whereas the corrected alpha for comparing p-values between groups was 0.0002 (Table 2.2). For the complete network structure see Supplementary Figure 2.1. When visually inspecting the figures, the edges between insecure and anxious seem stronger in the strata under higher childhood trauma exposure with significant reinforcing loops between the three negative AMS: anxious, insecure, and down. However, differences in edges strength between the levels of trauma were not statistically significant (Table 2.2).

Figure 2.2 displays centrality indices in the three networks of childhood trauma exposure. In terms of node strength (Figure 2.2a), a similar pattern for all AMS was apparent. In all childhood trauma strata, closeness centrality as well as node strength was stronger for down (Figure 2.2b). Although there were differences in both centrality indices between the strata [a profile markedly dominated by the three negative AMS (anxious, down, insecure) in the high childhood trauma network] neither dose-response pattern nor any consistent pattern in the other centrality measures was present. Regarding the betweenness centrality, the low childhood trauma group, 'cheerful' displayed the highest value, while in the high childhood trauma group this was the case for 'down' (Figure 2.2c).

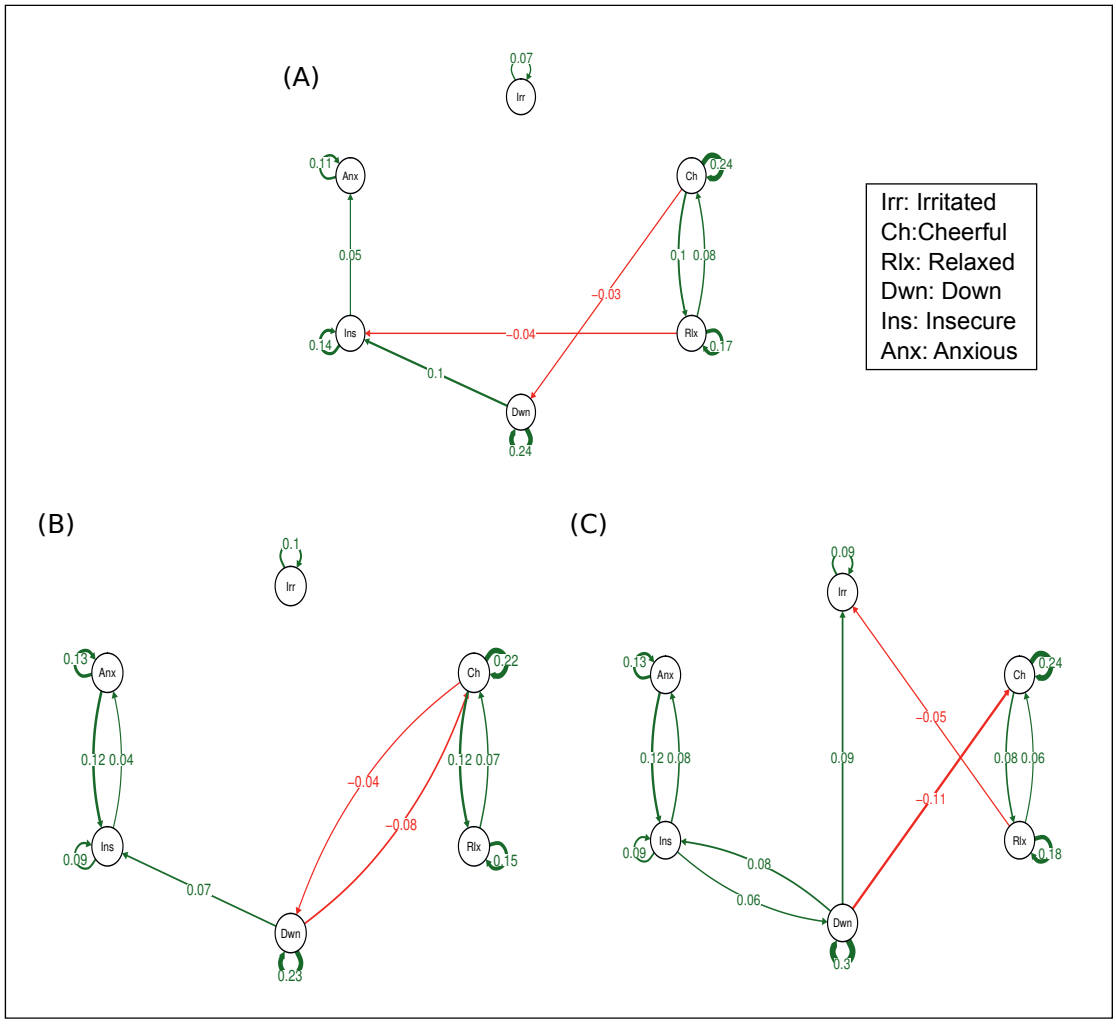

FIGURE 2.1 Networks of momentary affective mental states (AMS) in subjects with low (A), Medium (B) and high exposure to childhood trauma (C).
In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low childhood trauma network, there is an arrow from "*relaxed*" to "*cheerful*," meaning that "*relaxed*" at *t−1* predicts "*cheerful*" at *t* with a B coefficient of 0.08. Green arrows represent positive associations, and red arrows represent negative associations. The linewidth represents the strength of the association and is determined by the regression weights: the wider the line, the stronger the association (and vice versa). Only significant associations after Simes correction for multiple testing are displayed (alpha is 0.0162).

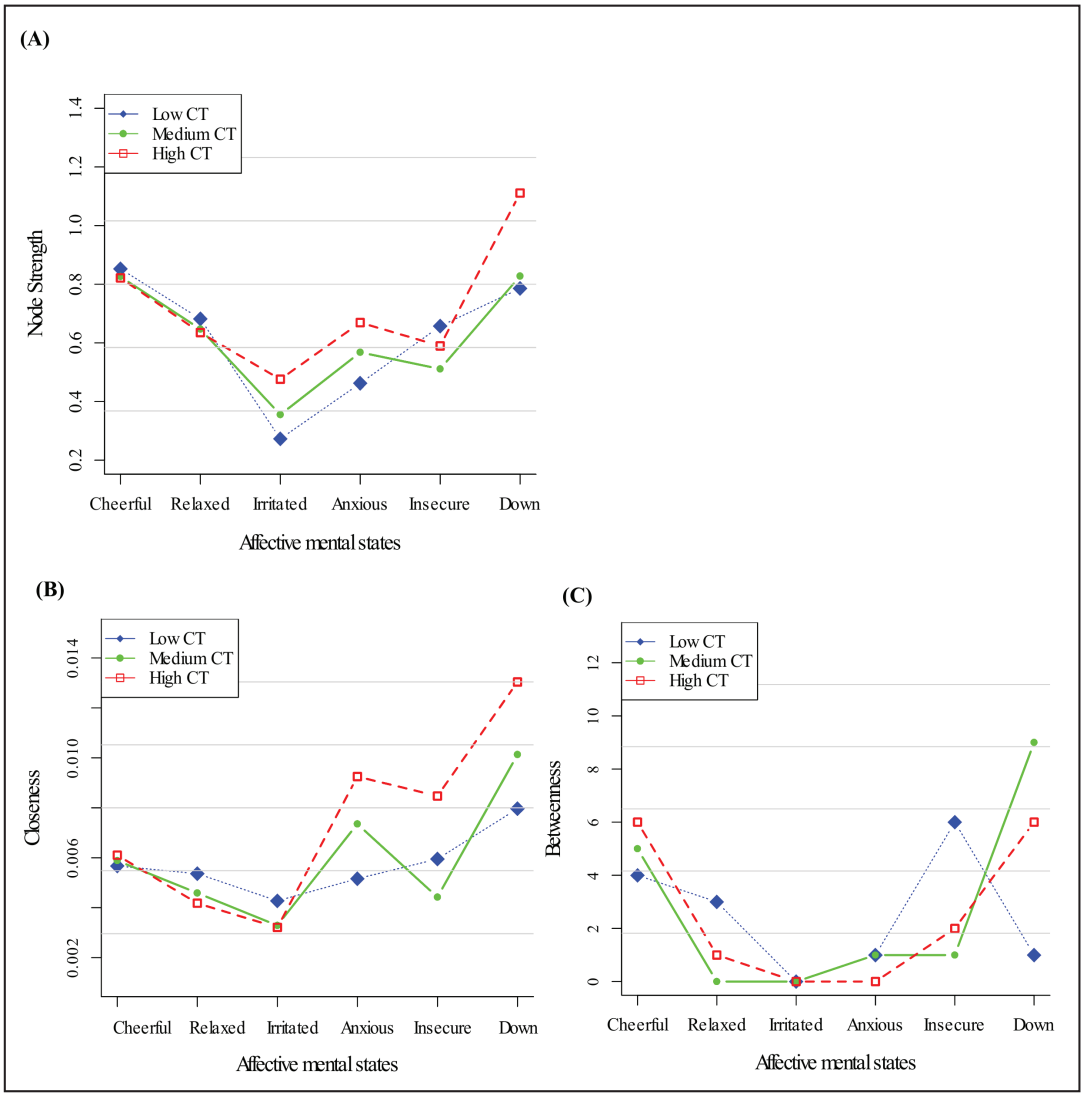

FIGURE 2.2 Centrality measures for the childhood trauma exposure networks.
Three node centrality measures: Node Strength (A), Closeness (B), and Betweenness(C), of low, medium, and high levels of childhood trauma exposure.

TABLE 2.2 Comparison between regression coefficients in the three childhood trauma strata (*p*-values presented were obtained from permutation tests of between group differences, Simes corrected alpha = 0.0002).

	$Cheerful_t$	$Insecure_t$	$Relaxed_t$	$Anxious_t$	$Irritated_t$	$Down_t$
MEDIUM VS. LOW LEVEL OF CHILDHOOD TRAUMA						
$Cheerful_{t-1}$	0.45	0.28	0.57	0.95	0.72	0.66
$Insecure_{t-1}$	0.41	0.22	0.38	0.92	0.61	0.75
$Relaxed_{t-1}$	0.82	0.39	0.55	0.6	0.67	0.39
$Anxious_{t-1}$	0.88	0.1	0.58	0.7	0.54	0.67
$Irritated_{t-1}$	0.57	0.32	0.57	0.56	0.52	0.56
$Down_{t-1}$	0.56	0.45	0.79	0.71	0.87	0.75
HIGH VS. MEDIUM LEVEL OF CHILDHOOD TRAUMA						
$Cheerful_{t-1}$	0.87	0.39	0.61	0.79	0.57	0.78
$Insecure_{t-1}$	0.68	0.19	0.2	0.22	0.9	0.13
$Relaxed_{t-1}$	0.4	0.3	0.74	0.3	0.13	0.81
$Anxious_{t-1}$	0.23	0.17	0.59	0.71	0.18	0.24
$Irritated_{t-1}$	0.5	0.16	0.54	0.91	0.58	0.37
$Down_{t-1}$	0.15	0.6	0.39	0.91	0.35	0.21
HIGH VS. LOW LEVEL OF CHILDHOOD TRAUMA						
$Cheerful_{t-1}$	0.53	0.85	0.3	0.81	0.79	0.81
$Insecure_{t-1}$	0.62	0.96	0.68	0.18	0.53	0.24
$Relaxed_{t-1}$	0.52	0.85	0.37	0.59	0.3	0.55
$Anxious_{t-1}$	0.3	0.83	0.95	0.94	0.46	0.12
$Irritated_{t-1}$	0.94	0.71	0.22	0.49	0.95	0.76
$Down_{t-1}$	0.38	0.84	0.52	0.62	0.44	0.11

Genetic effects on the affective regulation network

Figure 2.3 (Simes corrected) and Supplementary Figure 2.2 (complete network) show the networks stratified by genetic liability. Visual inspection of the complete networks across the three strata of genetic liability indicates that, the loops between "anxious", "insecure" and "down" were stronger in the subgroup under higher genetic exposure when comparing it to the one under a low exposure. Additionally, the network in the intermediate liability subgroup was most different with stronger negative association between AMS of different valences, i.e., between 'anxious' at t-1 and 'relaxed' at t, between 'relaxed' at t-1 and 'irritated' at t, and between 'relaxed' at t-1 and 'down' at t. By statistically testing for significance and after Simes correction of the alpha (alpha=0.0162), only the connection between 'relaxed' at t-1 and 'down' at t remained significant, and none of the differences between the strata were statistically significant (alpha=0.0002, Table 2.3).

Figure 2.4 shows the centrality indices for the three genetic liability subgroups. Feeling 'down' displayed a high node strength in all three strata and strength with a maximum in the high liability group (Figure 2.4a). The positive mental state 'relaxed' appeared to play a central position in the intermediate liability group, only. When visually checking betweenness, this same pattern was visible. Closeness centrality was also high for 'down' in all three strata (Figures 2.4b and 2.4c).

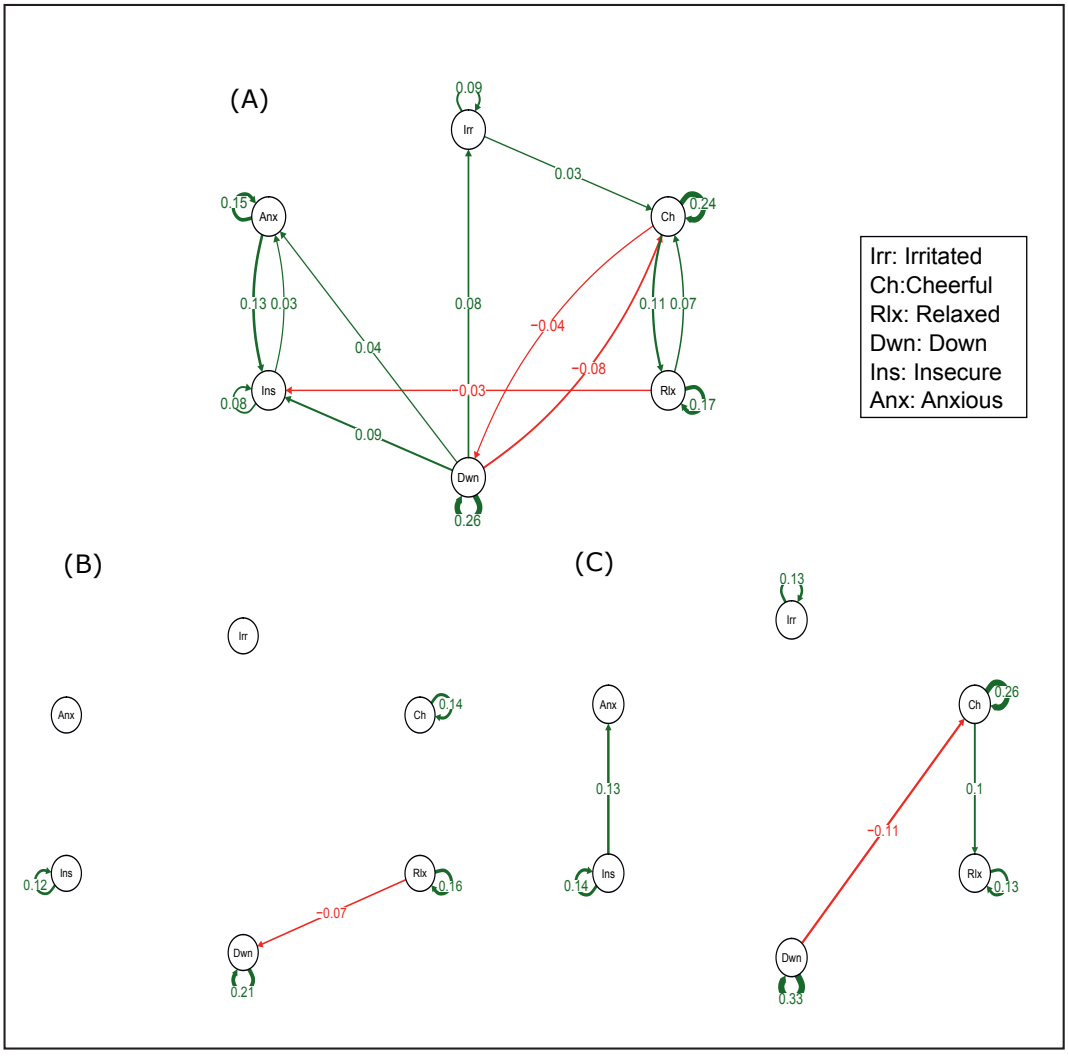

FIGURE 2.3 Networks of momentary affective mental states (AMS) in participants with low (A), intermediate (B), and high genetic liability for psychopathology (C).
In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low genetic liability network, there is an arrow from "relaxed" to "cheerful," meaning that "relaxed" at t−1 predicts "cheerful" at t with a B coefficient of 0.07. Green arrows represent positive associations, and red arrows represent negative associations. The line width represents the strength of the association and is determined by the regression weights: the wider the line, the stronger the association (and vice versa). Only significant associations after Simes correction for multiple testing are displayed (alpha is 0.0162).

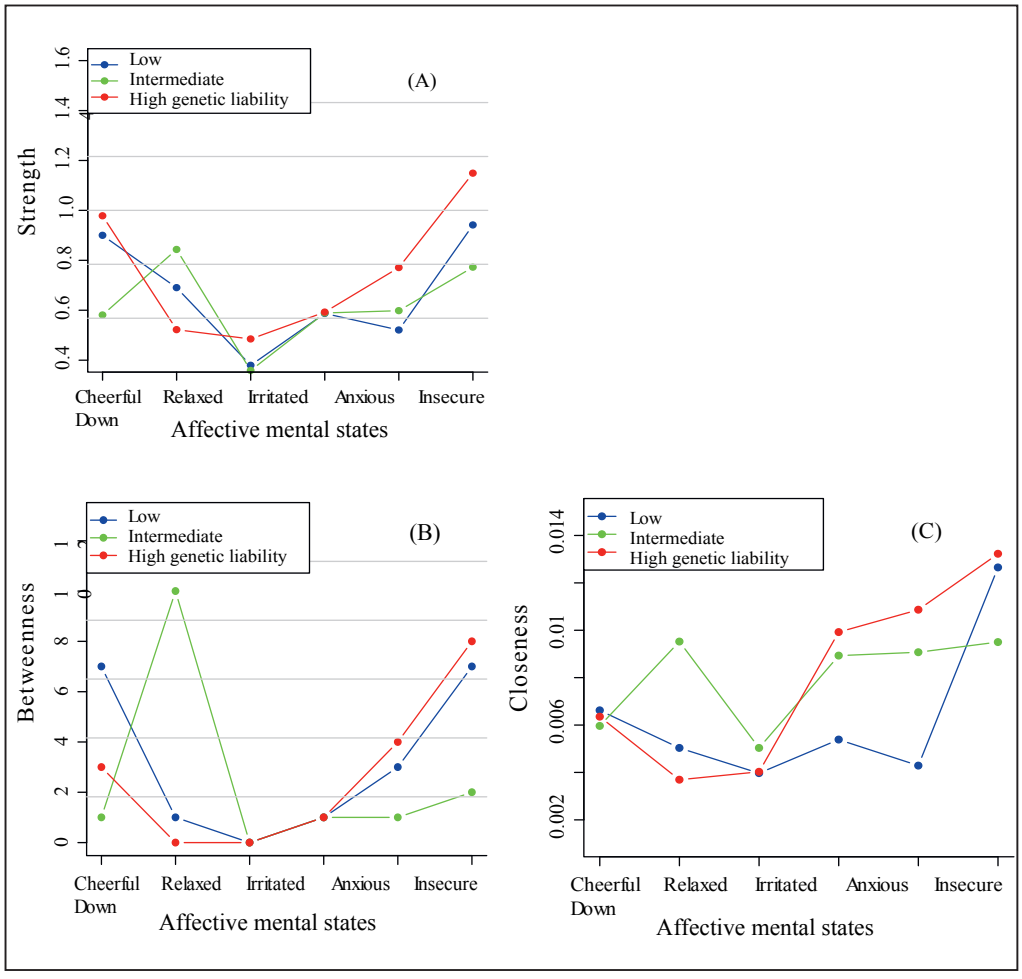

FIGURE 2.4 Centrality measures for the networks across levels of genetic liability for psychopathology. Three node centrality measures: Strength (A), Betweenness (B), and Closeness (C), of low, intermediate, and high genetic liability for psychopathology networks.

TABLE 2.3 Comparison between regression coefficients in the three genetic liability strata (p-values presented were obtained from permutation tests of between group differences, Simes corrected alpha = 0.0002).

	$Cheerful_t$	$Insecure_t$	$Relaxed_t$	$Anxious_t$	$Irritated_t$	$Down_t$
INTERMEDIATE VS. LOW LIABILITY						
$Cheerful_{t-1}$	0.07	0.9	0.4	0.23	0.56	0.31
$Insecure_{t-1}$	0.68	0.38	0.91	0.44	0.25	0.60
$Relaxed_{t-1}$	0.69	0.78	0.91	0.61	0.07	0.02
$Anxious_{t-1}$	0.98	0.17	0.56	0.6	0.86	0.90
$Irritated_{t-1}$	0.8	0.56	0.18	0.07	0.1	0.28
$Down_{t-1}$	0.84	0.91	0.55	0.91	0.23	0.48
HIGH VS. LOW LIABILITY						
$Cheerful_{t-1}$	0.48	0.7	0.79	0.64	0.82	0.9
$Insecure_{t-1}$	0.16	0.16	0.35	0.01	0.95	0.4
$Relaxed_{t-1}$	0.13	0.19	0.34	0.12	0.72	0.26
$Anxious_{t-1}$	0.11	0.64	0.37	0.32	0.72	0.84
$Irritated_{t-1}$	0.41	0.52	0.58	0.85	0.45	0.46
$Down_{t-1}$	0.6	0.85	0.81	0.95	0.88	0.21
INTERMEDIATE LIABILITY VS. HIGH						
$Cheerful_{t-1}$	0.04	0.67	0.6	0.17	0.73	0.34
$Insecure_{t-1}$	0.54	0.85	0.44	0.23	0.32	0.84
$Relaxed_{t-1}$	0.16	0.25	0.62	0.16	0.24	0*
$Anxious_{t-1}$	0.25	0.41	0.26	0.8	0.69	0.9
$Irritated_{t-1}$	0.73	0.35	0.46	0.09	0.08	0.12
$Down_{t-1}$	0.86	0.98	0.69	1.06	0.28	0.15

*$p < 0.0002$.

Discussion

We investigated the effect of genetic and environmental factors at the level of momentarily assessed AMS in daily life, from a dynamic network perspective. An initial objective of the study was to study differences in networks between strata of childhood trauma and genetic liability, when the networks included six AMS: 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated' and 'down'. Across different levels of trauma or with increasing genetic liability, we expected increased strength of the dynamical associations between AMS as was reported previously [36]. However, this previous study assessed strata of symptom severity as opposed to the present study that assessed strata of genetic liability and childhood trauma. In the present study, differences in strength were globally inconsistent and non-significant.

Visual inspection of the networks stratified by childhood trauma showed small differences in the direction of more reinforcement between negative AMS. The differences between the intermediate genetic liability network (i.e., high psychopathology in dizygotic co-twin) and the network in the other two genetic strata seemed larger (in the graphs including all slopes as well as in the graphs including

Simes corrected slopes, only). In addition, the small number of subjects in some of the genetic liability strata may have contributed to the observation that some findings did not survive Simes correction. For a more global overview of complete networks, we refer to Supplementary Figures 2.1 and 2.2. Network representations of momentary psychopathology in the ESM paradigm statistically may have low sensitivity in identifying and quantifying effects of childhood trauma or genetics, especially since many previous studies demonstrated specific molecular genetic significant associations with emotion dynamic parameters. Among them was the recent positive finding suggesting the link of the serotonin transporter gene polymorphism (5-HTTLPR) to emotional inertia of negative emotions applying the ESM methodology in collecting data [47]. Yet, this study used sum scores of emotions, i.e., NA, and PA, in which the possible intrinsic dynamic between individual negative or positive AMS exposed in the present paper would have been collapsed, and therefore blinded, to give emotional inertia overtime. Both approaches, using individual AMS and sum scores, might be complementary in future studies. Alternatively, however, it is possible that the combined impact of interacting environmental and genetic factors on emotion dynamics, as captured by ESM, may highly yield person-specific patterns of variation, making it more difficult to identify patterns that are valid at the level of the group and between groups. Another, related, reason for the lack of significant findings may be that ESM ratings of e.g., 'insecure' and 'relaxed' may have low reliability. Sum scores of related ESM items may be more reliable than individual items [48]. Finally, the fact that directionally visible differences remained statistically inconclusive across levels of genetic and childhood trauma exposure may be inherent to the low power of permutations tests in the context of the ESM network analysis.

Strengths and limitations

An important strength of the current study is that it used a large number of observations due to the nature of ESM methodology. This allowed us to compare three groups across both environmental and genetic exposures. Cross-sectional network analysis can be seen as an improved factor analysis or principal component analysis, visualising connections between mental states assessed once over periods of weeks or months, with standard instruments [5]. The present paper as well as other recent work [15] generated networks including a time component using ESM data, enabling studying changes in symptom levels over time rather than analysing a summarised measure over a longer period. Despite using a limited set of AMS, networks including a time component again showed the importance of clustering of symptoms. Additionally, it showed that networks are dynamic: clustering of symptoms changes from moment to moment.

It could be argued that childhood trauma can be a consequence of genetic liability because it can be a result of parents with more psychopathology having more problems with child upbringing (gene-environment correlation) [49]. However, a cross tabulation between childhood trauma and genetic liability in the present data showed only a mild correlation (in the lowest trauma tertial proportion of high genetic liability (29%) was lower than in the other trauma tertials (48%, 45%). Despite this association

most part of the trauma variable can be attributed to other factors than genetic liability and the study of both variables in two different sets of analyses is warranted.

This is the first study using the network methodology in answering an etiological research question involving genetic liability and early environment. As data were initially collected in the general population, some limitations are inherent. While the advantage of a representative sample is that it best captures the natural spectrum of psychopathology, a limitation is that NA items were rare and, therefore, not normally distributed. However, because items with high levels of variation were selected to avoid floor effects and because permutation tests (free of distributional assumptions) were performed, it did not lead to invalid methods of analysis. A second limitation was the impossibility to include random effects for the slope of all predictor variables in the model. Therefore, standard methods for testing the model coefficients would have led to invalid p-values. However, we have shown that by applying advanced statistical techniques, permutation tests, valid and interpretable results can be obtained. Such an approach may prove useful for other computational network problems; even though statistical power may be negatively affected. Third, considering that our participants were female with a high mean educational level, the results of this study may not be representative for men and those with lower educational level.

Conclusion and future work

The present analyses soughed to provide a micro-level perspective to what could be the phenotypic translation of the genetic and environmental liability to psychopathology. Although suggestive, this first study using the network methodology to study differences between genetic liability and environmental strata did not show any evidence to support the hypothesis that genes and early adversity have an impact on emotional dynamics in daily life as measured by the present network analysis. In future work, the present exploration of the effect of genes and environment on the affective regulation network should be replicated using the sum scores positive and NA before expanding it to molecular genetic measures of risk such as polygenic risk scores or to the interaction between childhood trauma and genetic liability. For this, both general population studies as well as case-control studies should be designed to complete our understanding of the mechanisms underpinning mental disorders. Furthermore, further testing of the basic network of AMS as an intermediate phenotype may also be of value as networks can be seen as ecologically valid phenotypes, complementary to categorical diagnostic phenotypes in genetic studies.

List of abbreviations

AMS Affective Mental State; EFPTS East Flanders Prospective Twin Study; ESM Experience Sampling Method; NA Negative Affect; PA Positive Affect; SCL-90-R Symptom Checklist-90-R; SD Standard Deviation; MZ Monozygotic; DZ Dizygotic

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Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors and Contributors

LH contributed to the conception of the work, the analysis, interpretation of data for the work, and to drafting it. MD contributed to the conception of the work, the analysis, interpretation of data for the work and to drafting and revising it. SG contributed to the interpretation of data for the work, drafting and revising it. WV contributed to the interpretation of data for the work, drafting and revising it. MD, CD and ET contributed to the acquisition of data for the work, and to revising it. JvO contributed to the conception of the work, the interpretation of data for the work and to revising it.

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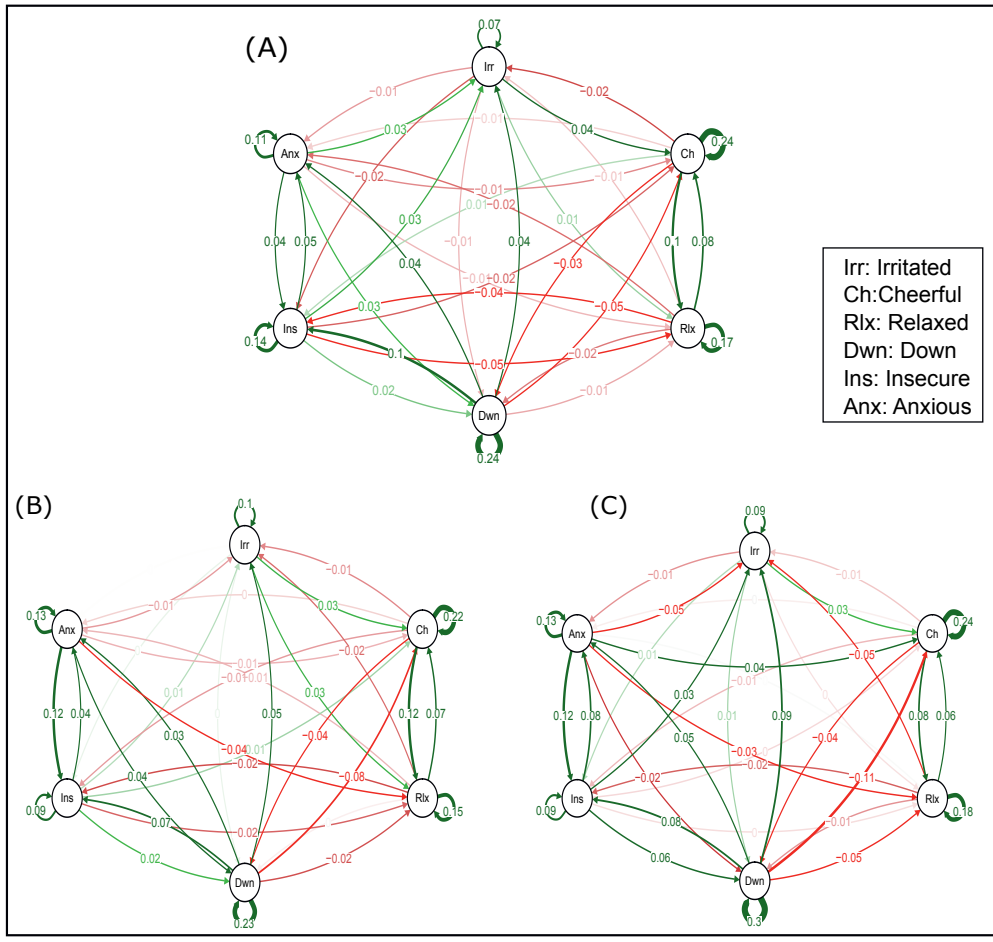
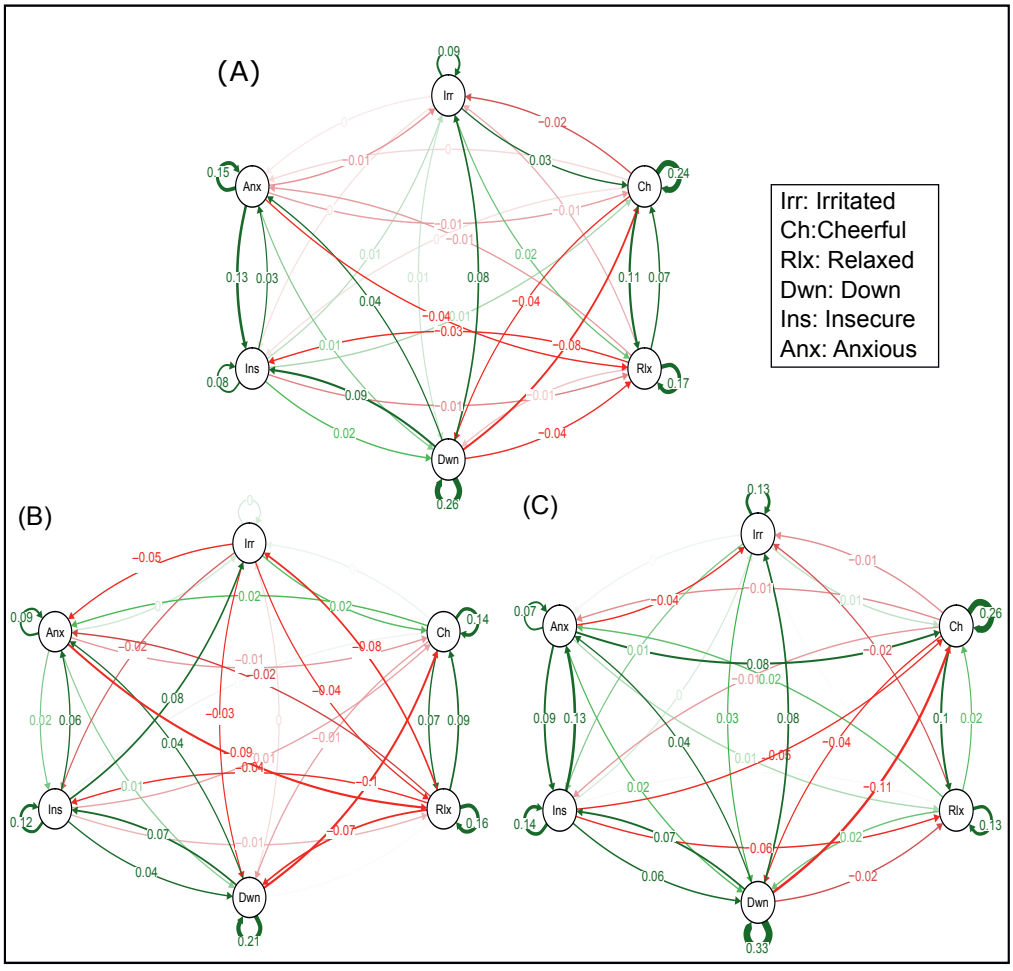
Supplementary Materials:



Supplementary Figure 2.1. Networks of momentary affective mental states (AMS) in subjects with low (A), medium (B), and high levels of childhood trauma (C).

In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low childhood trauma network (A), there is an arrow from 'relaxed' to 'cheerful', meaning that 'relaxed' at t−1 predicts 'cheerful' at t with a B coefficient of 0.08. Green arrows represent positive associations, and red arrows represent negative associations. The fading of the lines represents the strength of the association and are determined by the regression weights: the more solid the line, the stronger the association (and vice versa).



Supplementary Figure 2.2. Networks of momentary affective mental states (AMS) in participants with low (A), intermediate (B) and high genetic liability for psychopathology (C).
In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low genetic liability network, there is an arrow from 'relaxed' to 'cheerful', meaning that 'relaxed' at t−1 predicts 'cheerful' at t with a B coefficient of 0.07. Green arrows represent positive associations, and red arrows represent negative associations. The fading of the lines represents the strength of the association and are determined by the regression weights: the more solid the line, the stronger the association (and vice versa).

Chapter 3

Network Approach to Understanding Emotional Dynamic in Relation to ChildhoodTrauma and Genetic Liability to Psychopathology: Replication of a Prospective Experience Sampling Analysis

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Keywords: Emotional dynamic, network, time-series, genetic, psychopathology, childhood trauma

Abstract

Background: The network analysis of intensive time series data collected using the Experience Sampling Method (ESM) may provide vital information in gaining insight into the link between emotion regulation and vulnerability to psychopathology. The aim of this study was to apply the network approach to investigate whether genetic liability (GL) to psychopathology and childhood trauma (CT) are associated with the network structure of the emotions 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated', and 'down'—collected using the ESM method.

Methods: Using data from a population-based sample of twin pairs and siblings (704 individuals), we examined whether momentary emotion network structures differed across strata of CT and GL. GL was determined empirically using the level of psychopathology in monozygotic and dizygotic co-twins. Network models were generated using multilevel time-lagged regression analysis and were compared across three strata (low, medium, and high) of CT and GL, respectively. Permutations were utilized to calculate p values and compare regressions coefficients, density, and centrality indices. Regression coefficients were presented as connections, while variables represented the nodes in the network.

Results: In comparison to the low GL stratum, the high GL stratum had significantly denser overall ($p=0.018$) and negative affect networks ($p<0.001$). The medium GL stratum also showed a directionally similar (in-between high and low GL strata) but statistically inconclusive association with network density. In contrast to GL, the results of the CT analysis were less conclusive, with increased positive affect density ($p=0.021$) and overall connectivity ($p=0.042$) in the high CT stratum compared to the medium CT stratum but not the low CT stratum. The individual node comparisons across strata of GL and CT yielded only very few significant results, after adjusting for multiple testing.

Conclusions: The present findings demonstrate that the network approach may have some value in understanding the relation between established risk factors for mental disorders (particularly GL) and the dynamic interplay between emotions. The present finding replicates partially the original study, in respect to 'insecure' centrality and to a certain extent to negative emotions density, suggesting the interest on exploring genetic background of negative emotion dynamic in future work.

Keywords: Emotional dynamic, network, time-series, genetic, psychopathology, childhood trauma

Introduction

There is a growing interest in understanding the role of daily-life emotion dynamics underlying psychopathology [1]. Emotions are considered promising candidates for the study of mechanisms underlying the early expression of subthreshold mental phenomena. From a complex dynamic system theory perspective, alterations in personal emotion dynamics may serve as an early warning sign for a tipping point signalling a transition from a subthreshold state to a clinical state—akin to an electrical signal in epilepsy that is monitored to detect the tipping point before a convulsion[2,3]. In this regard, the network approach provides a useful analytical strategy to gaining insight into modelling interactive emotion dynamics, and identifying highly connected emotions that are critical in predicting transition to a more severe state. In the last few years, the network approach to psychopathology has brought a novel perspective to conceptualising mental disorders. Network studies investigate the network of symptoms mutually impacting each other in a variety of mental disorders such as depression and psychotic disorder[4]. However, one of the primary challenges for the network investigation is that most studies rely on static observations (signs and symptoms) collected from samples with static states (mental disorders) to master a highly fluid phenomenon[5]. With a design to prevent recall bias by capturing emotions in real time, the experience sampling method (ESM), using a rigorous structured diary method for intensive collection of emotions (e.g., sadness, cheerfulness) at random moments during the day, during a certain period (days or weeks), provides the essential platform for gathering data for emotion dynamics research [6].

Recently, the field has advanced to network analysis of ESM data [7-9]. Emotions have been found to interact with each other in the network, in which momentarily assessed emotions are represented by a node and the predictive regressive association of that emotion at moment *t-1* on the same or another emotion at the subsequent moment *t*, is represented by an edge [10, 11]. Previous studies demonstrated that an increase in connectivity between affective states was associated with an increased risk for mental disorders [12]. Utilising this approach, the persistence of an emotion over time—inertia—was found to be associated with both current and future depressive episodes[12]. By analysing the auto-regressive coefficient of the emotion, inertia can be studied applying the time series network approach [9, 13, 14].

There is growing evidence that the impact of environmental exposure spreads through the symptom network and increases the level of admixture rather than impacting on a particular symptom domain[15-18]. Using data from the general population, previous network investigations showed that the associations symptom between dimensions and network density increased as a function of the level of environmental exposure[19]. In a similar fashion, there is some evidence that familial vulnerability operates on increasing connections between symptoms, which in turn leads to a more static and persistent clinical state[20]. Given these findings, we previously investigated the network structure of dynamic emotions across environmental and genetic vulnerability strata in a female-female twin[21]. Although some differences were observed in the network structure between groups that might be suggestive of an increase in connectivity

as a function of vulnerability, findings in general were inconclusive. Now we have a second large twin sample available in which we have the possibility to replicate the findings of this previous study on the impact of vulnerability on emotion dynamics[21]. The present study therefore investigated in a general population mixed-gender twin sample whether genetic liability to psychopathology and childhood trauma (hereafter referred to as "GL" and "CT", respectively) are associated with the network structure of individual emotions— 'cheerful', 'insecure', 'relaxed', 'anxious', 'irritated', and 'down'—collected using the ESM method.

Methods

Participants

The study sample was derived from the East Flanders Prospective Twin Study register, a population-based prospective register, recording all multiple births in Flanders, Belgium, since 1964[22]. Zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase, and DNA fingerprints. Individuals who were registered in the EFPTS and who fulfilled the inclusion criteria were invited to participate in the TwinssCan project, a longitudinal study collecting data on adolescents and young adults between the ages of 15 and 35 years, including twins, their siblings, and parents. The TwinssCan project, which started enrollment in April 2010, is a general population based, ongoing longitudinal study [23, 24]. Participants were included if they understood the study procedure and were able to provide valid, reliable, and complete data. All participants gave written informed consent. For participants below the age of 18, parent(s) also signed an informed consent. Participants were excluded if they had a pervasive mental disorder as indicated by caregivers. The local ethics committee (Commissie Medische Ethiek van de Universitaire ziekenhuizen KU Leuven, Nr. B32220107766) approved the study. For the present study, only twins and siblings who completed the ESM protocol were analysed (n = 704).

Measurements

Experience Sampling Method (ESM)

Participants received an electronic medical Personal Digital Assistant, especially developed for this purpose. It is called the 'PsyMate'. The PsyMate is programmed to emit a signal ("beep") at ten unpredictable moments in each of the 90-minute time blocks between 7:30 and 22:30, on six consecutive days. After each beep, participants are asked to stop their activity and to enter their current thoughts, context (activity, persons present, and location), appraisals of current situation and mood in the PsyMate. The semi-random beep design prevents participants from anticipatory behaviours. The procedure has a high self-reported adherence as shown in a previous study [25]. The PsyMate records the time at which participants completed the assessment. Reports need to be completed within 15 minutes of the beep, otherwise the data for this time point won't be recorded, as previous work has shown that outside this interval, reports are less reliable and, therefore, less valid [6]. Participants with fewer than 20

reports will be excluded from the analysis. The items collected by ESM consist of around 40 variables indexing thoughts, current context (activity, social context, location), appraisals of the current situation, and Emotions. Emotion items at each beep were rated by participants on 7-point Likert scales ranging from 1 =’not at all’ to 7 = ’very’. As in the original study, only 6 affective states variables were chosen for analysis, given their maximum within-person time-lagged variability and therefore minimal floor effect, and given their covering of the whole emotional and core affect spectrum[26]. This resulted in the selection of the following emotional items: ‘cheerful’ (positive valence, high arousal), ‘relaxed’ (positive valence, low arousal), ‘irritated’ (loading in both the negative (NA) and the positive affect (PA) dimensions, high arousal), ‘down’ (negative valence, low arousal), ‘insecure’ and ‘anxious’ (negative valence, high arousal[21]. Genetic and environmental influences on the effective regulation network: A prospective experience sampling analysis. Manuscript submitted for publication).

Childhood Trauma

The variable CT was assessed using the shortened 25 item version of the 70-item Childhood Trauma Questionnaire [27, 28]. The CTQ-SF is widely used and validated in various languages including Dutch (Bernstein 2003, Thombs 2009). The continuous variable ‘CT’ reflected the total score of the 25 items on the questionnaire. To visualise the effect of CT on the network, the CT variable was recoded into 3 categories indexing increasing levels of CT total score and, therefore, severity of trauma (tertile groups). The regression coefficients, for the predictive association between the lag and the current affective states, were calculated for each of the three CT strata before being represented graphically as a network and compared (see below).

SCL-90-R

The Symptom Checklist-90-R (SCL-90-R), a reliable and valid self-report instrument for screening a range of symptoms occurring in the past week, was used to index the overall severity of psychopathology [29]. The SCL-90-R consists of nine subscales (Somatization, Obsessive-compulsive, Interpersonal-sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid Ideation and Psychoticism), covering the entire range of psychopathology. The SCL-90-R was assessed twice within an interval of 6 months. First, scores were averaged per participant. Then, consistent with previous analyses [29], a dichotomous measure of SCL-90-R was used in the analyses, based on the arbitrary cut-off point of 75th percentile. The resulting two-level variable (‘SCL-severity’) reflected the levels of severity of psychopathology [29].

Genetic liability to psychopathology

Genetic liability to psychopathology was determined on the basis of the SCL-90, value (i.e., ‘low’ or ‘high’ psychopathology) in the co-twin and zygosity status, consistent with previous work [30-32]. This procedure resulted in three categories of ‘genetic liability’: participants with co-twins having a low level

of psychopathology (the reference category at lowest genetic liability); participants with a dizygotic (DZ) co-twin with a high level of psychopathology (intermediate level of genetic liability for psychopathology) and participants having a monozygotic (MZ) co-twin with a high level of psychopathology (highest level of genetic liability for psychopathology).

Statistical analysis

All analyses were performed using Stata version 14.0. (StataCorp, College Station, TX, USA). To take into account the hierarchical structure of the data, multilevel (mixed-effects) linear regression models were fitted using the XTMIXED procedure in Stata, considering that level-one units (multiple observations per individual) clustered into level-two units (level of individual twins), that were nested within level-three units (twin pairs).

Associations between t-1 affective states and current affective states

Time-lagged variables were used as predictors in the multilevel models [33]. Cheerful at time t was predicted by (i) 'cheerful', (ii) 'relaxed', (iii) 'irritated', (iv) 'insecure', (v) 'anxious' and (vi) 'down' at t-1 (lag 1). All lagged variables were person mean-centred to disentangle within-subject from between-subject effects [34]. The same analysis was performed for each of the other affective states at time point t (dependent variable) in six separate models. Thus, the six affective states variables at t were predicted by all the six affective states variables at t-1. All lagged affective states variables were entered simultaneously in the model, so as to assess their independent effects. One example of a regression model is:

$Cheerful_{ijk} = (B0+e_{ijk}) + B1 * lag\ cheerful_{ijk} + B2 * lag\ insecure_{ijk} + B3 * lag\ relaxed_{ijk} + B4 * lag\ anxious_{ijk} + B5 * lag\ irritated_{ijk} + B6 * lag\ down_{ijk} + (B7+u_{7ijk}) * time_{ijk;}$

where time is the beep number over days (1-50), the subscript *i* stands for the assessment level, *j* for individuals, *k* for twin pairs and $u7_{ijk}$ for the random slope of time (see below). As the time between lagged and current moment must be contiguous, and all beep moments were in the wake period of the day, the first beep of the day was excluded in all analyses. Finally, person mean centring of the lags was performed as it is now standard analysis in the field of network analyses[34]. Analyses were performed across 3 strata of CT as well as across 3 strata of genetic vulnerability.

Random slope of time

A time variable (i.e., beep number, counting from 1 to 50) was included in all regression models since a lagged coefficient can be interpreted as an autocorrelation coefficient only if, conditional on all other fixed effects in the model, no systematic trend is present in the data. Because any trend that may be present could differ across participants, a random slope for *time* was added to the models at the individual level, representing the standard procedure for analysis in network research [34].

The construction of affective states networks

A complete set of analyses in one stratum yielded 36 unstandardized regression coefficients (B). These coefficients were represented in a graph using the following procedure: A 6-by-6 matrix with the regression coefficients (B) was constructed. The connection thus denotes the extent to which the affective states variable (e.g., cheerful) at time point t-1 predicts another affective states variable (e.g., relaxed; → $B_{cheerful\text{-}relaxed}$) at time point t, while controlling for all other variables. The elements on the diagonal are the autoregressive effects (self-loops, e.g., $B_{cheerful\text{-}cheerful}$). This procedure was applied across the 3 strata of CT and the 3 strata of GL, separately (in total 6 graphs). Visualisation of networks was obtained using R (qgraph package) [35]. Moreover, a value higher than the maximum absolute value of the whole set of regression coefficients, in the 3 strata of CT and then in the 3 strata of GL, was assigned to the argument 'maximum' in qgraph to scale the connections widths to allow for a visual comparison across each set of 3 networks[35]:

Assessment of the network structure: Density and node Centrality

In addition to the individual connections in the network, overall measures can contribute to insight in the differences between networks. Density -elsewhere called overall connectivity- is the average of the absolute values of all regression coefficients in each of the networks. Following previous literature that examined the vulnerability underlying emotional density specifically at the level of the personality (neuroticism), using time series networks, two parameters were calculated. NA density is the average of regression coefficient absolute values, that have both the outcome and the predictor as a negative emotion ('anxious', 'irritated', 'insecure', 'down'). PA density is the average of regression coefficient absolute values, that have both the outcome and the predictor as a positive emotion ('cheerful', 'relaxed')[9].

Centrality analyses allow for the identification of affective states that are more 'central' than others in the network. Given their centrality, they are able, when triggered, to create a 'domino effect' and activate the remainder of the affective states [11]. Two well-known centrality indices were calculated per network, allowing for a descriptive comparison across the three genetic liability and the three trauma strata: inward strength and outward strength centrality [35, 36]. In-strength of a certain node is the sum of all edges towards it (that node is the outcome variable). The out-strength of a particular node is the sum of all edges going from it (that node is the independent variable). The first will inform on which affect is the more regulated in the daily emotional experience and the second on which is the more influencing among the six emotions in the daily life experience. Self-loops (e.g. regression weight between e.g. down at t-1 and down at t) are counted both in the inward and in the outward strength, taking into account the fact that self-loops are good indicators of emotion inertia, previously described as an indicator of increased vulnerability and decreased psychological flexibility [2, 37].

All density and centrality parameters were calculated using Stata 14.0 (StataCorp, College Station, TX, USA). Permutation testing was used to calculate *p*-values for comparing them across strata (see below).

Permutation testing

Mixed-effects models should ideally include random slopes for all time-varying predictor variables (and use fully unstructured covariance matrices for the random effects)[38]. This procedure allows for standard errors and thus p-values to be correctly estimated. However, this approach is not feasible in the present context, due to the large number parameters needed given that the covariance is unstructured (attempts to fit such models result in convergence problems). Therefore, a single random slope for *time* was included in the model (see above) and in order to obtain valid p-values, the statistical significance of regression coefficients was examined using permutation tests.

Two different types of permutation tests were performed. The first type was used to obtain valid p-values for each regression coefficient (edge). The second type was performed to compare regression coefficients across different strata of GL and CT.

For the first set of permutations, the value of the outcome variable (e.g., 'cheerful' at *t*) was removed from each record of the original data file and reassigned to the same participant in random order in a copy of the original data set. Because assessments were shuffled within participants, the level of clustering within the data described above was unchanged. Refitting the model based on the permuted data then provides estimates of the model coefficients under the null hypothesis of no association. By repeating this process more than 1000 times, a distribution of the regression coefficients under the null hypothesis was generated. Then, the actually observed coefficients were compared with the respective null hypothesis distributions to obtain p-values (i.e., the proportion of times that the coefficient in the permuted data was as large as or larger than the observed coefficient; multiplied by two to obtain a two-sided p-value). Given 2 x 3 x 6 x 6 tests for statistical significance, Simes correction for multiple testing was applied [39]. Graphs derived from the analyses are shown both before and after Simes correction for multiple testing (alpha=0.0224). While main results are the Simes corrected slopes, presentation of the figures with all the slopes prevents conclusions being directly drawn on differences that are merely the result of differences in power related to sample size in subgroups during the calculation of the *p* values.

In the second set of permutations, the values of the CT variable were randomly assigned to the participants in another copy of the original data set. Again, regression coefficients in the original data were compared with regression coefficients under the null hypothesis of no difference in regression coefficients between the CT strata. With this procedure, all regression coefficients of the 36 connections (edges) in the network were tested for differences between the CT strata, regardless of the level of significance obtained with the first type of permutation testing. This same procedure was repeated for the different strata of genetic liability. Again, Simes correction for multiple testing was applied for individual edge differences (alpha 0.000462).

The same permutation testing procedure was applied for comparing density, inward and outward strength parameters between the strata. Assuming independence between each index calculation, no multiple testing correction was applied.

Results

Sample Characteristics

GL analyses included 598 participants (230 monozygotic and 368 dizygotic), because participants without information on their zygosity status, non-twin siblings and participants without information on psychopathology in the cotwin were excluded. CT analyses were performed with 688 individuals. Mean age of the participants was 17.6 years (SD 3.7). Forty percent of the total sample was male. The majority was still living with their parents (86%) and went to school (90%). In addition, 28% had a bachelor's degree while only 5% had a low level of education.

The average CTQ-SF sum score was 33.8 (SD 8.1). Demographic data and mean levels of ESM items per subgroup of CT and GL are presented in table 3.1. In general, the mean level of emotions in the third CT strata was higher than in the first and the second strata. 'Down' also differed between the second and the first strata. Except the difference in 'relaxed' between the third and the first strata, there were no differences between the GL strata.

Table 3.1. **Descriptives stratified by childhood trauma and genetic liability.**
SD, Standard deviation; DZ, Dizygotic twins; MZ, Monozygotic twins; Scl-90, Symptoms checklist.
* The difference in mean with category 1 is statistically significantly
† The difference in mean with category 2 is statistically significantly

Childhood trauma			
	Low	Medium	High
Number of subjects (number of assessments)	229 (9241)	258 (10438)	201 (7988)
% females	71%	56%	53%
% low education	2%	6%	8%
Mean age (SD)	17.8 (3.66)	17.4 (SD=3.81)	17.6 (SD=3.81)
Range	15-33	14-34	15-34
Mean Trauma Total Score (SD)	27.2 (1.38)	32.4 (1.68)	43.1 (9.17)
Assessment level			
Cheerful mean (SD overall; between; within)	4.99 (1.49; 0.81; 1.26)	4.88 (1.47; 0.80; 1.24)	4.56 (1.63; 0.97; 1.32) *†
Insecure mean (SD overall; between; within)	1.64 (1.17; 0.60; 1.01)	1.70 (1.16; 0.65; 0.98)	1.82 (1.25; 0.72; 1.03) *
Relaxed mean (SD overall; between; within)	5.2 (1.48; 0.69; 1.31)	5.15 (1.43; 0.69; 1.26)	4.82 (1.53; 0.76; 1.34) *†
Anxious mean (SD overall; between; within)	1.4 (0.93; 0.45; 0.82)	1.46 (0.92; 0.48; 0.79)	1.60 (SD=1.10; 0.63; 0.91) *†
Irritated mean (SD overall; between; within)	2.18 (1.62; 0.88; 1.36)	2.19 (1.52; 0.83; 1.29)	2.48 (1.66; 0.97; 1.36) *†
Down mean (SD overall; between; within)	1.59 (1.08; 0.55; 0.92)	1.69 (1.11; 0.64; 0.93) *	1.91 (1.27; 0.77; 1.02) *†
Genetic liability			
	Low liability	Intermediate liability	High liability
Number of subjects (number of assessments)	452 (18338)	90 (3553)	56 (2314)
% females	59%	63%	71%
% low education	6%	6%	10%
Mean age (SD)	17.5 (3.66)	16.4 (1.89)	17.9 (4.02)
Range	14-34	15-22	15-32
Assessment level			
Cheerful mean (SD overall; between)	4.85 (1.49; 0.84; 1.24)	4.76 (1.62; 0.91; 1.34)	4.56 (1.56; 0.93; 1.29)
Insecure mean (SD overall; between)	1.70 (1.16; 0.61; 0.99)	1.79 (1.29; 0.78; 1.06)	1.77 (1.24; 0.73; 1.01)
Relaxed mean (SD overall; between)	5.09 (1.45; 0.71; 1.28)	5.08 (1.47; 0.66; 1.32)	4.84 (1.54; 0.80; 1.32) †
Anxious mean (SD overall; between)	1.46 (0.93; 0.47; 0.81)	1.58 (1.11; 0.61; 0.95)	1.62 (1.12; 0.75; 0.86)
Irritated mean (SD overall; between)	2.26 (1.57; 0.89; 1.31)	2.40 (1.70; 0.87; 1.46)	2.29 (1.56; 1.03; 1.25)
Down mean (SD overall; between)	1.71 (1.12; 0.63; 0.94)	1.77 (1.21; 0.68; 1.01)	1.92 (1.35; 0.86; 1.05)

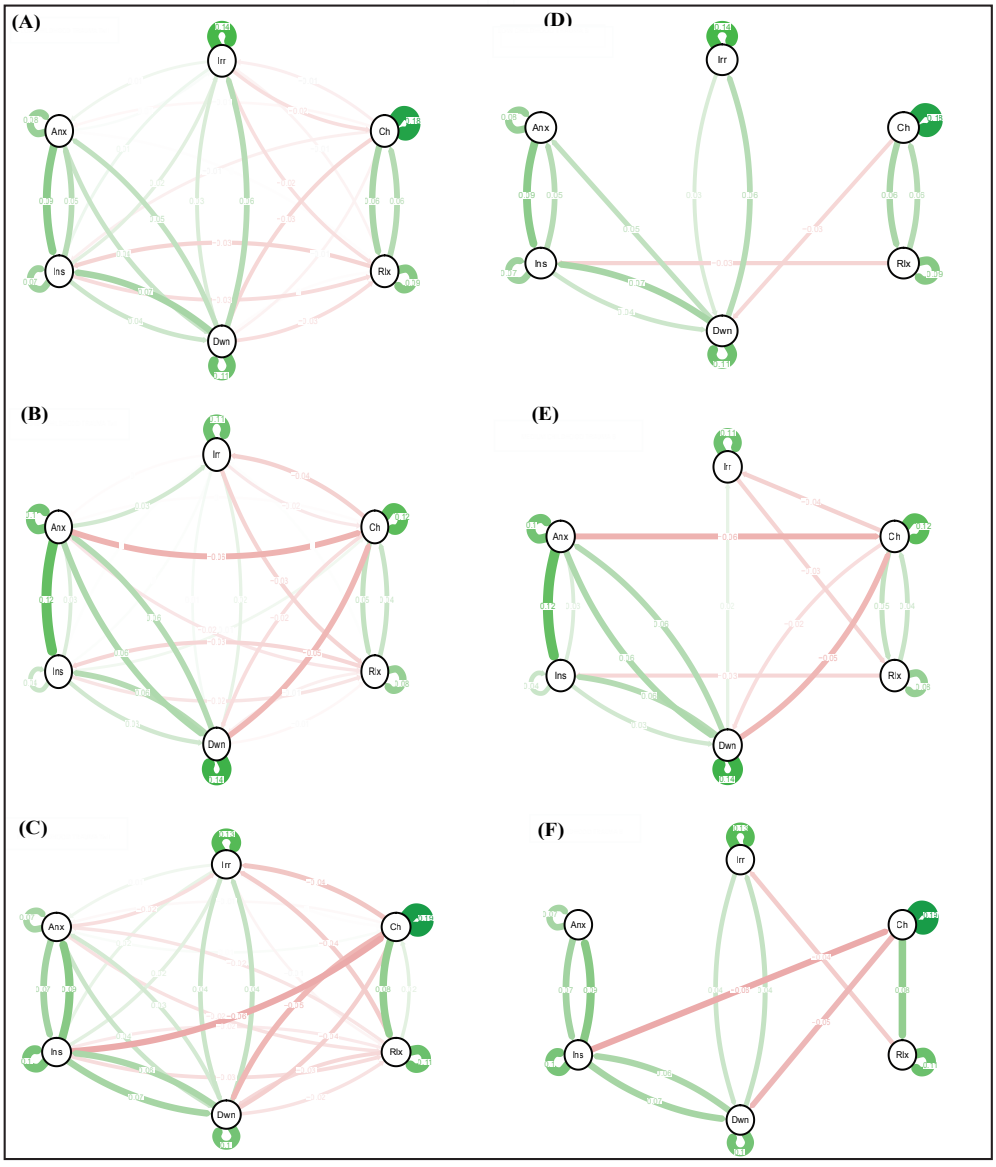

FIGURE 3.1 Emotions networks in subjects with low, medium, and high levels of childhood trauma. In this figure, the arrows represent associations Q4 Q5 over time; i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low CT network, there is an arrow from "relaxed" to "cheerful," meaning that "relaxed" at t−1 predicts "cheerful" at t with a B coefficient of 0.06. Green arrows represent positive associations, and red arrows represent negative associations. The fading of the lines represents the strength of the association and are determined by the regression weights: the more solid the line, the stronger the association (and vice versa). Note that we can predict the emotion item from the previous state of the item itself. These arrows are the self-loops in the network. CT, childhood trauma. Graphs (A–C) are for low, medium, and high CT respectively. The Graphs (D–F) are for low, medium, and high CT respectively but only with associations that resisted to Simes correction for multiple testing with $p < 0.022$.

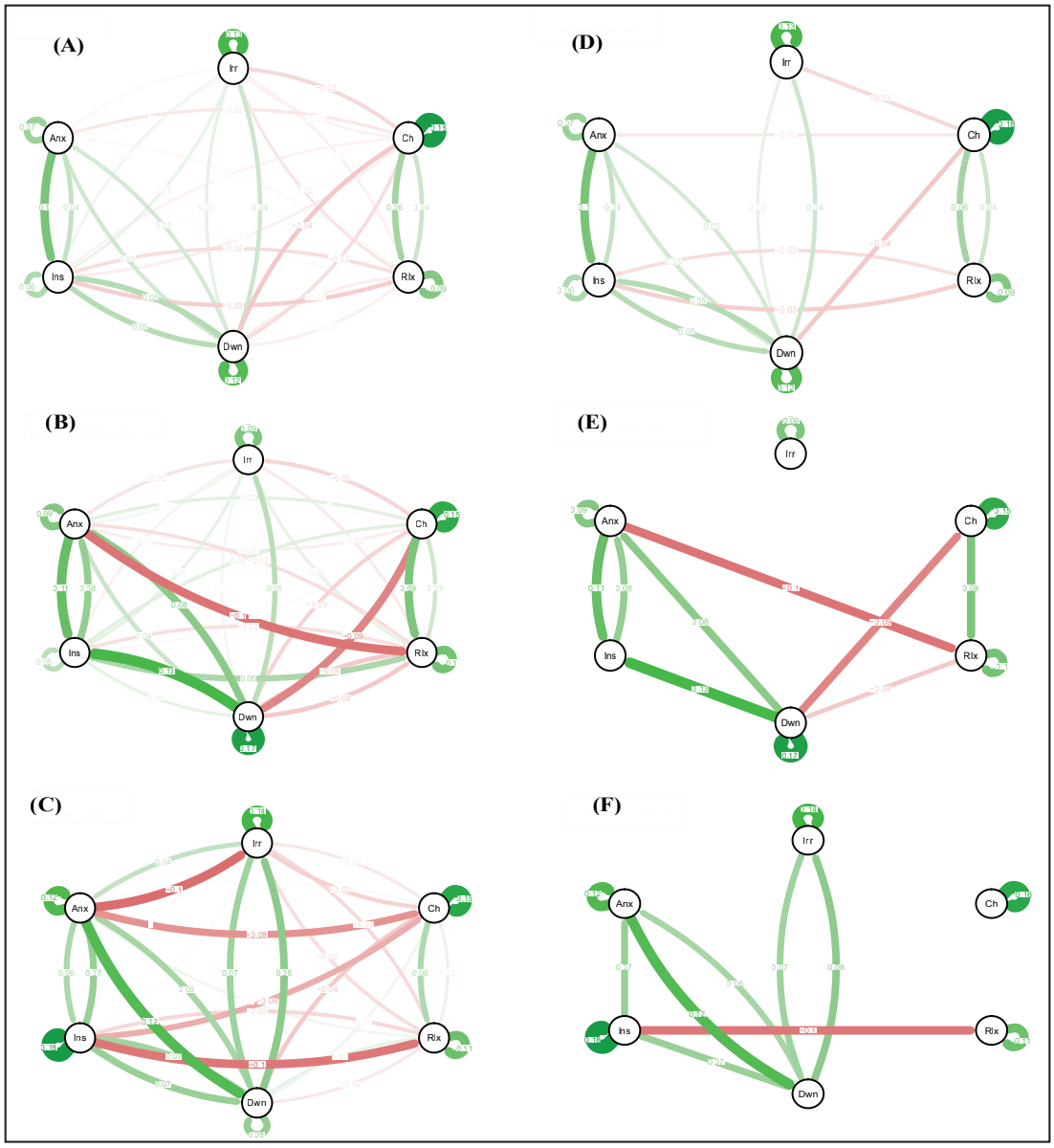

FIGURE 3.2 | Emotions networks in participants with low (A), intermediate (B), and high genetic liability for psychopathology (C).
In this figure, the arrows represent associations over time; i.e., the B coefficient expressing the effect size of the predictive associations. For example, in the low genetic liability network, there is an arrow from "relaxed" to "cheerful," meaning that "relaxed" at t−1 predicts "cheerful" at t with a B coefficient of 0.04. Green arrows represent positive associations, and red arrows represent negative associations. The fading of the lines represents the strength of the association and are determined by the regression weights: the more solid the line, the stronger the association (and vice versa). Note that we can predict the emotion item from the previous state of the item itself. These arrows are the self-loops in the network. Graphs (A–C) are for low, intermediate, and high GL respectively. The Graphs (D–F) are for low, intermediate, and high GL respectively but only with associations that resisted to Simes correction for multiple testing with $p < 0.022$.

Table 3.2. Emotional density across levels of childhood trauma and GL, respectively
* p<0.05

	Density values			P-values of comparison from Permutation tests		
	Low CT	Medium CT	High CT	Medium vs Low CT	High vs Low CT	High vs Medium CT
PA density	0.097	0.072	0.10	0.06	0.86	0.02*
NA density	0.054	0.051	0.058	0.7	0.6	0.36
Overall density	0.041	0.04	0.048	0.82	0.08	0.04*
	Low Gen. Liability	Inter. Gen. Liability	High Gen. liability	Inter. vs Low GL	High vs Low GL	High vs Inter. GL
PA density	0.09	0.09	0.08	0.89	0.66	0.66
NA density	0.05	0.06	0.08	0.22	0.00*	0.09
Overall density	0.04	0.05	0.06	0.05	0.02*	0.61

Table 3.3. Node strength centrality across levels of childhood trauma
* p<0.05

	Centrality values			P-values of comparison from Permutation tests		
	Low CT	Medium CT	High CT	Medium vs Low CT	High vs Low CT	High vs Medium CT
Inward strength						
Irritated	0.24	0.20	0.30	0.43	0.32	0.09
Cheerful	0.27	0.31	0.32	0.46	0.36	0.88
Relaxed	0.23	0.20	0.27	0.54	0.52	0.21
Down	0.25	0.29	0.33	0.43	0.11	0.40
Insecure	0.28	0.25	0.27	0.49	0.71	0.77
Anxious	0.20	0.20	0.23	0.97	0.54	0.49
Outward strength						
Irritated	0.24	0.17	0.21	0.20	0.49	0.54
Cheerful	0.31	0.23	0.37	0.15	0.20	0.01*
Relaxed	0.20	0.17	0.24	0.51	0.44	0.18
Down	0.31	0.34	0.30	0.74	0.88	0.60
Insecure	0.21	0.14	0.37	0.22	0.02*	0.00*
Anxious	0.21	0.39	0.23	0.01*	0.89	0.01*

Table 3.4. Node strength centrality indices and their relation to genetic liability to psychopathology
* $P<0.05$

	Centrality values			P-values of comparison from Permutation tests		
	Low Gen. Liability	Inter. Gen. Liability	High Gen. liability	Inter. vs Low GL	High vs Low GL	High vs Inter. GL
Inward strength						
Irritated	0.23	0.21	0.37	0.34	0.37	0.16
Cheerful	0.27	0.29	0.36	1.19	0.67	0.64
Relaxed	0.22	0.41	0.31	0.01*	0.59	0.16
Down	0.28	0.31	0.40	0.70	0.14	0.37
Insecure	0.25	0.34	0.34	0.24	0.44	0.89
Anxious	0.17	0.31	0.31	0.03*	0.11	1.07
Outward strength						
Irritated	0.20	0.15	0.31	0.18	0.29	0.05
Cheerful	0.34	0.35	0.28	1.22	0.21	0.36
Relaxed	0.18	0.23	0.20	0.53	1.16	0.52
Down	0.28	0.56	0.32	0.00*	0.91	0.01*
Insecure	0.21	0.23	0.49	1.17	0.02*	0.02*
Anxious	0.21	0.36	0.50	0.25	0.05	0.40

Table 3.5. Significant Edge Differences across different levels of GL
* $P<0.0004$, † $P<0.02$. Simes corrected alpha for differences across subgroups is 0.0004 and for edge significance is 0.022.

	Differences						Coefficients					
	Low vs Intermediate GL		Low vs High GL		Intermediate vs High GL		Low GL		Intermediate GL		High GL	
Edges	Diff	*p*	Diff	*p*	Diff	*p*	B	*p*	B	*p*	B	*p*
Insecure *t*-1 →Insecure *t*,	0.01	0.87	-0.12	0.00*	-0.13	0.01	0.06	0.00 †	0.05	0.11	0.18	0.00 †
Insecure *t*-1 →Relaxed *t*.	-0.09	0.01	0.06	0.14	0.16	0.00*	-0.03	0.01 †	0.06	0.05	-0.10	0.01 †

Discussion

Using a dynamic network approach, we compared the time-lagged network structures across genetic and environmental risk strata. The primary goal of the study was to identify the impact of CT as an early environmental factor, and GL as a proxy for genetic factor, on the structure of a time series network of six emotions—'irritated', 'cheerful', 'relaxed', 'down', 'insecure' and 'anxious'—at the levels of emotional density, node strength centrality and individual connections (edges). The principal findings were: (i) compared with the low GL stratum, the high GL stratum had significantly denser overall and NA networks, while the medium GL stratum also showed a directionally similar but statistically insignificant association with network density; (ii) in contrast to GL, the results of the CT analysis were essentially inconsistent with our initial hypothesis (iii) after adjusting for multiple testing, the individual edge comparisons across strata of GL and CT yielded only very few significant results.

Genetic liability: the emotion network density

Considering the network density across different levels of GL, our current findings suggest an increase in overall and NA density as a function of the extent of GL. As far as we know, differences in density depending on GL have not been studied before. The current study partially replicate our first previous study[21, 40], Genetic and environmental influences on the effective regulation network: A prospective experience sampling analysis. Manuscript submitted for publication], in that we observed a difference in overall density and NA density between high GL and medium GL (as opposed to between high GL and low GL in the present data).

To the degree that higher genetic loading may predict greater severity, some studies are in apparent agreement with the present results. First, a denser cross-sectional network at baseline was associated with persistence of clinical depression[12, 41]. Second, in analyses using ESM data, patients with depression, compared to healthy controls, had a higher overall density and NA density, but not a higher positive density [8]. Although there was no direct estimation of density, several studies also showed that the more a person shifts toward severe states of psychopathology, the stronger the regression coefficients of mental states at *t-1* predict mental states at *t* [29, 42]. In agreement with this, higher levels of neuroticism have been associated with a denser emotion network (both overall and NA but not PA)[9]. However, a recent study investigating emotion dynamics in patients with psychosis, their first-degree relatives, and healthy controls found no difference in the overall density of the momentary mental state network but only the number of connections [7]. However, it should be noted that this study calculated a general network connectivity, also including nodes which were not emotional items in the ESM protocol, e.g., being alone and being active.

Considering the exploratory nature of the time-lagged network analysis of the ESM data and our previous findings, in which we found both higher overall density and higher NA density in high GL stratum than in medium GL stratum with no difference between low and high GL strata, we err on the side of caution when interpreting the current findings that might be suggestive of an increase in the connectivity of emotions as an extent of the degree of GL. There might be several explanations for the inconsistency between the previous and the current study. First, consistent with the assumption of the network theory of psychopathology and with previous work on affect regulation, the expected high between-subject variation might be contributing to reduction in reproducibility[13]. Second, it is plausible to speculate that the differences between characteristics of the two samples may have contributed to inconsistency—the previous study consisted only of female participants with a mean age of 27.7 years. Gender and age differences in terms of symptom profile, vulnerability factors, and epidemiologic features in mental disorders are well identified [43]. To the best of our knowledge, there exists no network analysis of ESM data investigating the influence of age and only one study examining a gender effect in a sample of patients with major depressive disorder (MDD) and healthy controls, which showed that

women with MDD had a denser NA network than men with MDD, while the gender effect was not observed in healthy controls [8]. In fact, these data—or lack thereof—indicate that there is a pressuring need to investigate the impact of basic demographic parameters (e.g., age and gender) on emotion networks before progressing to network analysis of mental disorder constructs in the context of vulnerability.

Childhood Trauma: the emotion network density

Regarding CT, findings were inconsistent, suggesting increased positive density and overall density in the high CT stratum compared to the medium CT stratum but not the low CT stratum, while NA density did not differ across CT strata. In contrast to the current findings, our previous study showed that NA density in the high CT was significantly higher than the medium but not the low CT, with no significant differences in positive and overall emotion density measures across CT strata.

Centrality characteristics of the network.

Similarly, the individual edge comparisons across strata of GL and CT yielded only very few significant and relatively inconsistent findings after adjusting for multiple testing with Simes correction to avoid spurious conclusions. In the previous female-female twin sample study, statistical comparisons between edges were also inconclusive. Regarding centrality comparisons, only the analysis of 'insecure' node across CT strata yielded a consistent pattern in terms of outward strength with this pattern replicating the original study. Feeling insecure- also studied under the term "uncertainty"- has been found to be a powerful stressor in previous studies[44]. In previous experiments with replicated results, informing the participants of a low probable electrical choc loaded more anxiety both at the emotional and physiological level (heart rate and skin conductance) than when the probability of 100 percent coming electrical choc was announced[45, 46]. Replicated finding of insecure differences across GL groups, might provide some support to the genetic support to the link between insecure and NA. We could then hypothesize that risky genes might influence more precisely a brain circuit acting on NA emotional regulation and more specifically emotional reactivity to insecurity.

Strengths and limitations

The present study replicated the methodology of a recent paper[21]. Genetic and environmental influences on the effective regulation network: A prospective experience sampling analysis. Manuscript submitted for publication] similar to a series of studies applying network analysis to the intensive time series data obtained using ESM to gain insight into dynamic changes in mental states [7, 33]. Many observations, inherent to the nature of ESM methodology, enabled us to compare three strata of both environmental and genetic exposures. Two other strengths are the use of permutation analyses as a correction for not including all random slopes and the subsequent correction of the alpha for multiple testing for both the p values of the significance of the regression coefficients and the comparison of

those regression coefficients individually across networks. Such an approach proved useful, but it might have negatively affected statistical power and led to type-II error.

There were several limitations. First, only a limited set of momentary emotional mental states was included to overcome convergence problems in the analyses. However, the interest of studying affective mental states was served by this approach. An advantage of analyses in a limited set is also that network graphs are easier to interpret. Second, as data were initially collected from the general population, NA items were relatively rarely reported by participants compared to a clinical population, and, thus, subject to floor effects. This limitation was dealt with by choosing items with the maximum moment to moment variation. Third, considering that our participants were young, mainly students, and living with their parents, the results of this study may not be representative of the overall population. Also, the network comparability could be biased by differences in mean emotion items and within-person variances. Means however are mostly analogous across GL strata and between the low and medium CT exposure. It hence seems improbable that differences in connection strengths and consequently in network indices, between these latter groups could be attributed to differences in variances. In contrast, the means in the group under high CT exposure are, for most of the emotional items, significantly different from the 2 other subgroups. Therefore, this could have been part of the reason explaining the lack of replicability between the two studies regarding network density under CT exposure.

Finally, this study is one of few that have aimed to compare time series network despite the lack of specific and a valid methodology balancing both type I and type II errors. Further methodological studies are needed and could for example test other advanced methods previously used on comparing cross sectional based networks and replicate them in ESM based networks on different samples [47].

Conclusion and future work

The present results represent a partial replication of previous work. The micro-level approach to what could be the phenotypic translation of the genetic liability to psychopathology was demonstrated in both samples, providing a potential link with NA density. The fact that genes impact on the extent to which NA infect each other is important as it helps to expose the complex ways by which genes are affecting mental health. These findings have relevance to future research into the genetics of psychiatry. First, it may help to explain current problems with replications across studies and, second, it may shine light on the need for novel designs that can take into account the complexity of genetic influence in the development of psychopathology.

List of abbreviations

CT Childhood Trauma; GL genetic liability; EFPTS East Flanders Prospective Twin Study; ESM Experience Sampling Method; NA Negative Affect; PA Positive Affect; SCL-90-R Symptom Checklist-90-R; SD Standard Deviation; MZ Monozygotic; DZ Dizygotic

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Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors and Contributors

LH contributed to the conception of the work, the analysis, interpretation of data for the work, drafting it. MD contributed to the conception of the work, the analysis, interpretation of data for the work and to drafting and revising it. SG contributed to the interpretation of data for the work, drafting it and revising it. CM, J D, R.vW, DC, PD, MD, CD, ET, NJ, and BPFR contributed to the acquisition of data for the work, and to revising it. MW contributed to the conception of the work, the acquisition, the interpretation of data for the work and to revising it. JvO contributed to the conception of the work, the interpretation of data for the work and to revising it.

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Supplementary Materials

Preamble: The results presented below are from supplementary analysis done upon the original network study twins sample[1].

Table S1. Emotional density across levels of childhood trauma and genetic liability to psychopathology, respectively

	Density values			P-values of comparison from Permutation tests		
	Low CT	Medium CT	High CT	Medium vs Low CT	High vs Low CT	High vs Medium CT
PA density	0.15	0.14	0.14	0.54	0.53	0.97
NA density	0.06	0.06	0.08	0.87	0.05	0.04*
Overall density	0.05	0.05	0.06	0.69	0.12	0.06
	Low Gen. Liability	Inter. Gen. Liability	High Gen. liability	Inter. vs Low GL	High vs Low GL	High vs Inter. GL
PA density	0.15	0.11	0.13	0.11	0.32	0.53
NA density	0.06	0.05	0.08	0.11	0.29	0.03*
Overall density	0.06	0.05	0.06	0.03*	0.87	0.03*

* p<0.05

Table S2. Node strength centrality across levels of childhood trauma

	Centrality values			P-values of comparison from Permutation tests		
	Low CT	Medium CT	High CT	Medium vs Low CT	High vs Low CT	High vs Medium CT
Inward strength						
Irritated	0.20	0.20	0.32	1,00	0.09	0.08
Cheerful	0.45	0.41	0.47	0.62	0.75	0.41
Relaxed	0.36	0.38	0.35	0.76	0.92	0.70
Down	0.34	0.34	0.45	0.99	0.05	0.06
Insecure	0.35	0.32	0.31	0.62	0.59	0.93
Anxious	0.23	0.22	0.27	0.87	0.55	0.46
Outward strength						
Irritated	0.17	0.16	0.16	0.86	0.83	0.96
Cheerful	0.41	0.41	0.37	0.93	0.48	0.56
Relaxed	0.33	0.27	0.32	0.34	0.80	0.44
Down	0.49	0.48	0.67	0.86	0.06	0.06
Insecure	0.30	0.19	0.27	0.13	0.72	0.29
Anxious	0.23	0.36	0.40	0.20	0.09	0.75

Table S3. Node strength centrality indices and their relation to genetic liability to psychopathology

	Centrality values			P-values of comparison from Permutation tests		
	Low Gen. Liability	Inter. Gen. Liability	High Gen. liability	Inter. vs Low GL	High vs Low GL	High vs Inter. GL
Inward strength						
Irritated	0.23	0.17	0.35	0.10	0.98	0.18
Cheerful	0.45	0.37	0.53	0.14	0.66	0.15
Relaxed	0.39	0.37	0.32	0.20	0.09	0.91
Down	0.35	0.38	0.49	1,29	0.15	0.18
Insecure	0.33	0.27	0.34	0.37	1,04	0.44
Anxious	0.25	0.30	0.28	0.77	0.82	0.89
Outward strength						
Irritated	0.16	0.16	0.18	1,61	1,24	0.61
Cheerful	0.41	0.24	0.44	0.02*	0.93	0.05
Relaxed	0.30	0.46	0.21	0.08	0.09	0.02*
Down	0.59	0.42	0.66	0.17	0.50	0.10
Insecure	0.17	0.33	0.44	0.42	0.01*	0.22
Anxious	0.36	0.23	0.31	0.05	0.32	0.46

*** p<0.05**

Reference:

1. Hasmi L, Drukker M, Guloksuz S, Viechtbauer W, Thiery E, Derom C, et al. Genetic and environmental influences on the affective regulation network: a prospective experience sampling analysis. Frontiers in psychiatry. 2018;9:602.

Chapter 4

What makes the psychosis 'Clinical High Risk' state risky: Psychosis itself or the copresence of a non-psychotic disorder?

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Abstract

Aims:

Although attenuated psychotic symptoms in the psychosis clinical high-risk state (CHR-P) almost always occur in the context of a non-psychotic disorder (NPD), NPD is considered an undesired 'comorbidity' epiphenomenon rather than an integral part of CHR-P itself. Here, we examine to what degree the 'risk' in CHR-P is indexed by NPD rather than attenuated psychosis *per se*.

Methods:

We examined the incidence of early psychotic experiences (PE) with and without NPD (mood disorders, anxiety disorders, alcohol/drug use disorders), in a prospective general population cohort (n=6,123 at risk of incident PE at baseline). Four interview waves were conducted between 2007-2018 (NEMESIS-2). The incidence of PE, alone (PE-only) or with NPD (PE+NPD) was calculated, as were differential associations with schizophrenia polygenic risk score (PRS-Sz), environmental, demographical, clinical, and cognitive factors.

Results:

The incidence of PE+NPD (0.37%) was lower than the incidence of PE-only (1.04%), representing around a third of the total yearly incidence of PE. Incident PE+NPD was, in comparison with PE-only, differentially characterized by poor functioning, environmental risks, PRS-Sz, positive family history, prescription of antipsychotic medication and (mental) health service use.

Conclusions:

The risk in 'clinical high risk' states is mediated not by attenuated psychosis *per se* but specifically the combination of attenuated psychosis and NPD. CHR-P/APS research should be reconceptualised from a focus on attenuated psychotic symptoms with exclusion of non-psychotic DSM-disorders, as the 'pure' representation of a supposedly homotypic psychosis risk state, towards a focus on poor-outcome NPDs, characterised by a degree of psychosis admixture, on the pathway to psychotic disorder outcomes.

Keywords: Psychosis, Risk, Epidemiology, Prevention

Introduction

There is considerable interest in the psychosis Clinical High-Risk state (CHR-P) as a paradigm to identify the risk factors, mechanisms and early intervention potential associated with the onset of psychotic disorder [1]. CHR-P is defined mainly by the presence of attenuated psychotic symptoms which, accordingly, represent the central part of the definition of Attenuated Psychosis Syndrome (APS) in (the appendix of) DSM-5 [2]. Although some have proposed that the CHR-P/APS construct may be valid [3, 4], others point to epistemic, conceptual and methodological limitations surrounding different aspects of CHR-P research[5] [6, 7]. Clarification of these issues is urgently required given increasingly large-scale research projects based on theCHR-P paradigm.

One major validity issue is related to non-psychotic 'comorbidity' in CHR-P research. Non-psychotic 'comorbidity' does not form part of the CHR-P/APS construct. Rather, it is treated as an exclusion factor in the criteria for APS and CHR-P through formulations like "*attenuated psychotic symptoms are not explained better by another DSM disorder*" [3]. Nevertheless, the samples collected in the context of CHR-P research invariably show that the vast majority of individuals have a diagnosis of non-psychotic disorder. A recent systematic review including 56 studies showed that 49% presented with comorbid depressive disorders, 22%with bipolar disorder, 38%with anxiety disorders and 20% with substance use disorders (sum of percentages is greater than 100 due to comorbidity)[3].

This situation represents an unacceptable conundrum: according to definitions, CHR-P/APS can only include attenuated psychotic symptoms that are not "better explained" by another DSM-disorder – yet the vast majority of individuals meeting CHR-P/APS criteria present with another DSM-disorder. The likely explanation for this apparent paradox is misspecification of the CHR-P/APS construct itself. Thus, the co-presence of non-psychotic disorder in CHR-P/APS samples may not be an 'unwelcome' epiphenomenon but rather represent an integral part of the CHR-P/APS construct itself. Non-psychotic disorder may be what mediates the 'risk' in the concept of CHR-P and represent the mechanism for the relatively poor outcome over time associated with the CHR-P/APS state, whether or not 'transition' took place [8]. While this explanation initially may not seem straightforward, it is from the perspective of population-based sampling. Research shows that individuals with mental health difficulties typically experience multiple diagnoses over the life course, often beginning with NPD[9], whereas the artificially 'pure' CHR-P samples advance a competing, but incorrect, notion that psychosis is somehow inherently homotypic and therefore inconsistent with transdiagnostic symptoms [6, 10]. However, population-based research shows that a prior diagnosis of mood disorder, neurotic disorder, eating disorder and substance use disorder – or basically any diagnosis outside the schizophrenia spectrum increases the risk of a later diagnosis of schizophrenia 10-20 fold [9] or 5-fold [11]. Indeed, recent prospective work showed that much more of the clinical psychosis incidence is attributable to prior mood and drugs use disorders than to psychosis clinical high-risk states [12].

One of the weaknesses of CHR-P sampling frames is that they are based on non-epidemiological opportunity sampling of selected help-seeking individuals with a non-psychotic disorder, yielding sample-specific results that are neither representative [5] nor generalizable [6]. Indeed, 'transitions' in these individuals largely arise as a function of risk enrichment strategies embedded in specific sampling procedures [13], limiting their use as a model of the onset of psychosis in the general population. Population-based cohort studies, however, can address the dynamics of attenuated psychotic symptoms and the role of NPD over time in representative samples [14]. These studies have shown that co-presence of NPD, present in around 50% of individuals with attenuated psychotic symptoms [15, 16], is a crucial distinguishing factor in relation to aetiological load, clinical relevance and outcome [17-22]. Also, attenuated psychotic symptoms in isolation are either not [23, 24], negatively [25] or weakly 26, 27 associated with polygenic risk for schizophrenia (PRS-SZ), but tend to show progressively stronger association with PRS-SZ in combination with more environmental exposure, more affective comorbidity and more clinical relevance [12, 25, 28]. PE may be associated with subjective [29] or objective cognitive alterations [30-32]; there is evidence, however, that the association with cognitive alterations is dependent on the degree of comorbid non-psychotic psychopathology [33]. Indeed, recent follow-back studies from representative incidence samples of psychotic disorder have shown that the origins of psychotic disorder can be traced to *non-psychotic disorders*, the severest of which develop a degree of psychosis admixture over time [34]. Indeed, studies using prospective approaches show that nonpsychotic syndromes are frequently observed not just alongside psychotic experiences/symptoms, but even before them [35, 36].

Here, we investigated the clinical significance of the co-presence of non-psychotic disorder (NPD) in first-onset psychotic experiences (PE). To this end we calculated, for the first time, the incidence rate of PE, alone (PE-only) and as a function of co-presence of NPD (PE+NPD - mood disorders, anxiety disorders and alcohol/drug use disorders) in a risk set of people without PE at baseline. We also analysed the differential impact of relevant clinical, etiological, cognitive, and demographic factors on the incidence of PE-alone and PE+NPD.

We hypothesized that a minority of people with incident PE would have co-presence of NPD, and that clinical, demographic, etiological and cognitive factors, known to be associated with psychotic disorder, would display stronger and/or qualitatively different associations with the incident PE+NPD phenotype in comparison with the PE-only phenotype.

Method

Sample

The four waves of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) were used (n=6,646 at baseline or T0). NEMESIS-2 was conducted over the period 2007-2018 to study the

prevalence, incidence, course, and consequences of mental disorders in a representative sample of the Dutch general population (for description see supplemental material).

Sample Risk set

Individuals, with confirmed psychosis at baseline and therefore not at risk anymore of developing incident psychosis, were not included in the risk set. Thus, individuals with a diagnosis of any psychotic disorder according to the DSM-IV (n=43) were excluded from analysis. Also, those who had PE present in the year before T0 were excluded (n=480), leaving 6,123 participants at T0 considered at risk of developing incident PE. Individuals, who had PE in the past, more than one year before baseline and not in the year before baseline, were considered at risk of developing new incident PE and included in the risk set. The 6,123 individuals thus included in the risk set yielded 19,115 observations over T0-T3. Of the 6,123 individuals at T0, 4,930 remained at T1 after a mean follow-up of 3.02 years; 4,314 remained at T2, after a mean follow-up of 6.01 years; and 3,748 remained at T3, after a mean follow-up of 9.04 years.

A planned sensitivity analysis was carried out with a more restricted risk set, excluding all participants with any PE at baseline (n=5,565 at baseline, total sample n=17,282). Given the age range of the sample (18-65 years at baseline), another sensitivity analysis was conducted in order to examine if results would be similar when restricted to the sample aged 18-35 at baseline (n=1439, 26%), the age range during which most psychosis onset takes place. As the definition of non-psychotic diagnoses (NPD) included drug abuse and dependence, a further sensitivity analysis of the association with cannabis use was conducted excluding individuals with drug abuse or dependence from the definition of NPD.

Finally, for the measures split at the xth percentile (social functioning, digit span, childhood trauma, PRS), which may be considered arbitrary, we included sensitivity analyses with continuous scores.

Assessment of non-psychotic disorders

The following CIDI, version 3.0, non-psychotic diagnoses (NPD) were assessed, as described in the supplemental material: major depression, dysthymia, bipolar disorder, panic disorder, agoraphobia, social phobia, specific phobia, GAD, alcohol abuse and dependence, drug abuse and dependence. The analyses thus focused on people who developed incident PE over the period of observation, either alone (PE-only) or in the co-presence of NPD (PE+NPD).

Assessment of PE

In NEMESIS-2, a psychosis add-on instrument based on the G section of previous CIDI-versions was included. This add-on instrument consists of 20 psychotic symptoms corresponding to the symptoms

assessed in a previous population survey in the Netherlands, NEMESIS, the precursor of NEMESIS-2 [37, 38]. Detailed descriptions of the specific PE items can be found in previous work using NEMESIS [39] and NEMESIS-2 [40] and are described in the supplemental material. PE was dichotomized consistent with previous work in NEMESIS and NEMESIS-2 [19, 21, 22]. Presence of delusions was defined as having at least one delusion endorsed and presence of hallucinations was similarly defined (supplemental material).

Exposure variables

We examined 17 exposures associated with psychotic disorder. Dichotomous measures of exposure were created at the 75th percentile unless a previous publication had used another cut-off in which case this was used for reasons of consistency (see below).

Working memory performance

The digit-span task, subtest of the Wechsler Adult Intelligence Scale (WAIS-III) [41], was performed by participants at T1 and T3. The digit-span task was split into two sections, a forward (six items) and backward (six items) task condition. The sum score at T1 and T3 was computed, and the average of these two values was considered as a person-level indicator of cognitive ability for all waves. In the analysis, a dichotomized variable was used, with cut-off at the 75th percentile, the highest value indicating poorer performance.

Jumping to conclusion bias (JTC bias)

The presence or absence of a JTC bias was assessed at T2, utilizing the beads task (supplemental material), and used as a person-level, time-invariant dichotomous variable in the analyses.

Childhood adversity

Childhood adversity was assessed at T0 using a questionnaire based on the NEMESIS trauma questionnaire [38], and used as a dichotomous variable in the analyses (supplemental material).

Cannabis use

Cannabis use was assessed with the section substance use disorders of the CIDI at each interview wave and used as a dichotomous variable in the analyses (supplemental material).

Urbanicity

The degree of exposure to the urban environment until the age of 16 years, was assessed at T0 and used as a dichotomous variable in the analyses (supplemental material).

Family history

Family history was assessed as a person-level characteristic in two stages, as described previously [21] and detailed in the supplemental material.

Hearing impairment

Hearing impairment was assessed during the face-to-face interview at all interview waves, by asking whether participants had experienced deafness or serious hearing impairment in the past 12 months. Ratings were yes (1) or no (0).

Social functioning

The evaluation of social functioning covered the past 4 weeks, and was assessed at each interview wave, applying a 2-item, 6-point subscale of the Medical Outcomes Study Short-form Health Survey (MOS SF-36)[42, 43], with a Cronbach's alpha of 0.78. Impaired social functioning includes issues in one's normal social activities as a result of somatic or emotional troubles. It was used as a binary variable in the analysis, dichotomized around the 75th percentile.

Service use for mental problems

Use of any form of care or specific mental health dare, as well as use of antipsychotic medication, was assessed at each interview wave (supplemental material).

Perceived status gap

The *perceived status gap* is a dichotomous variable indicating the difference between the subjective desired and actual social status (supplemental material).

Adult stressful life events

Based on the "Brugha Life events section" [44], participants were asked at each interview whether they experienced one of 9 life events within the last 12 months. Examples of items are serious sickness, death of family member or close friend, and serious financial problems. A dichotomous exposure was created around at least one life event in the last year.

Polygenic risk score for schizophrenia

The PRS-SZ were created from best-estimate genotypes at six different *p*-thresholds (0.5, 0.1, 0.05, $5 \cdot 10^{-3}$, $5 \cdot 10^{-5}$, $5 \cdot 10^{-8}$), as described in the supplemental material. For our primary analyses, we used the *p*-threshold of < 0.05, as this threshold explained most variation in liability in the Psychiatric Genomics Consortium analysis [45] and was shown to perform well for the current phenotype of SF-36 mental health [46]. Further details on the genotyping procedure and polygenic risk scores calculation, as

described previously [12, 19], are provided in the supplement. Consistent with previous analyses, statistical analyses with PRS-SZ were adjusted for three principal components [47]. Material for DNA analysis of sufficient quality, and hence for polygenic risk scores calculation, was available for 3,104 individuals (47%) at T0 (supplementary material). Excluding individuals who at interview has been assessed as member of an ethnic minority (supplemental material), given lack of generalizability of polygenic risk scores to this group, and individuals diagnosed with a psychotic disorder, left 3,037 for PRS calculation, of whom 2,836 remained in the risk set for incidence analysis as defined below. These 2,836 with polygenic risk scores yielded 9,737 observations over the four interview waves. Values for important and time-varying clinical, environmental, cognitive, and demographic variables were very similar in a comparison between the 9,737 observations in the subsample with polygenic risk scores data available and the 10,238 observations in the risk set with missing polygenic risk scores data (supplemental Table 2).

Demographic factors

Demographic variables included were sex (0=male, 1=female), age in years and dichotomous ethnic minority status (Moroccan, Turkish, Surinamese, Antillean, Indonesian or another non-Western ethnic group). Age was analysed as a dichotomous variable, defining a younger age group encompassing the range most at risk of onset of psychotic disorder (18 to 35 years, 24% at baseline) versus the older group.

Analysis

PE-only and PE+NPD groups

Two outcomes were defined to test the hypotheses regarding PE in relation to the context of NPD. The first was defined as PE without NPD, the second as PE in the co-presence of NPD. For each group we established (i) the incidence and (ii) associations with cognitive, clinical, demographic, and etiological variables, expressed as hazard ratio's (HR) and their 95% confidence intervals (CI) from cox proportional hazards regression.

Analysis of incidence and predictors of incidence

The STSET command was used to obtain the format of survival data in Stata, guiding treatment of time-varying and fixed independent variables in the analyses. Incidence was calculated using failures in single-failure per subject data (i.e., one single event was defined as failure, with a single record per subject), divided by the number of person-years. Incidence was calculated using the Stata STSUM routine. Cox regression was done using the Stata STCOX routine. The proportional-hazards assumption was tested with the Stata ESTAT PHTEST routine, which detected no violations.

Results

Sample characteristics

Mean age of the 6,123 participants in the risk set at T0 was 44.4 years (S.D.=12.5, range 18–68), 55% were female. More than a third (37%) had a higher professional education or university degree, 32% had completed up to higher secondary education, 27% up to lower secondary education and 5% had completed primary education only; 74% were married or cohabiting; 20% lived alone; 70% were in paid employment; 7% pertained to an ethnic minority group.

Incidence of PE-only and PE+NPD combinations

The incidence of PE-only was 1.04% (Table 4.1). The incidence of NPD and PE combined was 0.37%, or around 25% of the total PE incidence [(0.37/ (1.04+0.37)] (Table 4.1). *PE-only and PE+NPD associations with clinical, demographic, cognitive and etiological factors* The distribution of clinical, demographic, cognitive and etiological factors tended to be different across the PE-only and PE+NPD groups, in comparison with the remainder of the sample, for most variables (Table 4.2). Supplemental Table 4.3 displays the pattern of time-varying and time-constant exposures for the PE-only and PE+NPD incidence analysis. Supplemental Table 4.4 details the person-years, failures, and incidence rates of PE-only and PE+NPD as a function of the various binary demographic, clinical, etiological, and cognitive risk factors. Hazard ratios are presented in Table 4.3 and the pattern of results is summarized in Figure 4.1.

The pattern of results, as displayed in Table 4.3 and Figure 4.1, was that most hazard ratio effect sizes were much higher for PE+NPD as compared to PE-only. Perceived status gap, low social functioning, care use, antipsychotic use, childhood adversity, life events, PRS_{75}, urbanicity and family history discriminated between PE-only and PE+NPD, as evidenced by non-overlapping confidence intervals of the hazard ratios. In addition, suggestive differences (large and significant hazard ratio in PE+NPD; small and non-significant hazard ratio in PE-only) were apparent for cannabis use and ethnic minority status. The suggestive differential association with cannabis use remained after excluding individuals with drug abuse/dependence from the definition of NPD (PE-only: HR=1.83, 95% CI: 0.59-5.69; PE +NPD: HR=6.27, 95% CI: 1.99-19.76).

The sensitivity analysis with the more restricted risk set, excluding all participants with psychotic experiences at baseline revealed results that were very similar to the results in Table 4.3, quantitatively and qualitatively (supplemental Table 4.5). The other sensitivity analysis restricted to individuals aged 18-35 at baseline (n=1439, 26%) similarly revealed a very similar pattern of results (supplemental Figure 2). Finally, for the measures split at the xth percentile (social functioning, digit span, childhood trauma, PRS) results for the continuous exposures yielded similar significant discrimination between PE-only and PE+NPD for social functioning, childhood trauma and PRS, and similar lack of significant discrimination between PE-only and PE+NPD for digit span (supplemental Table 4.6).

Table 4.1. Incidence of psychotic experiences (PE), either alone or co-present with Non-Psychotic Disorders (NPD)

Incident experience	Participants	Time at risk (years) *	Number of incident cases	Incidence %
PE-only	4930	37898.1	395	1.04
PE + NPD	4930	38721.3	142	0.37

PE: psychotic experiences; NPD: non-psychotic disorders

** The total number of person-years, derived from the sum of persons and the length of their individual follow-ups, in years.*

Table 4.2. Distribution of risk factors (proportions) as a function of Psychotic Experiences (PE), either alone or in combination with Non-Psychotic Disorder (NPD) across T0, T1, T2 and T3 repeated observations (6,123 individuals yielding 19,115 observations)

Binary exposure	No PE (n=18,476) (proportion)	PE-only (n=462) (proportion)	PE+NPD (n=177) (proportion)	Total (n=19,115) (proportion)	Total exposed (n)
Young age group	0.16	0.16	0.18	0.16	3,045
Female sex	0.54	0.60	0.66	0.55	10,458
Perceived status gap	0.18	0.27	0.53	0.18	3,487
Low social functioning	0.32	0.42	0.77	0.33	6,217
Any care	0.11	0.15	0.64	0.12	2,233
Mental health care	0.06	0.07	0.42	0.06	1,193
Antipsychotic use	0	0.01	0.06	0.004	74
Cannabis use	0.02	0.01	0.04	0.02	348
Childhood adversity	0.18	0.26	0.49	0.18	3,487
Life events	0.47	0.55	0.67	0.47	8,980
Ethnic minority	0.07	0.08	0.16	0.07	1,363
Hearing impairment	0.03	0.06	0.06	0.03	549
Urbanicity <16 yrs.	0.39	0.33	0.50	0.39	7,377
Family history	0.58	0.72	0.92	0.59	11,217
PRS_{75}	0.25	0.22	0.42	0.25	2,331
JTC bias	0.51	0.54	0.61	0.51	8,481
Altered digit symbol	0.28	0.39	0.50	0.29	4,144

Young age group: aged 18-35 years; Perceived status gap: difference between actual and desired social position; Low social functioning: SF36 social functioning 75th percentile cut-off; Any care: any informal, medical or mental health care for mental problems or addiction; Cannabis use: once per week or more in the period most frequent use; Childhood adversity: 80th percentile cut-off continuous adversity score before age 16 years; Life events: at least one life event in the last year; Minority: Moroccan, Turkish, Surinamese, Antillean, Indonesian or other non-western ethnic group; Hearing

impairment: T0 deafness or serious hearing impairment in the past 12 months; Urbanicity: 2 highest levels of 5-level urbanicity classification before age 16 years; Family history: family history mental disorder; PRS_{75}: schizophrenia polygenic risk score 75th percentile cut-off; JTC: beads task decision 2 or less beads; Altered digit symbol: cut-off 75th percentile continuous score.

Discussion

Findings

We found that of the total incidence of PE (around 1.4%), approximately 25% involved a combined phenotype of PE+NPD. Compared to PE-only, the combined phenotype was differentially characterized by perceived status gap, low social functioning, care use, antipsychotic use, childhood adversity, life events, family history, urbanicity and PRS-SZ, with additional suggestive differences for cannabis use and ethnic minority status – a pattern of results that is close to findings reported for psychotic disorder [48]. We suggest that differential associations between PE-only and PE+NPD with various risk factors confirms that PE-NPD is integral to transitions to psychosis, in line with recent prospective work showing that much more of the clinical psychosis incidence is attributable to prior mood and drugs use disorders than to psychosis clinical high-risk states [12]. Other arguments are, first, clinical face validity, given that the finding of differential associations with poor functioning, use of mental health care and psychotropic medications represents actual clinical status differentiation, which is a necessary requirement for later poor outcome. Second, differential associations with greater aetiological loading (childhood adversity, cannabis use, PRS-SZ) are associated with poorer outcome of psychotic states [49-51]. Third, prospective studies have shown greater risk of transition and other poorer outcomes of psychosis risk states for many of the factors differentiating between PE-only and PE+NPD in this study including childhood adversity and cannabis use [52-54], non-psychotic comorbidity [9, 12, 20, 55] and social functioning [56].

Table 4.3 Differential associations of incident Psychotic Experiences (PE), alone (PE-only) and in the context of Non-Psychotic Disorder (PE+NPD), with demographic, clinical, etiological, and cognitive factors

Binary exposure	**PE-only**				**PE+NPD**			
	HR*	**95% CI**		**p**	**HR**	**95% CI**		**p**
Young age group	1.54	1.18	2.01	0.001	1.84	1.21	2.78	0.004
Female sex	1.27	1.04	1.56	0.019	1.37	0.98	1.93	0.069
Perceived status gap	1.66	1.33	2.08	0.000	4.77*	3.43	6.64	0.000
Low social functioning	1.40	1.15	1.71	0.001	6.21*	4.22	9.14	0.000
Any care	1.24	0.94	1.65	0.124	13.87**	9.83	19.58	0.000
Mental health care	1.03	0.70	1.52	0.886	10.79**	7.73	15.05	0.000
Antipsychotic use	2.73	1.02	7.31	0.046	16.98*	7.92	36.39	0.000
Cannabis use	1.82	0.58	5.67	0.302	10.36**	4.23	25.35	0.000
Childhood adversity	1.66	1.32	2.08	0.000	3.92*	2.82	5.46	0.000
Life events	1.33	1.09	1.62	0.005	2.35*	1.66	3.34	0.000
Ethnic minority	1.29	0.90	1.84	0.166	2.33**	1.45	3.75	0.000
Hearing impairment	2.07	1.34	3.18	0.001	1.96	0.96	4.00	0.065
Urbanicity <16 yrs.	0.85	0.69	1.04	0.113	1.54**	1.11	2.14	0.010
Family history	1.91	1.54	2.37	0.000	8.57*	4.74	15.48	0.000
PRS_{75}	0.80	0.56	1.13	0.204	2.47**	1.48	4.10	0.000
JTC bias	1.08	0.88	1.33	0.461	1.30	0.92	1.84	0.144
Altered digit symbol	1.56	1.24	1.97	0.000	2.10	1.41	3.12	0.000

HR = hazard ratio, 95% CI = 95% confidence interval. Young age group: aged 18-35 years; Perceived status gap: difference between actual and desired social position; Low social functioning: SF36 social functioning 75th percentile cut-off; Any care: any informal, medical or mental health care for mental problems or addiction; Cannabis use: once per week or more in the period most frequent use; Childhood adversity: 80th percentile cut-off continuous adversity score before age 16 years; Life events: at least one life event in the last year; Minority: Moroccan, Turkish, Surinamese, Antillean, Indonesian or other non-western ethnic group; Hearing impairment: T0 deafness or serious hearing impairment in the past 12 months; Urbanicity 2 highest levels of 5-level urbanicity classification before age 16 years; Family history: family history mental disorder; PRS_{75}: schizophrenia polygenic risk score 75th percentile cut-off; JTC: beads task decision 2 or less beads; Altered digit symbol: cut-off 75th percentile continuous score.

** HR significantly greater in PE+NPD group compared to PE-only group, based on non-overlapping confidence intervals. ** HR significant in PE+NPD group but not in PE-only group*

Does PE-only reflect the risk for psychotic disorder?

The results indicate that 74% of the incidence of PE, namely the part not arising in combination with NPD is less likely to be of clinical relevance. Although the incidence of PE-only was not clinically neutral – as evidenced by some degree of association with most of the 17 factors under examination, these associations were (significantly) weaker as compared to PE+NPD and there was no association with health care use. These results concur with the previously documented suggestion that clinically relevant psychosis is an indicator of severity in the constellation with non-psychotic psychopathology and should not be considered in isolation [6, 34, 57].

The role of PRS and cognitive alterations

PRS-SZ was not associated with PE-only in terms of either direction or significance of association, whereas the PE+NPD phenotype was significantly and more strongly associated. It could be argued that this represents a chance finding imputable to imposing an arbitrary cut-off on the continuous PRS-SZ. However, a sensitivity analysis with the continuous PRS-SZ quartile group score revealed similar results with additional evidence for dose-response association, supporting underlying causality (supplemental Table 4.7). A plausible explanation for the differential associations with PRS-SZ may have to do with the nature of PRS-SZ. While generally interpreted as polygenic risk for a mental disorder, it can also be interpreted as polygenic risk for poor outcome of a manifestation of transdiagnostic psychopathology, which is conceptually different. PE are transient in 80% of cases whereas schizophrenia is transient in less than 20% of cases [58]. The differences in association with PRS-SZ thus may represent absence of association with relatively good outcome for the phenotype PE-only and a positive association with poor outcome for the phenotype PE+NPD. A recent study has reported a conceptually similar association between PRS-SZ and illness course in a clinical sample [50]. Cognitive alterations, including the JTC task did not discriminate between PE-only and PE+NPD outcomes , in agreement with previous work [30-32]. The results are compatible with the suggestion that cognitive alterations may not represent the 'core' of the psychosis syndrome [24, 59], but instead become associated with the current poor-outcome definition of psychotic disorders because they moderate, together with PRS-SZ, the outcome of early non-psychotic states [24]. In the presence of high PRS-SZ, together with higher levels of environmental exposure, cognitive alterations may channel early states of non-psychotic psychopathology towards a poor outcome psychosis phenotype, whereas cognitive alterations in combination with low PRS-SZ may divert early psychopathology towards the more benign PE-only phenotype.

Implications for CHR-P/APS

These findings suggest a significant, genetically rooted discriminative function between the PE-only phenotype with relatively benign outcome and the poorer outcome PE+NPD phenotype. In the same direction, our evidence supports further investigation, in prospective CHR-P settings, of the hypothesis that non-psychotic psychopathology represents a necessary factor in the ontogenesis of

psychotic disorders, such that the pathway from psychosis risk to clinical psychosis outcome requires a non-psychotic intermediary state, interacting with multiple conditions including cognitive alteration, high PRS-SZ and environmental exposure. Indeed, a recent follow-back study of a representative incidence sample confirmed this supposition [34]. Therefore, CHR-P/APS research should be reconceptualised from a focus on attenuated psychotic symptoms with exclusion of DSM-disorders providing a "better explanation" of the psychotic state, towards a focus on poor-outcome non-psychotic disorders, characterised by a degree of psychosis admixture, on the pathway to psychotic disorder outcomes [12, 34, 57].

Methodological issues

The results should be interpreted in the context of a number of limitations. First, although the sample was sizeable, many participants were past the period of greatest risk for psychosis, reducing power. However, contrary to what is often thought, mean age of onset of psychotic disorder in the general population, not selected for age cut-off or poor outcome-related specific diagnostic criteria, is around 30 years for men and 40 years for women, replicated across different studies of treated incidence over extended periods in geographically defined areas [60, 61]. The relatively high incidence of psychosis outcomes in the current study confirms the age-related incidence pattern of psychosis. Second, although most important time-varying measures were dynamically captured over time, others were not. Thus, the measures of cognition were only assessed twice and modelled as a person-level average, not permitting dynamic modelling of incidence states of cognitive alterations, similar to the incidence states of NPD and PE. Third, PRS-SZ was available for less than 50% of the sample, however this is unlikely to have biased the results given similar distributions of dependent and independent variables as a function of PRS-SZ availability. Finally, some of the comparisons between the states of PE-only and PE+NPD suffered from low power. For example, there were substantial effect size differences in the association with cannabis use and PRS-SZ, however the statistical resolution of these differences was limited. Similarly, even though the sample was relatively large and the follow-up extensive, the incidence of the outcome of interest, PE+NPD, was not high, occurring in 177 participants in the risk set of whom 142 counted as incident. As a result, confidence intervals sometimes were wide, particularly for rarer exposures.

Declaration of interests

Dr O'Donovan is supported by a collaborative research grant from Takeda Pharmaceuticals. Takeda played no part in the conception, design, implementation, funding, or interpretation of this paper. No other disclosures were reported.

Availability of data and materials

The data on which this manuscript is based are not publicly available. However, data from NEMESIS-2 are available upon request. The Dutch ministry of health financed the data, and the agreement is that

these data can be used freely under certain restrictions and always under supervision of the Principal Investigator (PI) of the study. Thus, some access restrictions do apply to the data. The PI of the study is last author of this paper and can at all times be contacted to request data. At any time, researchers can contact the PI of NEMESIS-2 and submit a research plan, describing its background, research questions, variables to be used in the analyses, and an outline of the analyses. If a request for data sharing is approved, a written agreement will be signed stating that the data will only be used for addressing the agreed research questions described and not for other purposes.

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Supplementary material

Methods

NEMESIS-2 Sample

The baseline data of NEMESIS-2 were collected from 2007 to 2009, follow-up continued until 2018. The study was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care and written informed consent was collected from participants at each wave. To ensure representativeness of the sample in terms of age (between the ages of 18 and 65 at baseline), region, and population density, a multistage random sampling procedure was applied. Dutch illiteracy was an exclusion criterion. Non-clinician, trained interviewers applied the Composite International Diagnostic Interview (CIDI) version 3.0 [1, 2] and additional questionnaires during home visits. Details of NEMESIS-2 are provided elsewhere [3, 4].

The first wave (T0) enrolled 6,646 participants (response rate 65.1%; average interview duration: 95 minutes), who were followed up in 3 visits within 9 years: successive response rates at year 3 (T1), year 6 (T2), and year 9 (T3) were 80.4% (*n* = 5,303; excluding those who deceased; interview duration: 84 minutes), 87.8% (*n* = 4,618; interview duration: 83 minutes), and 86.8% (n = 4,007; interview duration: 102 minutes), respectively. Occurrence at baseline reflects lifetime occurrence; occurrence at T1 to T3 reflect approximately 3-year interval (T0-T1, T1–T2, and T2-T3) occurrence. Attrition between T_0 and T_3 was not significantly associated with any of the individual disorders at T_0 after controlling for sociodemographic characteristics [5].

Assessment of non-psychotic disorders

The following CIDI, version 3.0, diagnoses were assessed: major depression, dysthymia, bipolar disorder, panic disorder, agoraphobia, social phobia, specific phobia, GAD, alcohol abuse and dependence, drug abuse and dependence. Non psychotic diagnoses were made according to the fourth version of the Diagnostic and Statistical Manual of Mental disorders (DSM-IV) at T0, T1, T2 and T3, using the Composite International Diagnostic Interview (CIDI) version 3.0 [6]. Validity [7, 8] and test-retest reliability were determined, demonstrating good validity in providing diagnoses for almost all non-psychotic disorders and good to excellent kappa coefficients for most diagnostic sections [9].

For this study, the incidence of any NPD, thus defined between intake and each follow-up was assessed. As individuals with psychotic experiences at T0 were excluded from the risk set (see below), only people with NPD who for the first time ever developed psychotic experiences over the period of observation were studied. Participants with a diagnosis of schizophrenia, as assessed through CIDI interview and clinical follow-up interview detailed below, were excluded.

Assessment of PE:

As CIDI methodology to assess psychotic experiences in versions of CIDI 1 and CIDI 2 was not included in CIDI 3.0, a psychosis add-on instrument was constructed, based on the G-section of psychotic symptoms in CIDI versions 1 and 2. This part of the interview consisted of 20 psychotic experiences, each rated "yes," "no," "don't know," or "refuse," over the lifetime period. At baseline, lifetime prevalence of PE was assessed and T0-T3 interviews focused on interval occurrence.
The 20 experiences corresponded to the symptoms assessed in previous population surveys in the Netherlands [3, 10]; detailed descriptions of the specific PE items can be found in previous work using NEMESIS [11] and NEMESIS-2 [12]. Whenever a psychotic experience was endorsed, the subject was asked to state, on a 1 (rarely) to 4 (almost always) scale, how often this experience occurred (Frequency), how much it bothered them (Distress), and to what extent the experience had an influence on their daily professional and social activities (Impact). The sum scores for frequency and impact of psychotic experiences, as well as distress by psychotic experiences were calculated as the mean of the sum scores of these items across the 20 psychotic experiences. Psychotic experiences were considered secondary if all endorsed psychotic items were caused by use of drugs/alcohol or physical illness. Because clinical relevance of psychotic experiences may be difficult to diagnose by lay interviewers [13], and because the interviewers made no clinical judgment about participants' answers, the reported experiences may be considered an extension of "self-report."

A clinician performed follow-up telephone interview when participants reported a psychotic symptom to assess whether this symptom was a true PE using questions from the Structured Clinical Interview for DSM-IV. At baseline, a total of 1,081 participants (16.3%) endorsed at least one self-reported PE. Of these, 794 participated in clinical re-interview (73.5%), of whom 340 (42.8%) reported at least one clinician validated PE. At T1, 440 out of a total 5,303 (8.3%) participants reported that at least one self-reported PE had occurred since the previous interview. Of these, 367 (83.4%) participants were available for clinical re-interview, of whom 172 (46.9%) reported at least one clinician validated PE. At T2, 284 out of the total 4,618 (6.2%) participants reported at least one self-reported PE since the previous interview. Of these, 230 (81.0%) participants were available for clinical re-interview, of whom 135 (58.7%) reported at least one clinically validate PE. At T3, 222 out of the total 4,007 (5.5%) participants reported at least one self-reported PE since the previous interview. Of these, 207 (93.2%) participants were available for clinical re-interview, of which 77 (37.2%) reported at least one clinically validate PE. PE were dichotomized consistent with previous work in NEMESIS and NEMESIS-2 [14-16]. Presence of delusions was defined as having at least one delusion endorsed and presence of hallucinations was similarly defined.

Given similarities between (i) CIDI self-reported and clinician validated PE, (ii) CIDI ratings of primary and secondary psychotic experiences, and (iii) PE with and without distress, in terms of associations, predictive value and outcome [12, 17-19], CIDI self-reported PE, i.e. any rating of 'yes' for any of the 20 PE, were used in the analyses, thus increasing statistical power.

Working memory performance

The digit-span task, subtest of the Wechsler Adult Intelligence Scale (WAIS-III)[20], was performed by participants at T1 and T3. The digit-span task was split into two sections, a forward (six items) and backward (six items) task condition. The sum score at T1 and T3 was computed, and the average of these two values was considered as a person-level indicator of cognitive ability for all waves. In the analysis, a dichotomized variable was used, with cut-off at the 75th percentile, the highest value indicating poorer performance.

Jumping to conclusion bias

The "jumping to conclusions" bias (JTC bias) is a well-established finding in schizophrenia and is manifest, when performing the beads task, as a tendency to decide on the color of the jar after seeing only one or two beads. The presence or absence of a JTC bias was assessed at T2, utilizing the beads task. This is an experimental task aimed to measure individuals' reasoning style in ambiguous situations [21]. Participants were shown two jars containing red- and blue-coloured beads in opposite ratios. Similar to previous research, we used the more difficult version of the beads task with a colour ratio of 60:40 beads, to increase sensitivity to detect JTC bias in a general population sample [22]. Following previous work, JTC bias was defined as making a decision based on two or less bead [22]. JTC is typically considered more as a trait than a state [23, 24], therefore and in line with previous work [25], the number of beads drawn at T2 was considered constant trough the four waves and used as a person-level, time-invariant variable to T0, T1 and T3.

Family history

Family history was assessed as a person-level characteristic in two stages, as described previously [14]. First, for participants who screened positive for the following CIDI psychiatric diagnoses, presence of the disorder in direct relatives was assessed at each interview wave: alcohol/drug abuse/dependence, depression/dysthymia, mania, and anxiety disorders (panic disorder, social phobia, agoraphobia, generalized anxiety disorder). More than 40% of the sample thus screened family history positive at any of the waves. Second, at T1, self-reported parental history of "severe anxiety or phobias", "severe depression" and "delusions or hallucinations" were assessed in the entire sample: around 20% thus

screened positive. Using these two sources of information, the proportion of the sample in which family history could be assessed (hereafter: 'family history') was 94%, as described previously [14].

Childhood adversity

Childhood adversity was assessed at T0 using a questionnaire based on the NEMESIS trauma questionnaire [3]. Whenever a subject reported having experienced one of five types of childhood adversity before the age of 16 years [emotional neglect (not listened to, ignored, or unsupported), physical abuse (kicked, hit, bitten, or hurt with object or hot water), psychological abuse (yelled at, insulted, unjustly punished/treated, threatened, belittled, or blackmailed), peer victimization (bullying), and one time or more sexual abuse (any unwanted sexual experience)], they were asked to state how often it had occurred. The item 'sexual abuse' was rated on a scale of 1 (once) to 5 (very often), while all other items (namely, emotional neglect, physical abuse, psychological abuse, and peer victimization or bullying) were rated and on a scale of 1 (sometimes) to 4 (very often). Consistent with previous research, the childhood adversity score was dichotomized at the 80th percentile [26-28].

Cannabis use

Cannabis use was assessed with the section substance use disorders of the CIDI at each interview wave. If subjects reported cannabis use, they were rated on frequency of use in the period of most frequent use on a scale of 1 (never) to 7 (every day). Consistent with previous work [14, 15], a binary variable (absent = "0" and present = "1") was constructed by using the cut-off value of once per week or more in the period most frequent use.

Urbanicity

The degree of exposure to the urban environment until the age of 16 years, assessed at T0, was defined at five levels based on the Dutch classification of residence topography or population density: (1) countryside (distances to facilities is larger), (2) village (<25 000 inhabitants), (3) small city (25 000–50 000 inhabitants), (4) medium city (50 000–100 000 inhabitants), (5) large city (>100 000 inhabitants). Consistent with previous work, the cut-off of at least > 50 000 inhabitants was used to define the binary variable of urban area [29].

Hearing impairment

Hearing impairment was assessed during the face-to-face interview at all interview waves, by asking whether participants had experienced deafness or serious hearing impairment in the past 12 months. Ratings were yes (1) or no (0).

Social functioning

The evaluation of social functioning covered the past 4 weeks, and was assessed at each interview wave, applying a 2-item, 6-point subscale of the Medical Outcomes Study Short-form Health Survey (MOS SF-36)[30, 31], with a Cronbach's alpha of 0.78. Impaired social functioning includes issues in one's normal social activities as a result of somatic or emotional troubles. It was used as a binary variable in the analysis, dichotomized around the 75th percentile.

Service use for mental problems

As described elsewhere [32], any care received indicates at least one contact with informal care (alternative care providers, pastoral care, persons in one's close social network, self-help groups, telephone help lines, online care), general medical care (general practitioners, company doctors, social work, home care or district nurses, physiotherapists or haptonomists, medical specialists or other professionals working within this care sector) or mental health care (psychiatrists, psychologists, psychotherapists, addiction care). Service use was measured based on the service use section of NEMESIS [33] at each interview wave. A variable of receiving any mental health care was defined separately.

Perceived status gap

The *perceived status gap* was assessed at T1, T2 and T3 using two questions. First, the MacArthur Scale of Subjective Social Status [34] was used to rate subjective social status. In an easy pictorial format, it presents a "social ladder" with 10 levels and asks individuals to place an "X" on the rung on which they feel they stand. The second question was about a similar ladder, but this time with regard to the *desired* level of social status. The difference between the subjective desired and actual social status was used as independent variable in the analyses. The mean value of T1-T3 was used to replace missing values at T0. In the analyses, it was dichotomized around the perception of being more than one level below desired social status.

Adulthood stressful life events

Based on the "Brugha Life events section"[35], participants were asked at each interview whether they experienced one of 9 life events within the last 12 months. Examples of items are serious sickness, death of family member or close friend, and serious financial problems. A dichotomous exposure was created around at least one life event in the last year.

Genotyping procedures, quality control, imputation, and Polygenic Risk Score (PRS) calculation

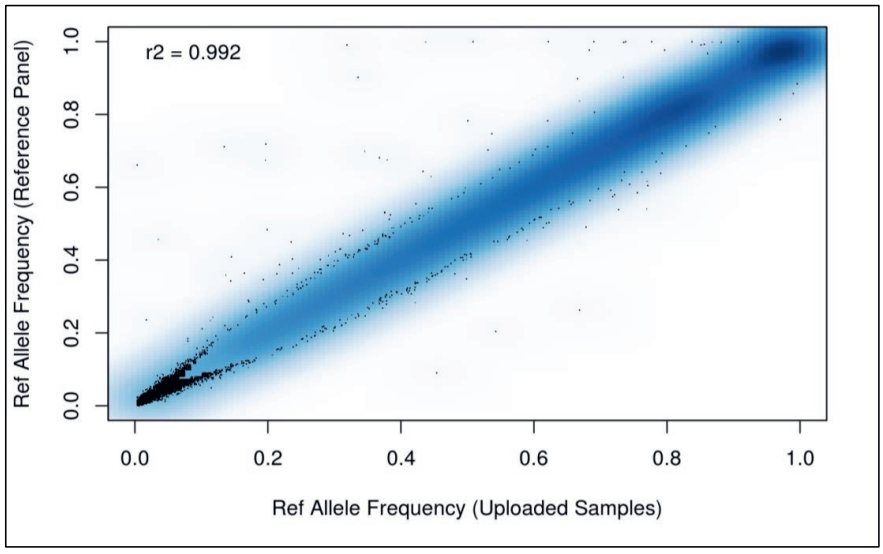
A. Target Genotype Data Processing

Genotyping procedures and quality control steps before imputation.

NEMESIS-2 samples were genotyped on an IPMCN chip (Institute of Psychological Medicine and Clinical Neurology, Cardiff University), which was custom-made for EUGEI (588,628 genotyped variants for 4,043 participants)[36]. Quality control (QC) was done using PLINK v1.9 [37] as follows**.** There were 3,861 samples matching with phenotypes. Single nucleotide polymorphisms (SNPs) and samples with call rates below 95% and 98%, respectively, were removed. A strict SNP QC only for subsequent sample QC steps was conducted. This involved a minor allele frequency (MAF) threshold > 10% and a Hardy-Weinberg equilibrium (HWE) *P*-value > 10^{-5}, followed by linkage disequilibrium (LD) based SNP pruning ($R^2 < 0.5$). This resulted in ~60K SNPs to assess sex errors (n=145), heterozygosity (F< 5xSD the standard deviation (SD), n= 73), and relatedness by pairwise identity by descent (IBD) values > 0.1 (n= 170). Genetic outliers (n=154) were identified by principal component analysis (PCA, see below). In total, 3,104 individuals passed these QC steps. After removing failing samples (n = 757), a regular SNP QC was performed (SNP call rate>95%, HWE p>1e-06, MAF> 0.16%; as the IPMCN chip contains many rare variants, half the SNPs would have been removed if we had applied MAF> 1%; therefore, we loosened MAF threshold to 0.16% =10/(2*sample size of 3,104)). Next, strand ambiguous SNPs and duplicate SNPs were removed, resulting in a total of 298,104 genotyped variants.

Imputation on Michigan server.

The QC-ed dataset was chunked by chromosome, and then converted into *.VCF files. The Michigan server was used for imputation with the following settings: reference panel as HRC R1.1 2016; phasing as Eagle v2.3; population as European; model as QC & imputation. The imputation resulted in 47,101,073 single nucleotide polymorphisms (SNPs). The general imputation quality is shown in supplementary figure 1.



Supplementary Figure 4.1. Correlation of SNPs MAF from NEMESIS-2 dataset with the reference MAF.

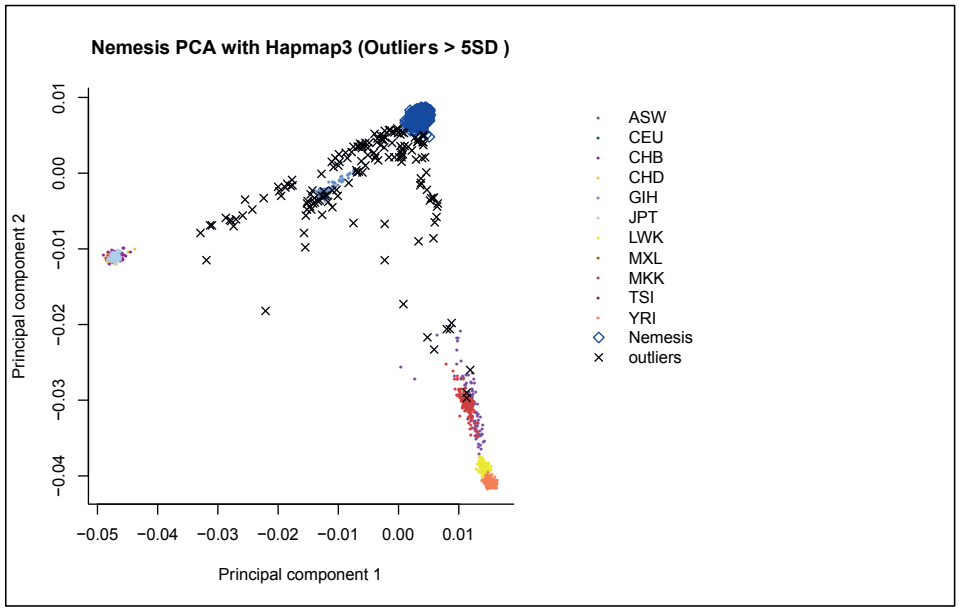
Quality control after imputation.

Poor quality SNPs were excluded: multi-allelic SNPs, SNPs with a minor allele frequency (MAF)<0.0016 or INFO<0.3, and strand ambiguous AT/CG SNPs. The VCF dosage files were converted into PLINK format dosage files. Finally, 10,356,437 SNPs and 3,104 individuals remained. For hard call (best guess) genotypes, an additional SNP QC (INFO>0.8 and HWE>10-6) was performed, resulting in 6,436,459 SNPs.

Principle components analyses (PCA)

The principal components (PCs) analyses within NEMESIS-2 samples, and NEMESIS-2 samples along with Hapmap3[38] populations were conducted by EIGENSTRAT[39]. A strict selection for SNPs with overlap with Hapmap3 SNPs was conducted: 1. MAF>0.05 and HWE>0.001; 2. Removal of 24 long LD regions (supplementary table 1); 3. LD pruning with an R^2 of 0.5; which resulted in 40,732 best quality genotyped SNPs used to calculate genetic PCs. PCs were firstly calculated with HapMap3 population to exclude European ethnic outliers: exceeding 5 times the standard deviation of Utah residents with Northern and Western European ancestry from the CEPH collection (CEU) and Toscani in Italia (TSI) populations for the first 2 PCs (supplementary figure 4.2)

The first 2 PCs explained > 84.3% of the total. In total, 141 individuals were excluded from this dataset. Secondly, another PCA was conducted using the same SNPs (n=40,732) but calculated only in NEMESIS-2. The first 2 PCs explained >30% of the total. Another 13 individuals were considered as ethnic outliers by the first 2 PCs exceeding 5 times the standard deviation in the NEMESIS-2 sample. In the end, 3,104 individuals remained. Compared with the self-report ethnic information, 93.75% of our ethnic-QCed samples are self-reported as "Dutch". We think some people may have understood the question as: "where were you born?", since non-former colony countries have 0 deviations from genetic QC, while former colonies have substantial deviations. In total, 154 samples were identified as European ethnic outliers and excluded. After post-imputation quality control steps, PCA was conducted using the same SNPs (n=40,732) within NEMESIS-2 samples (n=3,104). These PCs were then used as covariates in analyses to correct for population stratification.



Supplementary Figure 4.2. First 2PCs OF NEMESIS-2 samples with Hapmap 3 before exclusion of ethnic outliers.

Supplementary Table 1: The complex-LD regions (build GRCh37) removed for PCA analysis.

Chromosome	Base pair start	Base pair end
6	25392021	33392022
8	111930824	114930824
11	46043424	57243424
1	48287980	52287979
2	86088342	101041482
2	134666268	138166268
2	183174494	190174494
3	47524996	50024996
3	83417310	86917310
3	88917310	96017310
5	44464243	50464243
5	97972100	100472101
5	128972101	131972101
5	135472101	138472101
6	56892041	63942041
6	139958307	142458307
7	55225791	66555850
8	7962590	11962591
8	42880843	49837447
10	36959994	43679994
11	87860352	90860352
12	33108733	41713733
12	111037280	113537280
20	32536339	35066586

B. Training schizophrenia GWAS summary statistic processing and calculating polygenic risk score for schizophrenia

We used recent GWASs of schizophrenia [40] for PRS calculations [41]. As a quality control for PRS calculation, the SNPs that overlapped between the GWASs summary statistics (training datasets) and our dataset were extracted. Then, insertions or deletions, ambiguous SNPs, SNPs with minor allele frequency (MAF) <0.01 and imputation quality (R^2) < 0.8 in both training and target datasets were excluded. To account for complicated LD structure of SNPs in the genome, these SNPs were clumped in two rounds using PLINK 1.90b3z[42] according to previously established methods [43, 44]; round 1 with the default parameters (physical distance threshold 250kb and LD threshold (R^2) 0.5); round 2 with a physical distance threshold of 5,000kb and LD threshold (R^2) 0.2. Additionally, we excluded all SNPs in genomic

regions with strong or complex LD structures (e.g., the MHC region on chromosome 6; supplementary table 1). The odds ratios (ORs) were reported in the summary statistics and were log-converted to beta values as effect sizes. Sample overlap between NEMESIS-2 data with schizophrenia GWAS cohort (PCG and CLOZUK cohorts) is unlikely since all samples belong to different cohorts. We constructed PRS based on schizophrenia risk alleles weighted by their schizophrenia increasing effect estimate using the Purcell et al. method [37, 45], i.e. using PLINK's score function. PRS was calculated for 3,104 samples (those remaining after QC). Informed by the PGC analyses, PRS for schizophrenia with a significance cut-off $P < 0.05$ was used in the analyses to achieve a balance between the number of false-positive and true-positive risk alleles[46].

Supplementary Table 2: Comparison of frequencies of time-varying and fixed variables in analysis as a function of missing PRS data in the risk set.

	PRS data (n=9,339)	Missing PRS data (n=9776)	Total (n=19,115)
Young age group	0.16	0.16	0.16
Female sex	0.55	0.54	0.55
Perceived status gap	0.16	0.21	0.18
Low social functioning	0.31	0.34	0.33
Any care	0.12	0.12	0.12
Mental health care	0.06	0.07	0.06
Antipsychotic use	0.00	0.01	0.00
Cannabis use	0.02	0.02	0.02
Childhood adversity	0.18	0.18	0.18
Life events	0.47	0.47	0.47
Hearing impairment	0.03	0.02	0.03
Urbanicity	0.37	0.4	0.39
Family history	0.59	0.58	0.59
JTC bias	0.49	0.53	0.51
Altered digit symbol	0.28	0.3	0.29

Supplementary Table 3: Pattern of time-varying and time-constant exposures for PE-only and PE+NPD incidence analysis.

Exposure	PE-only incidence analysis			PE+NPD incidence analysis		
	Constant	Varying	Never missing	Constant	Varying	Never missing
Young age group	4600	330	4930	4589	341	4930
Female sex	4930	0	4930	4930	0	4930
Perceived status gap	3871	1059	4930	3838	1092	4930
Low social functioning	3088	1842	4929	3013	1917	4928
Any care	4042	888	4930	4013	917	4930
Mental health care	4413	517	4930	4411	519	4930
Antipsychotic use	4905	25	4930	4907	23	4930
Cannabis use	4850	14	4700	4851	11	4698
Childhood adversity	4930	0	4930	4930	0	4930
Life events	2217	2713	4930	2125	2805	4930
Ethnic minority	4930	0	4930	4930	0	4930
Hearing impairment	4930	0	4930	4930	0	4930
Urbanicity <16 yrs	4926	0	4926	4926	0	4926
Family history	4930	0	4930	4930	0	4930
PRS_{75}	2412	0	2412	2412	0	2412
JTC bias	4293	0	4293	4293	0	4293
Altered digit symbol	3595	0	3595	3595	0	3595

Supplementary Table 4: Person-year incidence rates for PE-only and PE+NPD as a function of absence (0) or presence (1) of binary risk factors

Binary exposure		PE-only					PE+NPD				
		n	Observations	Failures	Time	Incidence	n	Observations	Failures	Time	Incidence
Young age group	0	4425	11012	329	33215.7	0.99%	4436	11254	114	33948.2	0.34%
	1	835	1547	66	4682.5	1.41%	835	1577	28	4773.2	0.59%
Female sex	0	2238	5705	154	17183.6	0.90%	2238	5839	53	17588.1	0.30%
	1	2692	6854	241	20714.5	1.16%	2692	6992	89	21133.2	0.42%
Perceived status gap	0	4417	10170	287	30671.8	0.94%	4428	10403	68	31378.0	0.22%
	1	1572	2389	108	7226.3	1.49%	1594	2428	74	7343.3	1.01%
Low social functioning	0	4112	8372	231	25255.2	0.91%	4136	8559	34	25822.4	0.13%
	1	2660	4186	164	12639.8	1.30%	2711	4270	107	12892.8	0.83%
Any care	0	4699	11054	337	33335.8	1.01%	4698	11338	50	34194.6	0.15%
	1	1119	1505	58	4562.3	1.27%	1149	1493	92	4526.8	2.03%
Mental health care	0	4812	11745	368	35427.1	1.04%	4800	12030	82	36290.3	0.23%
	1	635	814	27	2471.0	1.09%	649	801	60	2431.1	2.47%
Antipsychotic use	0	4920	12507	391	37742.5	1.04%	4920	12786	135	38587.0	0.35%
	1	35	52	4	155.6	2.57%	33	45	7	134.3	5.21%
Cannabis use	0	4840	12158	379	36687.1	1.03%	4835	12432	121	37517.4	0.32%
	1	38	48	3	146.8	2.04%	38	46	5	140.3	3.56%
Childhood adversity	0	4039	10423	295	31435.8	0.94%	4039	10659	79	32150.2	0.25%
	1	891	2136	100	6462.3	1.55%	891	2172	63	6571.1	0.96%
Life events	0	3981	6773	185	20443.1	0.90%	4016	6897	47	20818.1	0.23%
	1	3662	5786	210	17455.0	1.20%	3719	5934	95	17903.2	0.53%
Ethnic minority	0	4584	11737	362	35407.4	1.02%	4584	12003	122	36211.3	0.34%
	1	346	822	33	2490.7	1.32%	346	828	20	2510.0	0.80%

Hearing impairment	0	4788	12200	373	36817.1	1.01%	4788	12448	134	37568.3	0.36%
	1	142	359	22	1081.0	2.04%	142	383	8	1153.0	0.69%
Urbanicity <16 yrs	0	3036	7704	258	23251.5	1.11%	3036	7918	73	23901.5	0.31%
	1	1890	4843	137	14611.0	0.94%	1890	4901	69	14784.2	0.47%
Family history	0	2193	5586	116	16846.3	0.69%	2193	5689	12	17157.5	0.07%
	1	2737	6973	279	21051.8	1.33%	2737	7142	130	21563.8	0.60%
PRS_{75}	0	1806	4709	151	14222.1	1.06%	1806	4843	33	14623.8	0.23%
	1	606	1577	40	4763.3	0.84%	606	1588	28	4797.5	0.58%
JTC bias	0	2098	5830	172	17563.0	0.98%	2098	5957	55	17946.0	0.31%
	1	2195	6055	195	18264.4	1.07%	2195	6196	75	18692.5	0.40%
Altered digit symbol	0	2559	7454	188	22451.0	0.84%	2559	7610	54	22924.2	0.24%
	1	1036	2965	116	8930.3	1.30%	1036	3043	45	9166.5	0.49%

Supplementary Table 4.5: Sensitivity analysis of differential associations of incident Psychotic Experiences (PE), alone (PE-only) and in the context of Non-Psychotic Disorder (PE+NPD), with demographic, clinical, aetiological, and cognitive factors, with more exclusive risk set (all individuals with PE at baseline excluded)

Binary exposure	PE-only				PE+NPD			
	HR*	95% CI		p	HR	95% CI		p
Young age group	1.45	1.06	1.99	0.019	2.40	1.48	3.88	0.000
Female sex	1.30	1.03	1.64	0.028	1.33	0.88	2.01	0.171
Perceived status gap	1.74	1.35	2.25	0.000	5.60	3.74	8.37	0.000
Low social functioning	1.49	1.18	1.88	0.001	6.84	4.25	11.02	0.000
Any care	1.22	0.87	1.70	0.252	10.85	7.24	16.25	0.000
Mental health care	0.92	0.56	1.50	0.726	10.92	7.27	16.42	0.000
Antipsychotic use	1.16	0.16	8.30	0.879	19.85	7.26	54.25	0.000
Cannabis use	1.98	0.49	7.97	0.335	14.60	5.34	39.92	0.000
Childhood adversity	1.41	1.07	1.87	0.016	3.22	2.13	4.86	0.000
Life events	1.20	0.96	1.51	0.115	2.47	1.61	3.79	0.000
Ethnic minority	1.29	0.85	1.95	0.237	2.08	1.14	3.81	0.017
Hearing impairment	2.25	1.40	3.63	0.001	2.17	0.95	4.97	0.066
Urbanicity <16 yrs	0.82	0.65	1.05	0.110	1.21	0.81	1.81	0.359
Family history	1.92	1.50	2.46	0.000	7.30	3.79	14.05	0.000
PRS_{75}	0.87	0.58	1.32	0.520	2.05	1.10	3.84	0.025
JTC bias	1.07	0.85	1.36	0.557	1.25	0.82	1.90	0.302
Altered digit symbol	1.60	1.23	2.10	0.001	1.94	1.21	3.12	0.006

HR = hazard ratio, 95% CI = 95% confidence interval

Young age group: aged 18-35 years; Perceived status gap: difference between actual and desired social position; Low social functioning: SF36 social functioning 75th percentile cut-off; Any care: any informal, medical or mental health care for mental problems or addiction; Cannabis use: once per week or more in the period most frequent use; Childhood adversity: 80th percentile cut-off continuous adversity score before age 16 years; Life events: at least one life event in the last year; Minority: Moroccan, Turkish, Surinamese, Antillean, Indonesian or other non-western ethnic group; Hearing impairment: T0 deafness or serious hearing impairment in the past 12 months; Urbanicity 2 highest levels of 5-level urbanicity classification before age 16 years; Family history: family history mental disorder; PRS_{75}: schizophrenia polygenic risk score 75th percentile cut-off; JTC: beads task decision 2 or less beads; Altered digit symbol: cut-off 75th percentile continuous score. # = zero cells; HR significantly greater in PE+NPD group compared to PE-only group, based on non-overlapping confidence intervals; HR significant in PE+NPD group but not in PE-only group.

Supplementary Table 4.6: Sensitivity analysis of differential associations of incident Psychotic Experiences (PE), alone (PE-only) and in the context of Non-Psychotic Disorder (PE+NPD), with continuous measures of exposure instead of dichotomization around the xth percentile.

Binary exposure	PE-only				PE+NPD			
	HR*	95% CI		p	HR	95% CI		p
Low social functioning	1.40	1.15	1.71	0.001	6.21	4.22	9.14	0.000
Childhood adversity	1.24	1.14	1.35	0.000	1.61	1.47	1.77	0.000
PRS	0.99	0.95	1.02	0.393	1.14	1.07	1.21	0.000
Digit symbol score	0.93	0.90	0.96	0.000	0.89	0.83	0.94	0.000

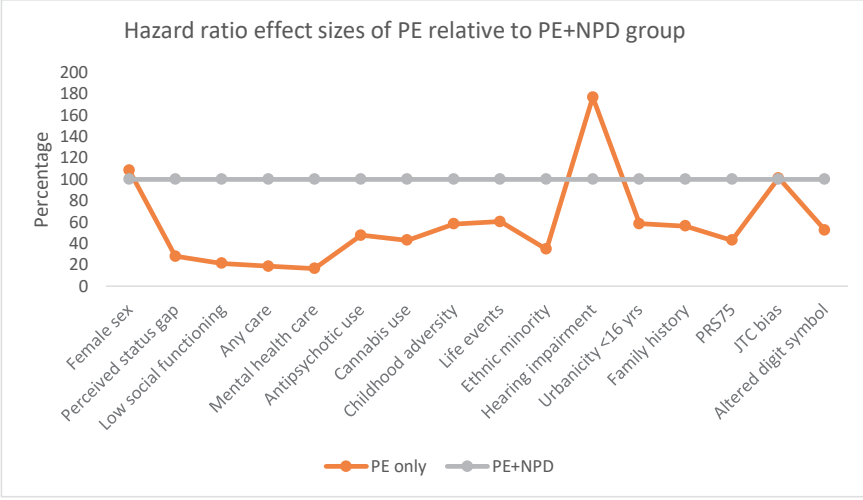
HR = hazard ratio, 95% CI = 95% confidence interval

Low social functioning: SF36 social functioning; Childhood adversity: Continuous adversity score before age 16 years; PRS: Schizophrenia polygenic risk score; Digit symbol score: continuous score.

HR significantly greater in PE+NPD group compared to PE-only group, based on non-overlapping confidence intervals

Sensitivity analysis in individuals aged 18-35 years at baseline.

Sensitivity analyses restricted to individuals aged 18-35 at baseline (n=1439, 26%) revealed a very similar pattern of results (supplementary figure 4.3).



Supplementary Figure 4.3. Hazard ratio (HR) effect sizes of binary clinical, demographic, etiological and cognitive factors in PE-only group relative to effect sizes of PE+NPD group (set at 100%, grey line), sample confined to those aged 18-35 years at baseline.

Perceived status gap: difference between actual and desired social position; Low social functioning: SF36 social functioning 75th percentile cut-off; Any care: any informal, medical or mental health care for mental problems or addiction; Cannabis use: once per week or more in the period most frequent use; Childhood adversity: 80th percentile cut-off continuous adversity score before age 16 years; Life events: at least one life event in the last year; Minority: Moroccan, Turkish, Surinamese, Antillean, Indonesian or other non-western ethnic group; Hearing impairment: T0 deafness or serious hearing impairment in the past 12 months; Urbanicity 2 highest levels of 5-level urbanicity classification before age 16 years; Family history: family history mental disorder; PRS_{75}: schizophrenia polygenic risk score 75th percentile cut-off; JTC: beads task decision 2 or less beads; Altered digit symbol: cut-off 75th percentile continuous score.

Supplementary Table 7. Sensitivity analyses of association between PRS, modelled as continuous quartile-group variable, and incidence of PE+NPD phenotype, showing dose-response relationship and significant linear trend. HR = hazard ratio. 95% CI = 95% confidence interval; p = p-value; 1* = reference category

PRS Quartile groups	PE+NPD				
		HR	95% CI		p
1*	1*				
2	2	1.15	0.42	3.18	0.783
3	3	2.60	1.09	6.24	0.032
4	4	4.10	1.79	9.39	0.001
HR linear trend		1.69	1.31	2.16	0.000

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Chapter 5

An n= 1 clinical network analysis of symptoms and treatment in psychosis

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Abstract

Introduction

Dynamic relationships between the symptoms of psychosis can be shown in individual net- works of psychopathology. In a single patient, data collected with the Experience Sampling Method (ESM–a method to construct intensive time series of experience and context) can be used to study lagged associations between symptoms in relation to illness severity and pharmacological treatment.

Method

The patient completed, over the course of 1 year, for 4 days per week, 10 daily assessments scheduled randomly between 10 minutes and 3 hours apart. Five a priori selected symptoms were analysed: 'hearing voices', 'down', 'relaxed', 'paranoia' and 'loss of control'. Regression analysis was performed including current level of one symptom as the dependent variable and all symptoms at the previous assessment (lag) as the independent variables. Resulting regression coefficients were printed in graphs representing a network of symptoms. Network graphs were generated for different levels of severity: stable, impending relapse and full relapse.

Results

ESM data showed that symptoms varied intensely from moment to moment. Network representations showed meaningful relations between symptoms, e.g., 'down' and 'paranoia' fuelling each other, and 'paranoia' negatively impacting 'relaxed'. During relapse, symptom levels as well as the level of clustering between symptoms markedly increased, indicating qualitative changes in the network. While 'hearing voices' was the most prominent symptom subjectively, the data suggested that a strategic focus on 'paranoia', as the most central symptom, had the potential to bring about changes affecting the whole network.

Conclusion

Construction of intensive ESM time series in a single patient is feasible and informative, particularly if represented as a network, showing both quantitative and qualitative changes as a function of relapse.

5.1 Introduction

The symptoms of mental illness have been represented as categories, dimensions and, more recently, mutually impacting states in a psychopathology network[1-3]. However, network models of psychopathology are difficult to study, as typical cross-sectional assessments of symptoms are not suitable to assess dynamic relationships between symptoms. Therefore, network models will profit from more fine-grained measures of psychopathology, represented as an intensive time series of experience and context, collected in the flow of daily life[4]. The assessment of symptoms as an intensive time series, randomly sampling experiences multiple times a day for a period, using the Experience Sampling Method (ESM), has become available for use in mental health practice, including psychosis[5, 6]. In this fashion, a unique dataset, allowing detailed ecologically valid examination of symptom interactions over time, can be collected at the level of the individual patient. ESM helps patients and professionals to gain insight in how symptoms impact on each other, and how treatments affect this pattern of dynamic interactions[7, 8]. As the number of connections between symptoms can become unmanageable, a focus on a priori selected key symptoms is required. Studies have shown that ESM symptom connections can be studied in relation to illness severity and clinical needs [9, 10], and can be represented by network graphs [11]. While ESM studies usually collect data for around 6 days, a more extended period is required for the monitoring of treatment effects[12].

Aim

We present ESM data, representing an intensive time series of symptoms and context, in a single patient over a relatively protracted period (one year). Together with the patient, an a priori selected subset of symptoms was explored; 'down', 'relaxed', 'paranoia', 'loss of control' and 'hearing voices'. The following questions were studied: (i) is it possible for a patient with a psychotic disorder to use ESM as a feedback tool for a year; (ii) to what degree do a priori selected symptoms co-occur and co-vary over the year; (iii) does the strength of the connections between symptoms depend on the within-person variation of illness severity? Given the focus on a single patient, no group-based hypotheses can be tested–the analyses presented are valid for a single patient. This study, however, also serves as proof-of-concept with implications for all patients treated for a mental disorder.

Case Description

Miss A has been in treatment for severe psychotic experiences for twenty years. She is rarely free of symptoms, but their severity varies considerably over time. Variation in symptoms impacts her well-being, particularly when she relapses into a state in which symptoms are at their most severe. Psychopathology includes imperative hallucinations, paranoid delusions, and low mood. Despite these challenges, she manages quite well, living independently and with a stable social network. She is a trained artist (painter) and passed her exams with distinction. In the last few years, she has taken up her profession as an artist again, making photographs and paintings, selling some of her work at expositions.

Her case manager visits her once a week; she has monthly appointments with the psychiatrist. In the late 1980s, she was admitted to a mental hospital with a first psychotic episode, followed by a long-term residential treatment programme. During this period, she attempted suicide several times. Ultimately, she became determined to reach the goal of independent living. This, and possibly a change in medication (clozapine) contributed to her personal recovery despite continuing psychopathology. Miss A used several antipsychotics, mood stabilisers, antidepressants, and benzodiazepines. Since the start of clozapine (about 14 years ago), a gradual but slow reduction of some other psychotropic medications became possible. She thus took the lead in the gradual discontinuation of benzodiazepines and promethazine, which was prescribed for insomnia and anxiety. She gradually learned to apply coping strategies to better deal with her symptoms. Over the last 10 years, she and her psychiatrist agreed on a degree of self-management of the clozapine dose, allowing her to increase the dosage with 50 or 100 mg/day for a certain period in case of an impending relapse or a full relapse of her psychopathology, characterized by respectively a marked (100 mg increase) or moderate (50 mg increase) increase in symptom severity. She had found that with a temporary increase in the clozapine dose, symptoms would soon go down to the level where they were more manageable. As soon as she felt better, she would reduce the medication to the maintenance dose of 350 mg. In the last 4 years, Miss A had developed obesity and diabetes mellitus type 2 related to clozapine use. During the ESM assessment period, Miss A was prescribed the following drugs: sulpiride 800 mg/day, clozapine 350 mg/day (with increases of 50 or 100mg as required), citalopram 20 mg / day, metformin 850 mg/day, omeprazole 40 mg/day and simvastatin 40 mg/day. According to Miss A, her mother had experienced symptoms of psychosis too. She does not know her biological father. Miss A was raised by her mother's sister, described as a callous woman, with whom she felt permanently unsafe. She describes a 'Cinderella' position in the family, her nieces being favoured whilst her needs were neglected. Her aunt passed away about 10 years ago. Miss A hears voices, most often her aunt, giving negative feedback, telling her she is not good or urging her to commit suicide. Her self-esteem is low, as is her basic trust, resulting in periods of paranoia and low mood. Miss A experiences daily life events as stressful with ensuing feelings of exhaustion, doubt, loss of control and increased severity of hallucinations and paranoia. Although there is awareness of these vulnerabilities and recurrent sequences of events, she can neither predict nor control the fluctuations in intensity and severity. Miss A and her psychiatrist agreed to monitor her symptoms, and fluctuations thereof, over an extended period, using ESM, given user-reported evidence that intensive monitoring may help to gain control and achieve better adjustment[13,14].

Method

Subject

The patient was Miss A, aged 46 years and diagnosed with schizophrenia, paranoid type, according to DSM-IV[15].

Informed consent

The study was approved by the IRB of the Institute for Mental health Care Eindhoven and De Kempen (GGZE), Eindhoven, The Netherlands. The patient received oral and written information on the planned use of the data she collected, and she signed an informed consent form. The duration of the study was for as long as the patient thought the self-monitoring procedure was helpful.

ESM procedure

ESM is a random time-sampling self-assessment technique. The subject is signalled by a device ten times a day at random moments between 7.30 AM and 10.30 PM. Details on the choice of number of beeps per day and the choice of random time sampling are discussed elsewhere[16]. After each signal (a beep), the subject is asked to answer questions on current psychopathology like mood, convictions, or hallucinations, as well as on context and appraisal of the present situation, using a mobile device. Subjects have 5 minutes to answers the question, as research has shown that larger lags impact validity[5]. Miss A used the device 4 days per week for around 12 months. Questions were in Dutch. ESM was usually done on the Monday, Wednesday, Friday, and Saturday, although sometimes other days were used if this was more convenient.

Assessment of psychopathology with ESM

ESM assesses experience and context with various items rated on 7-point Likert scales ('1' not at all to '7' very). Some items index psychotic psychopathology, for example, "I hear voices", as validated previously[5, 17-19]. Other items reflect positive affect or negative affect. For the present analyses, the following psychosis-related ESM items were used in the analyses: 'I hear voices', 'I feel suspicious' and 'I feel I am losing control', as these were most important for the patient. In addition, two affective items, reflecting opposite poles, were selected: 'I feel down', and 'I feel relaxed'.

Full relapse and impending relapse

'Full relapse' was defined as the collaborative decision to increase the clozapine dose to 450 mg/day. The decision to increase the dose to 400 mg/day because of a moderate increase in symptom severity will hereafter be referred to as 'impending relapse'. Medication was reduced to the maintenance dose of 350 mg/day as soon as Miss A felt her symptoms were less prominent and more manageable (hereafter: stable state).

Statistical Analysis

Statistical analyses and graphical representations were performed using Microsoft Excel 2010, Stata 13 [20]20, 21] and R[21]. First, we plotted mean daily severity levels of 'hearing voices', 'loss of control', 'paranoia' and mood ('down' and 'relaxed') to assess variation over time. Second, we generated network graphs, stratified by level of severity (stable state, impending relapse, and full relapse). Then

we analysed five linear regression models with 'down', 'loss of control', 'paranoia', 'hearing voices', and 'relaxed' as dependent variables. Independent variables, for all models, were the lag (t-1) of the same 5 variables. One example of a regression model is:

Down = B0 + B1 * lag down + B2 * lag loss of control + B3 * lag paranoia + B4 * lag hearing voices + B5 * lag relaxed + time + e.

In this model, time is used to detrend the analyses[22]. As opposed to most analyses, all data pertain to a single subject. Therefore, data do not have a multilevel structure and can be analysed with standard linear regression techniques.

Using the qgraph command in R[23], each network graph included 25 regression coefficients obtained from the regression analyses above. Thus, the 25 regression coefficients express the strength of the connections. In addition, Excel and the qgraph package were used to calculate indices of centrality, to compare the strengths of the networks across the three states (stable, impending relapse, full relapse) in a descriptive fashion [24]. The outward strength is the sum of the connections from a specific node to all other nodes. The inward strength is the sum of the connections from all nodes to a specific node. Node strength is the sum of the inward strength and the outward strength[25]. In weighted directed networks, the inclusion of the self-loop (e.g., slope between 'down' at t-1 and 'down' at t) is crucial. As the self-loop therefore was included in both the inward and the outward strength, the self-loop was included twice in the node strength. Closeness centrality indicates how close a specific node is to the other nodes; it is defined as the inverse sum of the shortest distances to all other nodes from a specific node[26]. A closeness-central symptom is one that most likely affects other symptoms[27]. Betweenness centrality is a measure of the number of shortest paths that passes the node, and it indicates the global influence of the node throughout the network[3]. For all centrality measures, stronger values indicate stronger connections. More detailed information on centrality indices can be found elsewhere[26].

Results

Feasibility of long-term ESM as a treatment tool

Miss A used the device for a year. She answered 943 beeps at 201 selected days (mean 4.7 beeps per day, sd = 1.49, range 1–9); that is 47% of all beeps on the selected days. Although questions were completed at 943 beeps, there were some partial missing data. Taking these into account resulted in a mean of 939 completed data points for the different ESM variables.

Symptom level and day-level variation

During the ESM year, there were 4 full relapses (mean 17.3 days, range 4–25) and 2 impending relapses (mean 19.0 days, range 7–31). Symptom levels were progressively greater across the impending relapse and full relapse states (Table 5.1). Generally, Miss A rated 'hearing voices' higher than 'paranoia',

'down' and 'loss of control' (Table 5.1). When inspecting day-level symptoms visually (figure 5.1), 'hearing voices' varied considerably from maximum to moderately severe levels. However, day-level standard deviations of the symptoms did not differ significantly across the three states. High levels of 'down' and low levels of 'relaxed' co-varied together, and vice-versa. In addition, levels of 'down' and 'paranoia' appeared to similarly co-vary. Generally, 'loss of control' was low. How- ever, during periods of impending relapse, levels of 'loss of control' increased.

Table 5.1. Descriptives stratified by proxies of levels of severity (all range 1-7)

	stable state, n=662		***impending relapse***, n=158		***full relapse***, n=119	
	mean	sd	Mean	Sd	Mean	sd
Down	2.13	1.57	1.96	1.60	2.64	1.78[1]
Loss of control	1.60	1.43	1.40	1.19	2.06	1.83[1]
Paranoia	2.76	2.01	2.53	1.93	2.95	2.08
Hearing voices	5.00	1.59	4.71[2]	1.59	4.78	1.63
Relaxed	4.05	1.41	4.01	1.32	3.54	1.30[1]

[1] In full relapse state, down and loss of control are significantly higher than in the stable state, whilst relaxed mood is significantly lower. [2] In the impending relapse state, hearing voices is significantly lower than in the stable state.

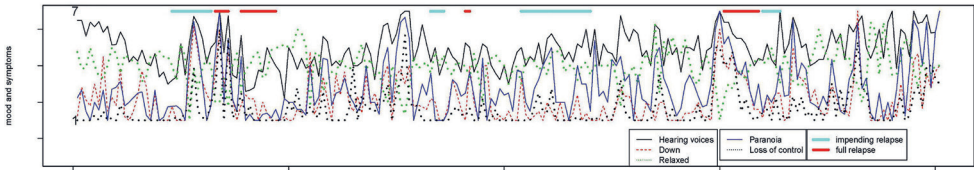

Figure 5.1: Variation in hearing voices, down, paranoia, loss of control and relaxed mood (range 1-7) during a year.

Symptom Networks

In the stable state, visual inspection showed a two-sided positive loop between 'down' and 'paranoia' (Fig 5.2, Fig 2.3, and Fig 5.4), indicating that these two symptoms mutually reinforced each other. In addition, a two-sided negative loop between 'relaxed' and 'paranoia' was visible (mutual reduction).

'Hearing voices' was only weakly connected with the other four symptoms; only 'relaxed' was moderately negatively connected with 'hearing voices' (B = -0.16). Finally, 'down' had a moderately (B = 0.21) positive connection with 'loss of control'. In the full relapse state, the strength of most connections increased (Fig 5.2, Fig 2.3, Fig 5.4, and Table 5.2). For example, the two-sided negative loop between 'relaxed' and 'paranoia' increased. The connection between 'down' and 'paranoia' was weaker, but the positive connection between 'paranoia' and both 'hearing voices' and 'loss of control' increased. In the full relapse state, 'paranoia' becomes the central node of the network. Although average levels of 'hearing voices' were relatively high, centrality indices for 'hearing voices' were relatively low (table 5.2). In general, node strength increased across the impending and full relapse state and 'paranoia' showed a more central role. In impending relapse and full relapse state, connections between 'paranoia' and all other symptoms became stronger (outward degree of 'paranoia', inward degree of the other symptoms).

Table 5.2. Centrality indices per psychopathological symptom in the networks in each of the three strata of severity

	Between-ness	Closeness	Inward degree	Outward degree	Node strength
Stable state					
Down	5	0.032	0.78	0.92	1.70
Loss of control	0	0.015	0.45	0.31	0.76
Paranoia	4	0.026	0.87	0.62	1.48
Hearing Voices	0	0.015	0.51	0.39	0.90
Relaxed	1	0.036	0.61	0.98	1.59
Impending relapse					
Down	2	0.056	0.74	1.07	1.81
Loss of control	0	0.040	0.51	0.64	1.15
Paranoia	7	0.058	1.16	1.34	2.49
Hearing Voices	0	0.026	0.90	0.35	1.25
Relaxed	0	0.039	1.05	0.95	2.00
Full Relapse state					
Down	1	0.025	1.08	0.72	1.80
Loss of control	3	0.027	1.12	0.44	1.56
Paranoia	7	0.109	1.04	2.18	3.22
Hearing Voices	0	0.050	0.95	0.95	1.90
Relaxed	0	0.041	0.69	0.59	1.28

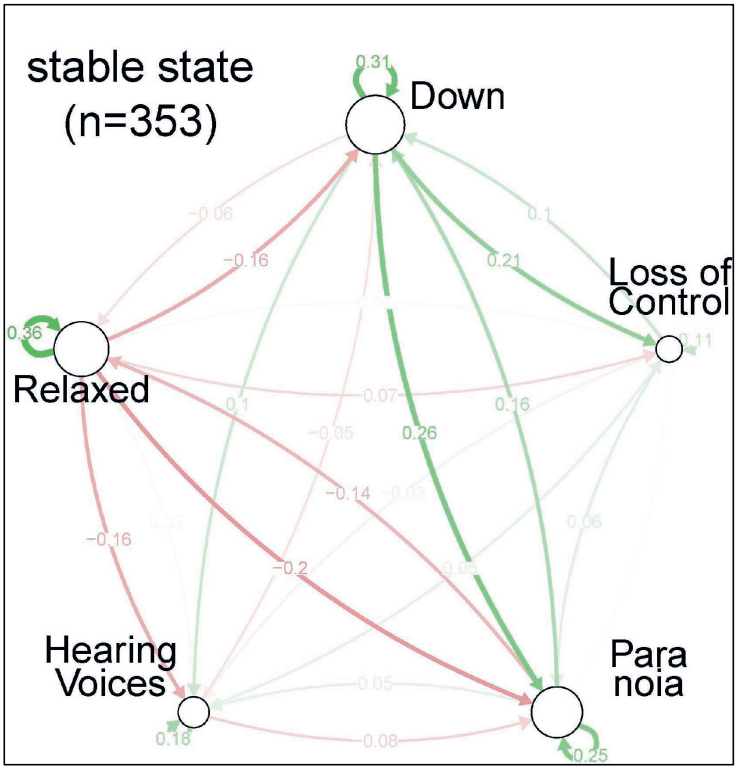

Figure 5.2: Network graph of five psychopathology items in the stable state. In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, there is an arrow from '*Dwn*' to '*Loss of control*', meaning that '*Dwn*' at t−1 predicts '*Loss of control*' at t with a B coefficient of 0.21. Green arrows represent positive associations, and red arrows represent negative associations. The size of the nodes represents centrality of the node (node strength).

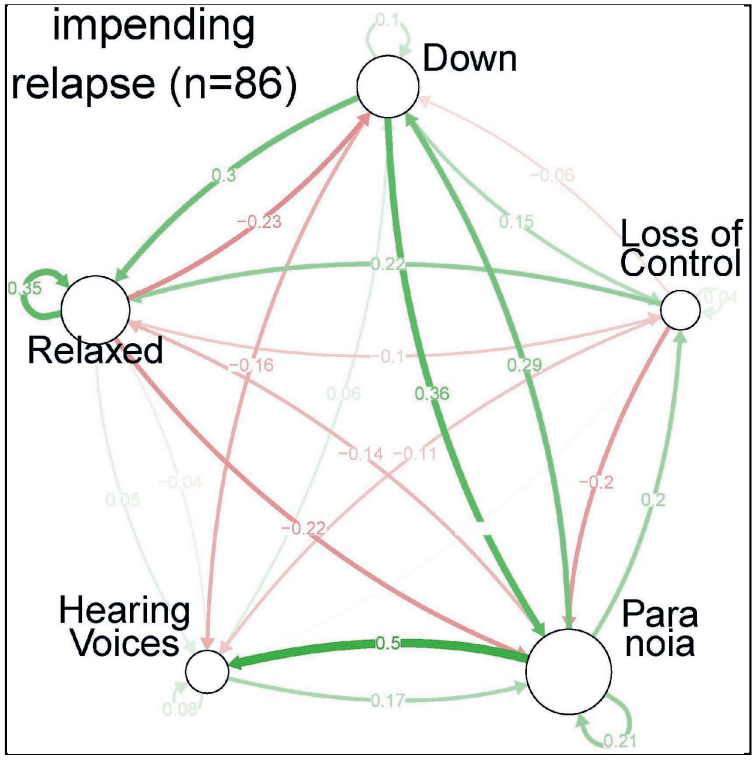

Figure 5.3: Network graph of five psychopathology items in the impending state. In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, there is an arrow from '*Dwn*' to '*Loss of control*', meaning that '*Dwn*' at t−1 predicts '*Loss of control*' at t with a B coefficient of 0.15. Green arrows represent positive associations, and red arrows represent negative associations. The size of the nodes represents centrality of the node (node strength).

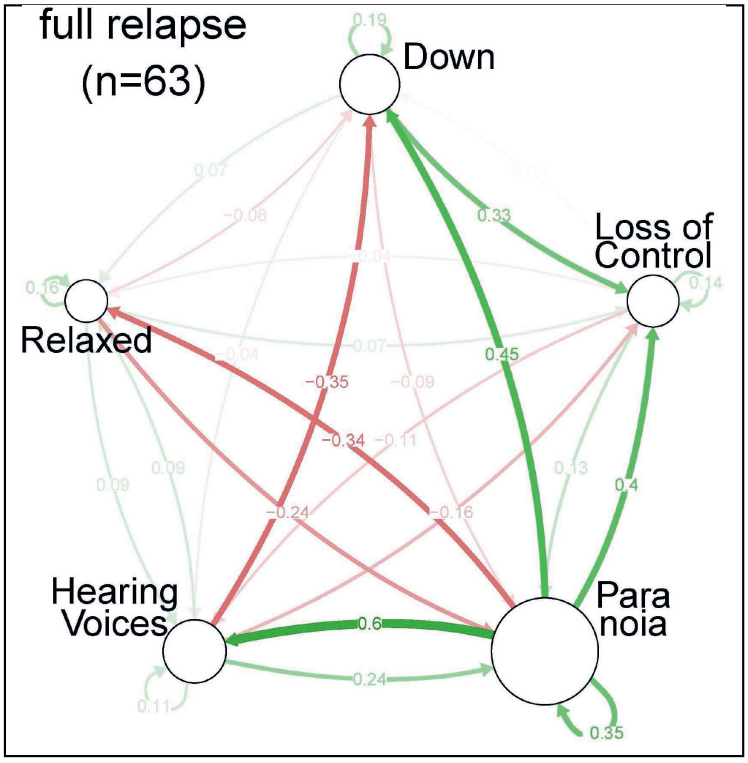

Figure 5.4: Network graph of five psychopathology items in the full relapse state.
In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, there is an arrow from '*Dwn*' to '*Loss of control*', meaning that '*Dwn*' at t−1 predicts '*Loss of control*' at t with a B coefficient of 0.33. Green arrows represent positive associations, and red arrows represent negative associations. The size of the nodes represents centrality of the node (node strength).

Discussion

ESM in the clinical n = 1 situation appears to be feasible for a relatively long period of time. ESM data showed that symptoms varied intensely from moment to moment and that during subjectively defined relapse states, symptom levels as well as clustering of symptoms increased. Finally, in the most severe state, connections between symptoms increased to the degree that the patterns that were present during the stable state were no longer apparent, indicating qualitative changes in the network. The most severe symptom was not necessarily the most central in terms of network dynamics, as discussed below.

ESM in treatment

Long term ESM assessment in a single patient was feasible and useful, yielding recognisable patterns of clinically relevant symptom interactions. Although only 47% of all potential beeps were rated, both patient and psychiatrist found the reported variability and clustering useful and interpretable.

Visualisation of these patterns and connections provided additional information for both patient and psychiatrist. The information included daily variation in symptoms and impact of context or treatment on changes in symptoms over time. Earlier studies suggested that ESM is an appealing tool for the evaluation of medication effects, helping to fine-tune dosing[7, 13, 28-30]. The current study confirmed this pattern from a network and self-management perspective. ESM is less biased by mood, attention and memory problems that frequently occur in patients with psychotic symptoms, given the fact that it requires rating in the moment without retrospection[31]. Therefore, not only for Miss A but also for other patients, a more accurate and personalised treatment plan may be developed using prolonged ESM assessment including momentary variation of psychopathology[6]. The data suggest that clinical network analysis yields insights about underlying symptom-symptom and symptom- context dynamics–beyond the usual severity scores–that are useful to both patient and clinician[4]. In addition, clinical network analysis can be used to uniquely assess the impact of pharmacological and non-pharmacological treatment at the level of how symptoms impact on each other. Clinical network analysis thus may be useful when starting medication, changing medication or when tapering off medication[13, 30, 32]. In addition, empowering the patient to collect his own diagnostic and treatment evaluation data aids shared decision-making in clinical practice and enhances 'ownership' of the clinical process. This may result in reduced medication use and less unwanted side effects. Discussing ESM results with a patient offers clues as to why and when symptoms vary, given certain stressors and contexts, with clues for protective mechanisms or coping strategies [33].

Symptom variability

During the one-year follow-up, the 5 a priori selected symptoms varied considerably. Visual inspection of Fig 5.1 showed stronger fluctuations of 'hearing voices', 'paranoia' and 'down' in periods of impending relapse and full relapse. In a previous report, increased levels of symptom severity were associated with the subjective sensation of 'loss of control' at the group level [34]. Miss A's choice to increase clozapine dosage may reflect periods of more psychopathology, in terms of severity or impact on daily life, resulting in a subjective feeling of loss of control. She learned over time that a temporary increase in clozapine dosage helps her to regain control.

Network analysis

During the stable state, 'down' and 'paranoia' were most strongly interconnected. Virtually all connections grew stronger in the impending relapse and full relapse state. This suggested that in relapse states, symptoms were more connected, as observed previously in other samples[19]. Centrality indices showed a shift towards 'paranoia' and to a lesser extent 'hearing voices', during relapse. Betweenness underlined the crucial role of paranoia in the network, whereas 'hearing voices' had a less important central role. These data suggest that while 'hearing voices' is the most prominent symptom subjectively (table 5.1); a strategic focus on 'paranoia' may bring about changes that affect other symptoms in the network (table 5.2). However, this type of clinical reasoning will only hold if one assumes that

connections between symptoms reflect causal relationships, which is uncertain. While two symptoms may impact on each other causally, their connections may also reflect a higher order alteration driving variation in both. The impending relapse state showed symptom connection strengths that were in between those observed in the stable and the full relapse state, validating the changes in medication dose that formed the basis for the definition of full relapse and impending relapse. In the impending relapse state, centrality indices were comparable to those in the full relapse state. Similarly, 'paranoia' was the most central symptom although less prominently than in the full relapse state. The data additionally suggest that patients can self-manage and self-monitor their medication use, within certain boundaries. This agrees with emerging evidence in other areas in medicine[35]. In addition, the increased level of clustering of symptoms during relapse suggests that greater levels of clustering of these symptoms are indicative of clinical need and dysfunction, as shown previously[9].

Binary diagnosis in relation to network analysis

The notion that mental disorders are dichotomous unidimensional entities defined by a set of criteria may be incomplete. Correlated symptoms are distributed over a continuum of severity; not all persons with some degree of expression of an extended phenotype meeting diagnostic criteria[25,36]. Given strong trans diagnostic correlations between symptoms, classification of mental symptoms into mental diagnoses results in a considerable overlap between psychiatric diagnoses at various levels[37]. Network analysis of extended phenotypic expression of symptoms may confer added validity to representations of mental disorder[3, 4, 38]. In addition, network analysis shows that symptoms cluster into patterns[25, 26,38-40]. Cross-sectional network analysis can be seen as an improved factor analysis or principal component analysis, visualising connections between symptoms two-dimensionally[3]. The present paper, in agreement with previous work[25, 26] generated networks including a time component with ESM data, provides a solution for the problem of temporal under-sampling of psychopathology in cross-sectional network analysis. ESM has the advantage of building intensive time series of experiences as emerging in the flow of daily life, which is not the case in the model using cross-sectional measures of psychopathology based on retrospection and interpretation[38]. Despite studying a limited set of symptoms, the present analysis including the time factor shows that networks are dynamic; the clustering of symptoms changes depending on external factors. Network analysis, therefore, can complement the practice of categorical classification.

Methodological issues

To our knowledge, this is the first study to use long-term ESM data collected in a single patient with a psychotic disorder, showing real life fluctuations in symptoms and the impact of symptom severity. MB is treating psychiatrist of Miss A. MB and Miss A discussed the raw data four times during the period of data collection. When interpreting the results, some limitations must be considered. First, generalizability in the strict sense is limited. The graphs in the present paper are specific for this patient.

On the other hand, the present results did show these graphs yield information that is interpretable and useful–and as such may be considered generalizable. Each patient has unique characteristics, and we believe that more attention to personal symptom variation and patterns of connectivity is helpful in developing a personalized treatment plan. In addition, the present results can be replicated in other patients with the same diagnosis, allowing for meta-analytic identification of group effects. Second, although Miss A used the ESM device for about a year, it was used only four days a week. ESM data covered a period of 201 days, collected over a period of one year. Thus, hypo- thetically, the data could have included a maximum of 2010 beeps with completed data. Instead, Miss A filled in questions at 943 beeps, which, considering partial missing data, resulted in a mean of 939 completed data points for the different ESM variables. When completing an ESM time series, it is unavoidable that the person misses beeps, regardless of the presence of mental illness [16]. Missing beeps may be unavoidable, for example in the morning when the participant is asleep or in the afternoon when the participant is taking a nap[41, 42]. The ESM sampling frame therefore oversamples up to 10 times per day to compensate. Furthermore, a higher proportion of missing beeps in the present paper may be expected given that the patient was diagnosed with psychotic disorder and used ESM for nearly a year. Previous work on ESM in patients with psychotic disorder has established that validity is preserved if at least 30% of beeps are completed[6]. Previous work on ESM in patients with psychotic dis- order has established that validity is preserved if at least 30% of beeps are completed [6]. There- fore, the fact that less than 50% of beeps were completed is unlikely to affect the validity of the results. Nevertheless, the information obtained was substantial. In addition, the number of valid beeps per day only slightly differs across stable (4.7; range 1–8), impending relapse (4.4 range 1–9) and full relapse states (5.0; range 2–8; $F = 1.08$, $p = 0.34$). This suggests that data are not biased because of oversampling or under sampling during periods of relapse. Third, although regression analysis is the tool to generate networks[26], results can be instable in the sense that multiple models with different coefficients can have similar fit. The use of Spearman partial correlations has been advocated to get stable results[43]. S1 Table and S1 Fig, S2 Fig and S3 Fig presents networks of Spearman partial correlations from a sensitivity analysis using the ppcor package in R and the accompanying centrality measures[44].

In stable and impending relapse states, results were essentially similar; only the connection between down and paranoia was less strong in the Spearman network. In the state of full relapse, the loop between down and relaxed was stronger. On the other hand, ‘betweenness’ was different between the original analysis and the sensitivity analyses (see S1 Table and S1 Fig, S2 Fig, and S3 Fig). Furthermore, the importance and clinical relevance of betweenness centrality and shortest paths in weighted networks of symptoms, as presented in the current paper, is uncertain. While in unweighted networks shortest paths are easy to define, in weighted directional networks, several paths may have approximately the same weight, making it difficult to identify a single shortest path. This is illustrated by the large differences in betweenness between the original analyses and the sensitivity analyses, while

connection strength and other centrality measures were similar. In addition, our regression analyses to obtain the strength of the connections included all symptoms (at t-1) simultaneously so that all connections only represent direct paths. In other words, all paths are important, not only the shortest. Therefore, the advantage of being located on the shortest path (betweenness) is limited. Finally, the 5 symptoms chosen a priori for the analysis are 5 key symptoms, identified jointly by Miss A and her psychiatrist (MB). It is a reduction of reality and represents a small proportion of the symptoms available in ESM. Although this simplification makes it possible to better identify the network dynamics of included symptoms, results may differ depending on which symptoms are chosen for inclusion in the analyses.

Conclusions and recommendations

Prolonged use of ESM self-monitoring is feasible in at least some patients diagnosed with psychotic disorder. Graphs of data pertaining to a single individual can be scrutinized to identify patterns that can be helpful in treatment. Although Miss A and her psychiatrist discussed raw data only, in the future, patients may benefit from more immediate 'on the go' graphs based on recent input. Network analysis shows that relapse in this patient coincided with a recognisable shift in symptoms. ESM, therefore, offers the possibility for accurate and personalised interventions in patients with mental disorder, including psychosis. It is another tool that can aide in understanding a patient's symptoms, how symptoms interact with each other and how symptoms are influenced by context. ESM data as collected by Miss A may assist in predicting relapse and other prognostic measures, facilitating the formulation of tailor-made interventions. However, the interaction between symptoms in psychotic disorders is complicated, and more work is required on how ESM n = 1 clinical network analysis can assist clinical practice.

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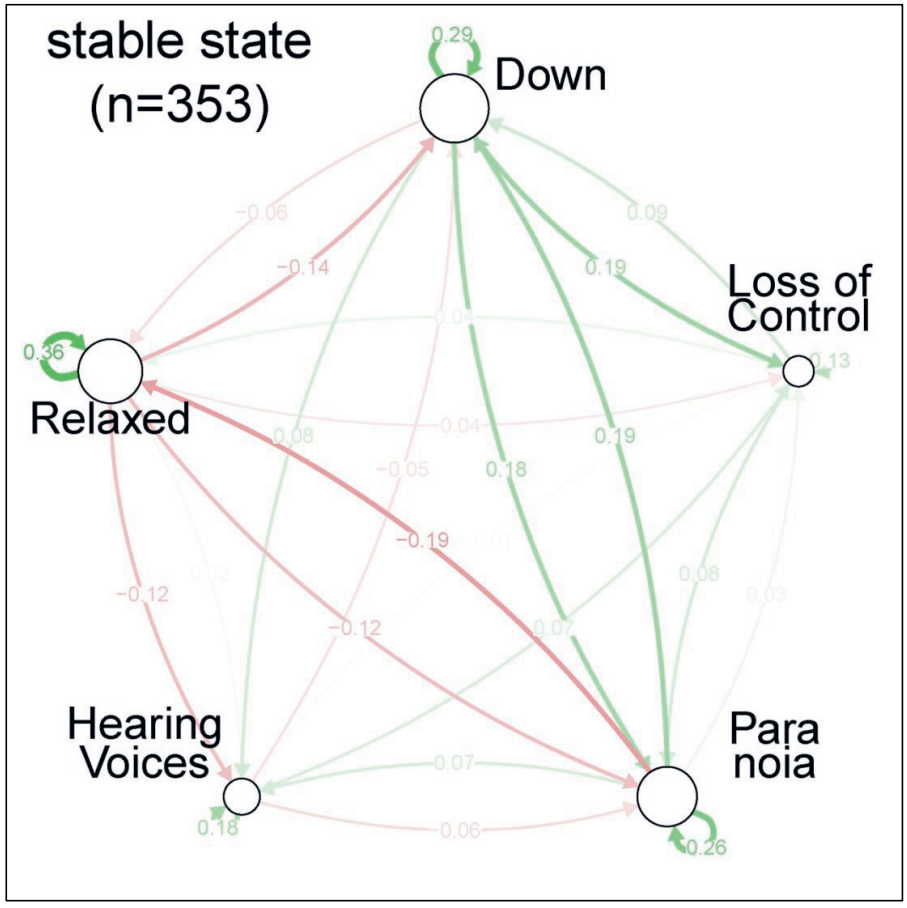
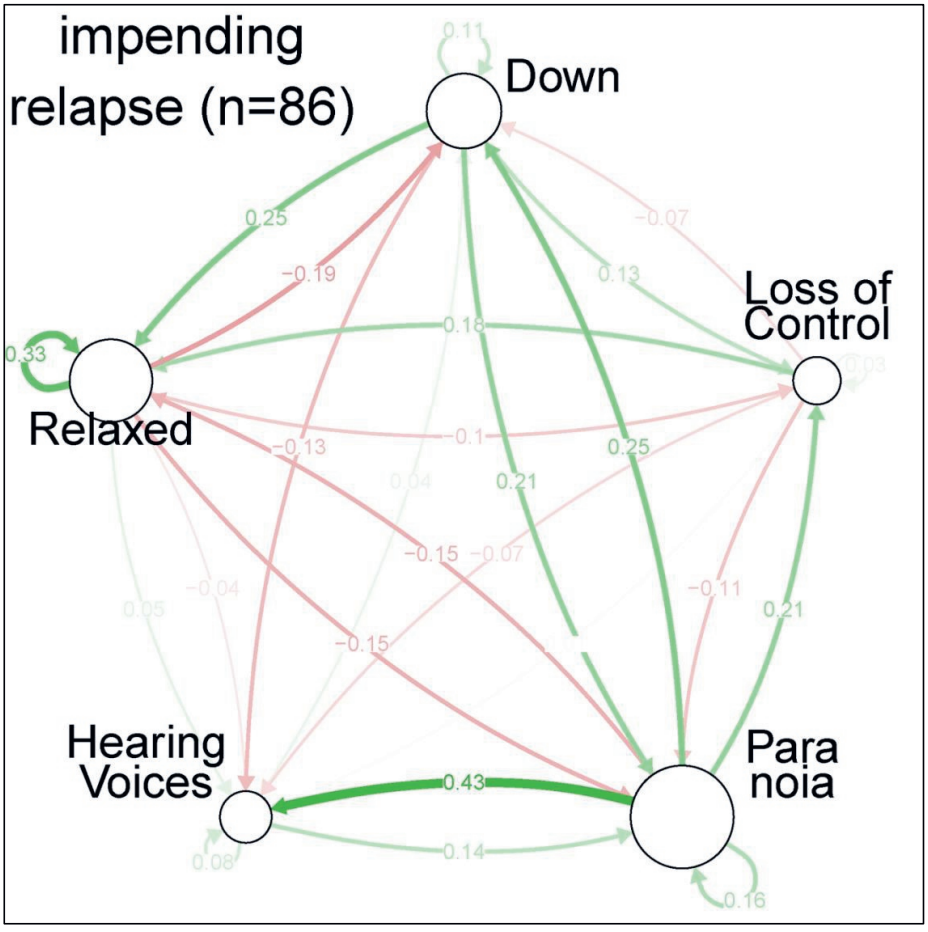
Supplementary Material

Table S1. Centrality indices per symptom, based on Spearman partial correlation coefficients, for each of the three strata of severity.

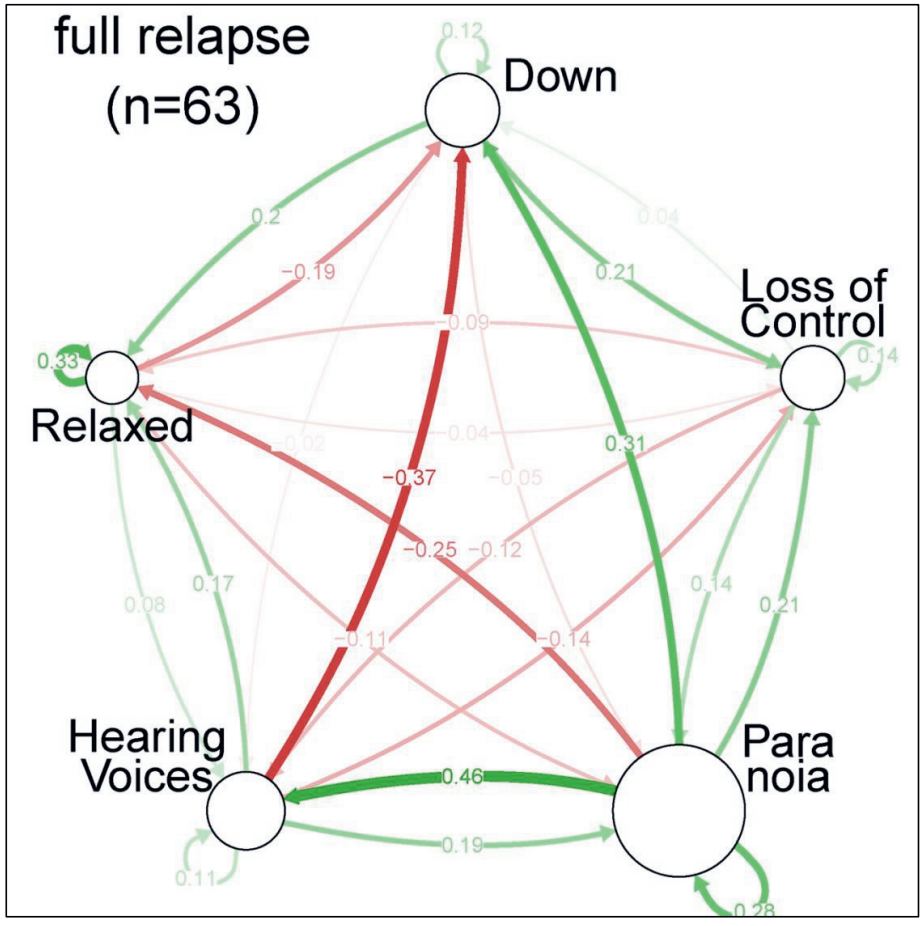
	Between-ness	Closeness	Inward degree	Outward degree	Node strength
Stable state					
'Down'	3	0.029	0.76	0.80	1.57
'Loss of control'	0	0.015	0.46	0.34	0.80
'Paranoia'	3	0.029	0.70	0.74	1.44
'Hearing Voices'	0	0.014	0.46	0.38	0.84
'Relaxed'	0	0.028	0.66	0.78	1.45
Impending relapse					
'Down'	0	0.042	0.65	0.83	1.48
'Loss of control'	0	0.027	0.48	0.45	0.93
'Paranoia'	6	0.056	0.77	1.20	1.97
'Hearing Voices'	0	0.023	0.80	0.31	1.07
'Relaxed'	1	0.032	1.04	0.82	1.77
Full Relapse state					
'Down'	1	0.029	1.03	0.60	1.63
'Loss of control'	2	0.027	0.74	0.53	1.27
'Paranoia'	3	0.071	0.77	1.51	2.28
'Hearing Voices'	0	0.048	0.80	0.98	1.78
'Relaxed'	0	0.028	1.04	0.76	1.79



S1 Fig. Network graph of five psychopathology items, based on Spearman partial correlation coefficients, items stratified by severity: stable state.



S2 Fig. Network graph of five psychopathology items, based on Spearman partial correlation coefficients, items stratified by severity: impending state.



S3 Fig. Network graph of five psychopathology items, based on Spearman partial correlation coefficients, items stratified by severity: state of full relapse.

Chapter 6

General discussion

Chapter 6
General discussion

Articulated in a mechanistic view of mental disorders, the current dissertation attempts to shed light on various ways to link mental states or symptoms to etiological factors, including genes and the environment. According to the network theory of mutual causality of mental states recognised as symptoms, we demonstrated, both at the experience sampling method (ESM)-study individual level (N=1 study) and at the cohort-study population level, that significant predictive links are present between momentary mental states and between momentary affective mental states (AMS). Furthermore, we examined the link between these AMS and genetic liability to psychopathology (GL), and with early environmental exposure separately. In doing so, we tested the network methodology in a way that acknowledges the complex mutual causal nature of psychopathology. This dissertation's chapters 2 through 5 comprise the final publications of four studies that offer insight on the topic.

The present thesis delves into the testing of 10 hypotheses, as outlined in Table 6.1. The findings support the notion that AMS can reliably and significantly predict each other over time. Furthermore, the findings indicate a higher overall AMS network density in MZ twins compared to non-twins, which was both validated and replicated. The present thesis investigates 10 hypotheses, which are presented in Table 6.1. The findings from the study support the idea that AMS can predict each other over time with significant reliability. Moreover, the study revealed that there is a higher overall AMS network density in MZ twins compared to non-twins, which was validated and replicated. Despite these promising results, some hypotheses remain inconclusive. Specifically, the sample of female twins assessed in the first study (Chapter 2/ section results) failed to yield conclusive findings regarding the differences between strata of increased GL and increased exposure to early trauma. To investigate these differences, individual slopes were calculated amid pairs of affective states at t-1 and t, and predictive associations were estimated using a conservative multiple testing statistical paradigm.

In the second study (Chapter 3), we compared node centrality parameters and temporal slope difference estimation between the strata of increased GL and increased exposure to early trauma. The results revealed that the high GL stratum had a significantly higher overall density and Na density than the low GL stratum. However, the medium GL stratum showed insignificant differences with the other two GL strata despite indicating a dose-effect relationship. In contrast, the analysis of the childhood trauma (CT) strata yielded results that were largely incompatible with our initial hypothesis. The comparison of

individual edges in GL and CT strata did not yield conclusive results after controlling for multiple testing.

Given that the network method has its limitations, we adopted a different strategy in the third study (Chapter 4) to investigate the relationship between mental states, etiological, and prognostic parameters. We zoomed out from the ESM micro-level to the level of combined diagnosis and symptoms. Based on the theory that a complex relationship between clinical and etiological variables determines the emergence of psychosis, we prospectively examined psychotic symptoms in relation to nonpsychotic disorders, etiological factors, and other specific parameters. The incidence of psychotic experiences

(PE) was measured over a 9-year period in a cohort of the general population. The analyses confirmed our hypothesis that a subset of people with incident PE would also have NPD, and that clinical, demographic, aetiological, and cognitive factors associated with psychotic disorders would have stronger and/or qualitatively different associations with the incident PE + NPD phenotype compared to the PE-only phenotype. The study revealed that the risk of the clinical high-risk state of psychosis (CHR-P) is mediated by a combination of attenuated psychosis and non-psychotic illness, rather than attenuated psychosis alone.

TABLE 6.1 SUMMARY OF OUR THESIS'S HYPOTHESES AND FINDINGS
AMS, affective mental states; MZ, monozygotic; NA, negative affect; CT, childhood trauma; PE, psychotic experiences*;* NPD*,* non-psychotic disorders; MMS, momentary mental states.

Chapter	Hypothesis	Outcome
2	AMS can significantly predict each other over time.	Supported
3	AMS can significantly predict each other over time.	Replicated
2	Differences of AMS lagged associations between strata of increased genetic liability to psychopathology (corrected alpha = 0.0002).	Inconclusive
3	Differences of AMS lagged associations between strata of increased genetic liability to psychopathology (corrected alpha = 0.0004).	Inconclusive
2	Differences of AMS lagged associations between strata of increased childhood trauma exposure (corrected alpha = 0.0002).	Inconclusive
3	Differences of AMS lagged associations between strata of increased childhood trauma exposure (corrected alpha = 0.0004).	Inconclusive
2	Higher overall AMS network density in MZ twins compared to non-twins (alpha = 0.05).	Supported
3	Higher overall AMS network density in MZ twins compared to non-twins (alpha = 0.05).	Replicated

2	Higher NA network density in MZ twins compared to non-twins (alpha = 0.05).	Inconclusive
3	Higher NA network density in MZ twins compared to non-twins (alpha = 0.05).	Supported
2	Higher overall AMS or NA network density in twins exposed to high CT compared to low CT (alpha = 0.05).	Inconclusive
3	Higher overall AMS or NA network density in twins exposed to high CT compared to low CT (alpha = 0.05).	Inconclusive
4	A subset of people with incident PE would also have NPD.	Supported
4	Clinical, demographic, aetiological, and cognitive factors associated with psychotic disorders would have stronger and/or qualitatively different associations with the incident PE + NPD phenotype compared to the PE-only phenotype	Supported
5	MMS can significantly predict each other over time (one year follow up time series with N = 1).	Supported
5	The temporal network of associated MMS differs between remission, and relapse phases of Schizophrenia (one year follow up time series with N = 1).	Supported

6.1 Novel Contributions

In this research, we aimed to contribute novel insights to the mechanistic study of psychiatric disorders. Firstly, evidence from two extensive, independent twin samples derived from the general population indicates that GL is associated with momentary emotions that influence each other over time and can be represented by a temporal network. Moreover, our findings suggest that the underlying genetic factors of affective dysregulation at the microlevel of human mental experience may be linked to the persistence and intensification of Negative Affect (NA) across time (Chapter 3). Secondly, apart from the empirically established assumption that NPD is a crucial component of the CHR-P/attenuated psychosis syndrome (APS) construct, our study findings, based on the NEMESIS cohorts (Chapter 4), demonstrate that PE become clinically significant only when associated with NPD, which are characterised by affective dysregulation. This is consistent with a recent systematic review of 56 studies that reported most individuals meeting CHR-P/APS criteria also had comorbid affective or anxiety disorders[1]. Third, various etiological factors, particularly environmental and genetic factors (estimated through schizophrenia polygenic risk scores - PRS), affect the risk of developing clinically significant psychosis only when there is a heightened symptom load accompanied by affective dysregulation (refer to Figure 6.1).

The overarching research goal of this dissertation was to predict the emergence of psychopathology using both symptoms impacting symptoms and the more traditional etiological parameters impacting symptoms. We have shown evidence that there is not only a link between causes and emergent psychopathology, but also a link between the symptoms themselves. In our case, NPD, the cluster represented by affective disorders and anxiety disorders, which are rooted in affective dysregulation at the micro-level, exacerbate psychotic symptoms and play a role that is not less important than the etiological factors themselves. This was demonstrated by the fact that the association with NPD (hereafter referred to as the comorbid state) was the element that led to clinically relevant psychosis with the need for care. Depending on the amount of exposure, genetic or environmental, either during the early stages of development or in adult life, there will be a corresponding consequence. This may result in either a clinical state severe enough to necessitate health care or simple PE with a benign prognosis. When examined more closely, exposure to stressful life events (i.e., caused by socioeconomic factors) without a high genetic load of psychosis and without other aggravating environmental factors will likely lead to only a benign clinical syndrome. However, if the exposure includes aggravating environmental factors and, at the genetic level, if there is a psychosis-associated polymorphism (i.e., a significantly elevated PRS), this will likely result in a psychotic phenotype of greater severity. However, there is additionally a mediator role for NPD, and this is supported by numerous studies in the literature[2, 3].

Figure 6.1 consolidates the study findings of the dissertation. Each vertice on the left side of the graph represents a predictor variable included in the cohort study (chapter 4); vertices on the centre (dark green and orange) are for phenotype variables (PE only, NPD + PE, NA at *t*, NA at *t-1*). Each arrow expresses the presence of a significant hazard ratio or a significant ß regression coefficient for ESM studies (here variables from the category of NA were selected and displayed in the zoom snippet), in the association between a variable and the outcome. The boxes on the far right were analysed as predictors in the cohort study. They are, however, symbolised in the figure with an arrow coming from the phenotype and ending in them, in line with the logical or empirical subsequence of some variables. Indeed, while antipsychotic use (APU), and use of MHC or of any care (AC) are subsequent to the emergence of symptoms and therefore will be represented on the far right of the graph, the connection with low social functioning (LSF) is less straightforward. Indeed, despite the fact that low social functioning (LSF) has been demonstrated to occur long before the onset of psychotic symptoms[4], it has also been linked to bad real life outcomes in individuals with psychosis in a large scale cohort study over 20 years[5] and was linked to higher use of mental health care (MHC) in other research[6], although the real connection of LSF with emergent psychosis might rather be bidirectional (LSF predicts psychosis and will in turn be worsened by negative symptoms and by the increasing social isolation[7] and internalised stigma[8]). In the next sections we will discuss these main points in more detail and in light of the literature.

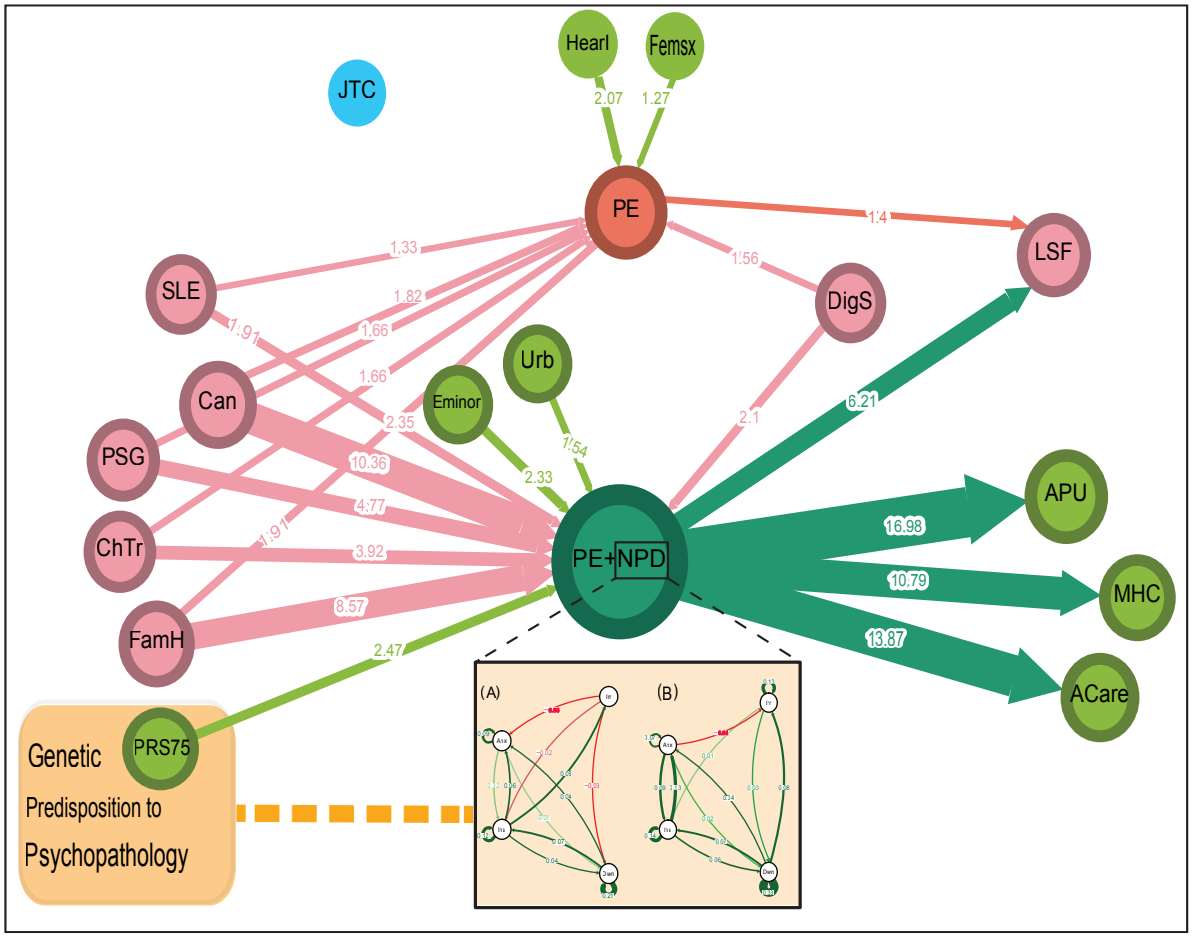


FIGURE 6.1 Visualization of the interplay between Mental States, Genetic and environmental Risk, and Psychopathology

Key findings from the present thesis are summarized in this figure. The interplay of mental states at the moment-to-moment level contributes to affective dysregulation (represented in the zoom caption), which is partially influenced by genetic vulnerability (as discussed in chapters 2 and 3). Affective dysregulation, in turn, determines the severity of psychotic symptoms and is a key component of most non-psychotic disorders (NPD). This intricate relationship is associated with a polygenic risk score for psychosis (PRS75) when affective dysregulation is present within the clinical presentation, and it correlates with an increased number of environmental factors. Variables are color-coded: Light green, denotes exclusive significant associations with the PE+NPD phenotype, while Pink indicates significant associations with both the PE only and PE+NPD phenotypes. Edge weights represent the hazard ratio value of the differential association between exposure or prognosis variables and the phenotypes PE or PE+NPD. The network excerpt displayed in the zoom caption is derived from findings in chapters 2 (supplementary figure 2.2). Networks of momentary affective mental states in participants with low (A), and high genetic liability for psychopathology (B). In this figure, the arrows represent associations over time, i.e., the B coefficient expressing the effect size of the predictive associations. For example, in A, there is an arrow from '*Dwn*' to '*Ins*', meaning that '*Dwn*' at t−1 predicts '*Ins*' at t with a B coefficient of 0.07. Green arrows represent positive associations, and red arrows represent negative associations. Only negative affective states are displayed, as they demonstrated more consistent significant results in network density comparison measures (chapters 2 and 3). Abbreviations: *PE*, psychotic experiences; *NPD*, non-psychotic disorders; *HearI*, hearing impairment; *Femsx,* female sex; *SLE*, adult stressful life events; *Can*, cannabis use; *PSG*, perceived social gap; *ChTr*, childhood trauma; *PRS75*, polygenic risk score for schizophrenia; *FamH*, familial history; *DigS*, digit-span task; *JTC*, jumping to conclusions bias; *Urb*, urbanicity; *Eminor*, ethnic minority; *LSF*, low social functioning; *APU*, use of antipsychotic medication; *MHC*, use of specific mental health care; *Acare*, use of any care. *Irr*: Irritated, *Dwn*: Down, *Ins*: Insecure, *Anx*: Anxious.

6.1.1 PRS is associated with the comorbid/multidimensional state and not with the mono-dimensional psychotic state.

Walsh et al. have shown that individuals with schizophrenia have more rare structural variants such as deletions and/or duplication of one or more genes compared to controls[9]. The most recent schizophrenia GWAS identified 270 loci significantly associated with schizophrenia[10]. These loci include genes involved in dopamine signalling, glutamate signalling, ion channel functioning, and immune response. Because these associations are common and have small or moderate effects, including all of them in regression models would strongly reduce the power due to the large number of variants, none of which are pathognomonic to schizophrenia. Therefore, utilizing a polygenic risk score (PRS), which sums the number of risk alleles weighted by their effect size, emerged as a viable solution[10].

Previous research has shown that in a general population sample, PRS is pleiotropically associated with measures of affective regulation, aberrant salience, and neurocognition[11]. Our own longitudinal study allowed us to evaluate the role of PRS more precisely in the emergence of psychopathology (chapter 4)[12, 13]. We found that PRS were associated with a phenotype that includes NPD, mostly represented by affective and anxiety disorders (referred to as the comorbid state), but not with the purely psychotic phenotype (PE-only: HR=0.80, 95% CI: 0.56-1.13; PE+NPD: HR=2.47, 95% CI: 1.48- 4.10). This finding is consistent with other studies demonstrating the association of PRS with NPD in the early stages of psychopathology, and with a 20-year follow-up of a case/control sample showing that among patients initially diagnosed with a psychotic affective disorder, a higher SZ PRS predicted whose diagnosis would change to non-affective psychosis[14], which is consistent with our results considering that our sample is a general population risk sample exploring the prodromal phase.

Taken together, these results suggest that genetic predisposition to psychosis may be mediated by affective processes, such as those related to mood and anxiety disorders, hence to affective dysregulation. Furthermore, although the relationship between PRS and the comorbid state can meet some of the Bradford Hill criteria for causality[15], including the temporal relationship, strength of association (a stronger association between PRS and the comorbid phenotype compared to the non-significant association with the purely psychotic phenotype) and, consistency with several cross sectional and cohort studies in different populations[16, 17]. One can argue that this relationship may not be fully causal given the lack of specificity of the association of PRS with the prodromal comorbid state of psychosis. From the other hand, if this association obligates the presence of another factor, here the environment to interact with it for it to cause psychosis, the causality doesn't need to be specific[18],[19]. Additionally, in the definition of a complex system, no factor is solely responsible for an outcome, rather the interaction of the components leads to the shift of the system to a definite outcome[20]. In that way, the PRS is plausible and can be causal but just in part (see next sections for more details).

6.1.2 In the case of comorbidity, the associated elements correspond perfectly to the known etiological, genetic, and environmental factors profile of the so-called schizophrenia.

The heredity of schizophrenia is estimated to be as high as 80% based on traditional twin research[13]. However, shared exposures (e.g., in utero) may be underestimated in twin and adoption studies, leading to an overestimation of the genetic component in the development of the disease. Studies have indicated that even conservative estimates of schizophrenia heritability, between 64 and 67%, are likely to be high[21]. Nevertheless, schizophrenia stands as one of the most heritable psychiatric disorders, a substantial number of heritability cannot however, be explained by the cumulative effects of known disease-associated genetic variations[22]. Furthermore, individual environmental variables have, on average, higher odds ratios compared to genetic factors reflected by common genetic variants discovered by GWAS [23]. In this dissertation, the comorbid state was associated with multiple key environmental and genetic factors known to predispose to psychotic disorders[12]. This is consistent with previous findings, which indicate that the risk of psychosis increases when there are several variants of genetic risk and many exposures to negative environmental conditions[24]. Furthermore, cannabis use, urbanisation, and belonging to an ethnic minority were not associated with the benign non-comorbid state. In contrast, exposure to daily life stressors and / or economic stress was also predictive of the simple mono dimensional phenotype but was not enough to increase the risk (table 3, chapter 4).

These results, along with the observation that not all cannabis users or urban dwellers develop clinical psychosis, suggest that environmental factors alone are insufficient to trigger a shift to a more vulnerable state. This inability of either genes or environment alone to produce a trait, and therefore the requirement of both, is an illustration of gene environment interaction (G×E)[25]. Additionally, the results of the heritability estimate from twin studies are substantially higher than those of molecular genetic research[26]. This difference between the heritability estimates from twin studies and the estimate from molecular data is known as the "heritability gap." This gap may be due to the fact that many genetic effects are influenced by environmental factors that are shared by individuals who grow up in the same family, but not by unrelated individuals[25]. This indicates that the aetiology of a trait is complex and involves many genetic variants with small effects that are influenced by the environment[25]. Twin studies, however, reveal that the shared environment has little or no impact on psychosis, despite the epidemiologically proven role of risk factors common to family members (such as minority status, urbanicity, or low socio-economic status)[22]. This is referred to in the literature as the shared environment paradox[25]. Thus, two siblings can share the same urban environment or the same ethnicity, but the meaning of these exposures will always be different for each person. In this sense, it would not be surprising that the shared environment does not contribute given that conceptually such a contribution is difficult to envisage. However, G×E may similarly offer a plausible explanation to the low apparent environmental impact in twin studies[25]. This mechanism can cause psychiatric problems in

different ways. Some processes operate within biological pathways through G×E, whereas others modify the epigenome and, through that, the behaviour. In the following section, we will explore five potential pathways in greater detail. However, it is important to acknowledge the existing inconsistencies in the literature, as studies investigating this specific area have yielded varying results[27].

6.1.3 Suggested GxE Pathways

Interaction studies between genetic factors and the environment have progressed from the stage where polymorphisms were the focus of the genetic part to GWA and PRS studies and recently to the development and use of PRS and Exposome scores. The latter is defined as an aggregate measure of environmental liability for schizophrenia[28]. One main reason for generating these scores was the small effect size of the associations when gene variants and environmental variables were added separately and the additional decrease in power when the interaction factor (GxE) was added to the regression equations[29]. On the other hand, although scores have their value in solving the power and effect size problem to prove the existence of the GxE interplay, we still need genetic variant studies to unravel the underlying neurobiological mechanisms of this interaction. In an effort to shed light on the biological underpinnings of the GxE, a number of studies have been conducted examining the impact of various environmental factors, including infectious diseases, cannabis use, and psychological or social trauma experienced during childhood or in daily life. These findings will be described in more detail below.

6.1.3.1 Infection

Despite initial epidemiological hypotheses suggesting that genes related to the development of schizophrenia may also be involved in susceptibility or immune response to Toxoplasma gondii or HSV-1, PRS studies failed to support this notion, finding no association between toxoplasmosis IgG seropositivity and schizophrenia in individuals carrying higher PRS[30]. Similarly, case-control studies examining polymorphisms of neuroinflammation markers yielded conflicting results or were unable to be replicated[10]. And recently, the SARS-CoV-2 virus, responsible for the COVID-19 pandemic which has affected over 20 million people[10], has been proposed to potentially cause neuropsychiatric symptoms through a cytokine storm induced by elevated levels of maternal IL-8 in the second and early third trimesters, which have been linked to an increased risk of schizophrenia in offspring[31]. However, to date, there is no evidence to suggest a connection between SARS-CoV-2 infection and psychosis[10].

6.1.3.2 Cannabis

The current evidence suggests that gene-environment interaction pathways are probably responsible for the link between cannabis and psychosis. Recent studies have employed genome-wide data and PRS scores, to strengthen the evidence for the association between cannabis use, schizophrenia and GxE. For instance, Wainberg et al. used self-reported psychotic events, cannabis use, and PRS scores to

investigate the association between schizophrenia and cannabis use in UK BIOBANK participants[32]. They found that cannabis users with the highest PRS values for schizophrenia had 1.58 times higher chances of exhibiting self-reported psychotic events than those with the lowest PRS levels[32]. Another study discovered an additive relationship between PRS scores for schizophrenia and the frequent use of cannabis[33]. Furthermore, several studies indicate that the effects of cannabis on psychosis outcomes, such as schizophrenia and psychotic symptoms, are influenced by the preceding manifestation of (genetic) susceptibility to psychosis[33]. A recent European Network of National Schizophrenia Networks Studying GxE Interactions (EUGEI) research indicated that there exists an additive interaction between genetic liability and regular cannabis use regarding the risk of developing schizophrenia[34]. This interaction is moderated by PRS. In other words, the joint influence of genetic risk and exposure to cannabis on the likelihood of developing schizophrenia is greater than the sum of the individual effects of each factor[34]. Moreover, the EUGEI cohort study differentiates the use of cannabis as a self-medication coping mechanism from the association between daily cannabis use and PRS load by documenting the time precedence of daily cannabis[34].

Taken together, these findings provide compelling evidence that cannabis use acts in synergy with multiple genetic variants, supporting this thesis finding that the link between cannabis use and emergent psychosis is more likely to be causal in part. Nonetheless, the causal mechanism of the relationship between cannabis use and psychosis is complex and multifaceted, and further research is warranted to understand the complex interplay between genetic, environmental, and neural factors underlying this relationship.

Further, in a previous study, GxE was calculated in five increasing levels of psychosis admixture with affective dysregulation[33]. The study found that the effects of cannabis and urbanicity on levels of psychosis admixture with affective dysregulation, and the level of clinical psychosis, were influenced by the preceding manifestation of genetic susceptibility to psychosis in the form of an additive GxE. However, there was a lack of a significant GxE interaction in the sub group with isolated PE[33]. This may explain our finding that the lack of a significant association of PE-only with cannabis and urbanicity, which suggests that these exposures were not potentiated by genetic factors and therefore did not predict the rise of the benign mono-dimensional phenotype (PE-only) in our analysis. Nevertheless, caution should be exercised when comparing the two studies due to differences in study design and the method of estimating genetic vulnerability[33].

6.1.3.3 Psychosocial Stress and Childhood Adversity

The umbrella term 'psychosocial stress' includes stress caused by the perception of social threat that results in emotional tension and discomfort[10]. In our study, we investigated urbanicity, minority status, stressful life events, and perceived social gap. All of these variables may be considered as environmental

factors, given their capacity to generate psychosocial stress[10], because they frequently involve situations of perceived social evaluation and social exclusion, or life event-induced distress at different intensity levels. Similarly, childhood adversity is studied through similar definitions and scales in the literature[35].

Schizotypal personality disorder (SPD) has been used as a genetic vulnerability proxy to psychotic disorders in a significant amount of the GxE literature about stress as an environmental factor in the GxE[36-38]. This commonly held belief has its origins in the work of P. E. Meehl, who claimed that a genetically based brain abnormality (schizotaxia) manifests as a distinctive personality organization (schizotypy) that reflects susceptibility to develop schizophrenia[39]. Everyday stresses in a 24-hour period predicted positive prodromal symptoms one year later in adolescents, including those with SPD; however, those with SPD, and therefore genetically susceptible to psychosis, had stronger perceptions of stress to the same daily stressors than their nonvulnerable peers[38]. Similarly, research involving GxE in twins revealed a substantial correlation between PRS scores and early adversity that modifies the manifestation of subclinical psychosis and stress sensitivity [40]. The researchers hypothesized that early trauma impacts susceptibility to ordinary pressures, indicating that the type, timing, and severity of stress may contribute to the development of psychosis[40]. In parallel, the EUGEI found an additive interaction between PRS and childhood adversity in 1699 patients and 1550 unrelated controls[34]. This adds to and is in line with research that has shown that an increase in the chance of developing psychotic symptoms is correlated with the duration and intensity of exposure to environmental risk factors, suggesting that further exposure may be necessary for the generation of clinical psychosis[11, 41, 42]

Taken together, daily life stressors and childhood adversity have been hypothesized to interact with genetic risk by enhancing stress sensitivity through various mechanisms, such as dysfunctional cognitive reappraisal or aberrant emotional salience[43, 44]. The latter is a reflect of a dysfunctional emotional regulation strategy, including over-selective or distorted perception and interpretation of psychosocial stimuli, and have been linked to psychotic positive symptoms[45, 36] and may therefore contribute to stress sensitivity in daily life situations. In sum, consistent with our findings, stress sensitivity as suggested mechanism of GxE might imply a form of affective dysregulation.

On the other hand, in our study we found a non-specific prediction of risk of SLE and PSG and childhood adversity that impacted both phenotypes (table 3, in chapter 4). This is in line with above mentioned results from the literature, that the interaction with genetic predisposition (PRS) in addition to a certain timing, and intensity of those stress variables among other factors, altogether influence the risk in a complex fashion[38, 40]. Therefore, the complex relationship between stress sensitivity, affective dysregulation, and GxE and how they contribute to the development of psychosis risk is not fully understood and require further investigation.

6.1.3.4 Epigenetics of psychosis

The full articulation of the neurobiological mechanisms of gene-environment interplay is beyond the scope of this dissertation, but it is specified in extensive reviews of the animal and human literature[35, 46]. In summary, differential DNA methylation and histone modification have been identified in genetic variants associated with schizophrenia in brain and blood tissue[46]. These changes may be epigenetic markers and are involved in the pathogenesis of the disease. However, the exact role they play in the disease is not yet clear[46]. The genes most implicated are involved in neurotransmission, immune function, and energy metabolism[46]. Additionally, microRNAs can help regulate the development and function of synapses and may also help regulate circadian clock entrainment. These findings suggest that psychiatric disorders may be caused by the dysregulation of these biological processes. Some studies suggest that epigenetic changes play a role in the development of schizophrenia[47], while others suggest that they may be a consequence of the disease[48].

6.1.4 Affective dysregulation as a key component in the complex dynamics of psychosis development.

In this dissertation, supplemented with findings cited above, affective dysregulation was shown to play a central role in a complex system, with environmental and genetic factors interacting with each other and leading ultimately to the emergence of clinically significant psychotic symptoms. This complex system is dynamical in nature, as its elements change over time, both at a very delayed scale (years) and at the moment-to-moment level (as shown in the zoom caption in figure 6.1, see also figure 6.2). In this dissertation, we found that genetic liability to psychopathology was associated with a higher network density of NA, that is, increased interconnectivity among negative emotions, resulting in an affective dysregulation or lack of the ability to change one's own affective state, which leads to the person staying trapped in negative emotions (chapter 2 and 3). Further, affective dysregulation can influence not only symptoms or states but also traits. Previous findings suggest that NA network density is related to neuroticism, that is a trait factor predisposing to affective and anxiety disorders (hereby representing most of NPD)[49].

Furthermore, together with the findings mentioned in previous sections, these results align with the conclusions of a cross-sectional analysis exploring the interaction between family history of affective dysregulation as a proxy of genetic factors and environmental factors[33]. These results revealed that within a specific stratum of psychosis admixture with affective dysregulation, the association with environmental risk variables was greater than additive when familial affective dysregulation was also present[33]. Additionally, while studying five psychopathological levels of the comorbidity (PE +NPD), the interaction contrast ratio (ICR) increased consistently, as the association inherent to the admixture

with causal factors was more than additive the more admixture increases[33]. The ICR is a statistical estimate of the excess risk due to interaction compared to the risk without exposure[50].

On the other hand, the superposition principle, addressing linear interactions and as described in the context of complexity science, suggests that the combined effect of multiple factors should be equal to the sum of their individual effects[51]. Consequently, the mentioned findings are another demonstration that the superposition principle does not hold true in the causal system of psychosis. Instead, the above reported results indicate a non-linear relationship between the studied components of the gene environment and affective dysregulation with different symptoms load and admixtures[33]. In other terms, the interaction between affective dysregulation, genetic and environmental factors in the development and severity of psychopathological states is not simply additive. Instead, it exhibits complex, nonlinear behaviours, emphasising the intricacies of these relationships.

These previous results together with findings of the third study (chapter 4) imply that genetic influence may be exaggerated across increasing comorbidity with affective dysregulation and that additional environmental mechanisms including those of parenting are likely to be at play. Recent research has revealed that non inherited parental genotypes can considerably predict the child phenotype when evaluated as a polygenic score[52, 53]. Consistent with our results (chapter 4), that a weaker but present association of PE-only with family history of affective dysregulation might be interpreted as an environmental factor. This is likely to explain why it did not lead to the severe comorbid state (PE +NPD); instead, it might have required the interaction with both affective dysregulation and the genetic factor reflected by the PRS[12].

In conclusion, the emergence of clinically significant psychosis was dependent on intricate, nonlinear interactions spanning multiple levels, from genetic to societal (Figure 6.1 and 6.2). These interactions involve affective dysregulation, which itself comprises subunits (e.g., AMS) that interact through regulatory loops (Chapters 2 and 3), creating a complex network of interactions. In parallel, extensive findings in etiopathology literature reveal that feedback loops traverse the multiple layers mentioned earlier (Figure 6.2). For example, low social functioning and cannabis use can both be considered bidirectional factors, the later acting both as a self-medication and causalfactors[4].

Viewing clinical psychopathology as the higher-level manifestation of a complex, developing system made up of subunits and regulatory loops allows us to consider how causal factors, as described in this dissertation, can influence these subunits, or alter the nature of interactions and regulatory networks (Figure 6.1 and 6.2).

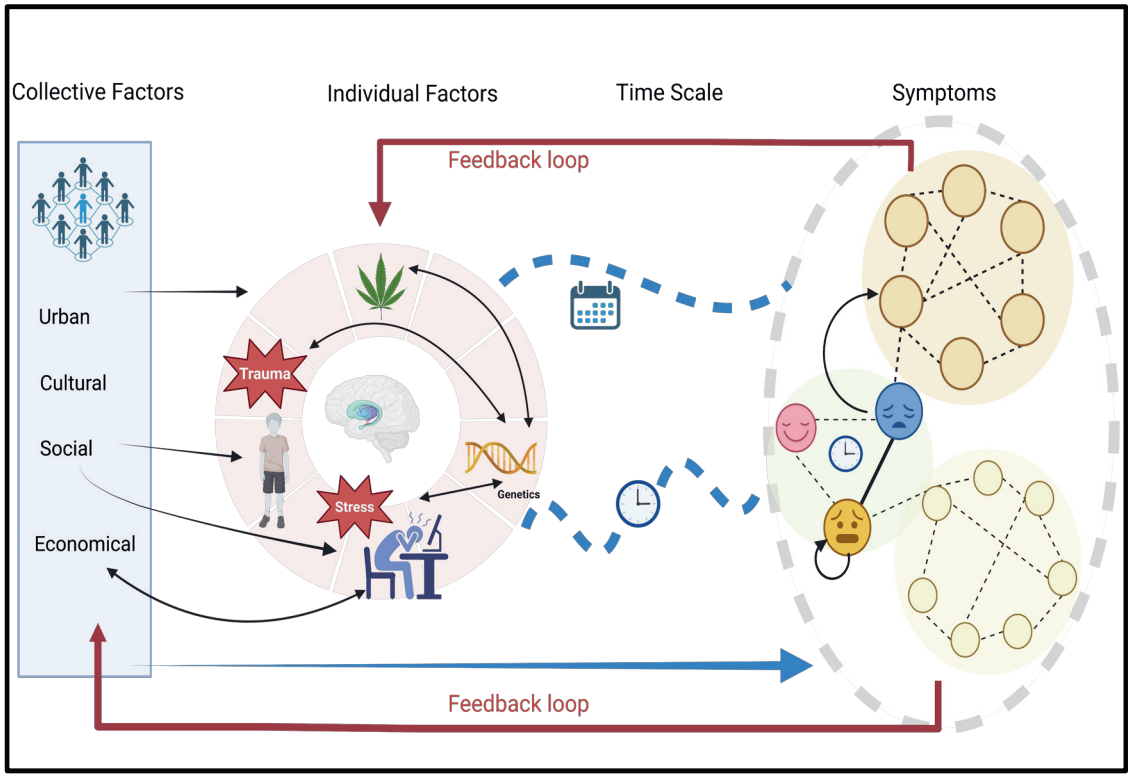


FIGURE 6.2 The Complex Multi-layered Interplay of Factors in the Emergence and Sustainment of Mental Disorders

This illustration portrays the complex array of factors contributing to the onset and maintenance of mental disorders. These factors are organized in a layered structure, spanning from macroscopic (collective) to microscopic (individual) levels. The most prominent element within this system is affective dynamics, where the pink emoticon represents positive affect, while the yellow and blue ones signify negative affect. These emotional factors interact with environmental and genetic compo-nents, ultimately culminating in the expression of clinically significant symptoms. The system's inherent complexity and dynamism stem from its constituent elements evolving over diverse time scales, ranging from long-term periods of months or years to transient, moment-to-moment fluctuations.

Conclusion of this section

Three key conclusions can be drawn from the discussion of this thesis results. First, consistent with earlier results, Findings show that the relationship between psychosis expression and risk loading (environmental and genetic) depends on affective dysregulation, adding credence to the notion of an affective path to psychosis. Second, when our findings were compared to research in similar samples, it showed that the accumulated risk load increased the probability of psychosis expression and its clinical relevance in a dose-response pattern, as anticipated by the liability threshold model, in which susceptibility to a phenotypic result may be treated as a continuous meter of measurable risk[41, 54]. This is not in contradiction with the conception of psychopathology as a complex dynamical system, as both conceptions need an increase in exposure load and the phenotypic result emerges after a shift in the system[18].

Third, the causal system of emergent psychopathology, and here emergent psychosis is taken as an example, is complex and made up of many exposures and dimensions (figure 6.1). If the exposure is minor or does not involve GxE interaction or affective dysregulation, it remains in the category of "normal". Affective dysregulation dimension results in mental health distress and the need for care, when added to another dimension. Together these factors are highly likely to be interacting a complex dynamical system as depicted in figure 6.2.

Consequently, the question, from both an academic and a clinical practice perspective, remains as to how to prevent the system from shifting to the pathological mode. There might be multiple entry points to try to change the unfavourable course. For instance, more social welfare at the public health and educational level could intervene at the environmental exposure entry point at an early stage (childhood or adolescence). Similarly, psychotherapy can help people in the stage of affective dysregulation and teach them how to cope with negative emotions. Thus, the interplay of genetic, environmental, and clinical factors gives a theoretical equal power to each of these entry points. Further experimental or early intervention studies at a large scale should test this hypothesis (see section future direction).

6.2 Limitations

This dissertation includes big representative general population cohort samples, that are the best for exploring the emergence of psychopathology including emergent psychosis, as it is now accepted that the very first phase (also called prodromal phase) is multi-dimensional in nature therefore not specific. Also, a general population sample of twins is best suited for the study of genetic vulnerability. Using patients with psychosis would have biased the data on CT and therefore of genetic vulnerability in emergent psychopathology including emergent psychosis.

On the other hand, while this research has resulted in three original publications and has contributed to our understanding of the link between symptoms and aetiologies in the emergence of psychopathology, it is worth recognising several limitations that may affect the interpretation and generalisability of the findings. One limitation is that emotion regulation may differ between affective disorders and in psychosis. In psychosis, emotions may tend to be overregulated i.e. quickly suppressed[55], whereas in depression and anxiety disorders, negative emotions may persist over time by lack of self-reassuring and self-regulation skills[56, 57]. By including the whole spectrum under the umbrella of GL using the sum score of the Symptom Checklist-90 (ScL-90), the effects of these differences may have been cancelled out, leading to weaker lagged regression coefficients. Additionally, it can be assumed that the brain mechanisms responsible for hallucinations, for instance, are different from those responsible for the lack of joy, and therefore they would differ at the GL level. However, the substantially higher representation of affective and anxiety disorders as NPD in the general population (and therefore also our both twin samples), let us assume that the interpretations discussed in this dissertation (figure1 and section 6.1) can be accurate as the GL based on Scl-90 scores would represent GL to affective dysregulation, and also to NPD.

In our study of a non-clinical twin population (as described in chapters 2 and 3), we observed non significant results using network analysis. One possible explanation for this could be the high number of variables included in the regression model, which may have reduced our statistical power, especially given the need for correction for multiple testing. However, our long-term cohort studies have more successfully shown the impact of affective dysregulation (chapter 4). Both approaches have their own value, but they may be better suited for different purposes. Network analysis has been more successful in individual case studies (chapter 5), while traditional cohort analysis has provided more conclusive results at the population level through traditional statistical analysis. Ultimately, both methods have proven to be complementary to one another, on a conceptual level (figure 6.1).

6.3 Future directions

With this dissertation, we demonstrated that the emergence and severity of mental disorders were not only related to the interaction between candidate genes and to the interplay between genes and the environment[58], but also to the admixture of affective dysregulation with the symptoms themselves. Yet, despite the progress made in this area of research, there is still a need for further research to fully address the topic at hand. Here, I propose three general directions for future research that will improve our understanding of this topic.

In term of future research sample/population, research centres must join forces and conduct large-scale multicentric cohort /early intervention studies outside of the limited scope of specialized early

detection centres, as this dissertation has highlighted the unspecific and multidimensional nature of early psychotic emergence states. Increasing the sample size will also allow for a better power and therefore allow for including the gene-environment interaction in the analysis. Furthermore, given the importance of intimate connections in the socialization of emotion regulation abilities and techniques, research would profit from performing dyadic, triadic, family and system-level studies[59]. These investigations have the potential to understand the social underpinnings of vulnerability and resilience, therefore, informing early intervention efforts and prevention of psychopathology. Additionally, research in countries with non-Caucasian populations is particularly necessary, as the accuracy of PRS decreases when applied to non-European populations due to the preponderance of European genetic data used to train PRS models[60].

In terms of the research question /choice of variables, our findings have relevance for future research in the field of psychiatry genetics. Studies on the topic of affect dynamic using ESM and techniques, like those studies published here (chapter 2 and 3), may allow for greater comparability with other cultural contexts because of the universality of emotions. This contrasts with the culture specificity of criteria of diagnostic categories. In other words, comparing emotional distress resulting from psychotic symptoms is universal versus psychotic symptoms, such as mystical delusions that are highly subject to cultural differences. Furthermore, testing the basic network of AMS as an intermediate phenotype may also be of value as the networks can be seen as ecologically valid phenotypes, complementary to categorical diagnostic phenotypes in genetic studies.

Overall, further exploration of symptom dynamics in daily life can provide valuable insights into the patterns and fluctuations of mental health symptoms, which can be useful for improving diagnosis accuracy and therapy interventions. By collecting frequent and real-time data on individuals' symptoms and experiences, researchers and clinicians can gain a more detailed and nuanced understanding of mental health conditions and can develop more tailored and effective treatments. Therefore, large scale clinical trials should be conducted to examine the effectiveness of time-intensive assessments in improving clinical parameters such as insight, affective regulation, and adherence to treatment. Additionally, future research should focus on replicating and expanding on the present exploration of the effect of genes and the environment on the affective regulation network, to gain a more complete understanding of the mechanisms underlying mental disorders. Furthermore, future research should use a combination of different research approaches and measures, including molecular genetics (or polygenic scores) and the environmental variables, that yielded strong prediction effect size in our work (chapter 4), besides the newly introduced Exposome score. This will allow to identify potential areas in need of intervention as a preventative measure.

In terms of future research designs and methodologies, research centres must join forces and conduct large-scale multicentric cohort early intervention studies outside of the limited scope of specialized early detection centres, as this dissertation has highlighted the unspecific and multidimensional nature of early psychotic emergence states. Increasing the sample size will also allow for a better power and therefore allow for including the gene-environment interaction in the analysis. Furthermore, given the importance of intimate connections in the socialization of emotion regulation abilities and techniques, research would profit from performing dyadic, triadic, family and system-level studies[59]. These investigations have the potential to understand the social underpinnings of vulnerability and resilience, therefore, informing early intervention efforts and prevention of psychopathology.

Our research may shed light on the need for novel designs that take into account the complexity of genetic influence in the development of psychopathology while considering the limitations of network studies or by combining various types of network analysis (e.g., together cross sectional, time series and directed acyclic graphs, for enhancing chances of causality inference).

Finally, there are implications for future research stemming from the broader topic of mechanistic research in psychopathology as well. For instance, it is generally accepted in the field of psychology, and as highlighted in previous sections, that mental health conditions can be highly individualized and complex. Hence, traditional methods of studying and diagnosing these conditions may not always be sufficient. Therefore, unconventional methods of study within the mechanistic framework may be required, such as combining different research approaches or incorporating new technologies. This could help to better understand the mechanisms of psychopathology.

Traditional statistical methodologies within this area of research pose additional problems, as mentioned in the previous section. Temporal network studies were not yielding strong effect sizes in the twin normal population sample, likely attributed to the use of traditional statistical methods. These methods, which are based on assumptions such as the linear statistical distribution of the data and the linear relationships between variables among others, require the specification of the model of relationship between variables. They are the standard in psychopathology research and networks of psychopathology. However, due to their assumptions and limitations, they may not always be appropriate for studying complex and individualized phenomena like psychopathology. Incorporating complexity science modelling, such as differential equations, can provide valuable insights in certain situations[61].

For example, in ESM data, the assumptions for differential equations might have been more easily met compared to those for multilevel regression (chapter 2 and 3). Differential equations are typically designed to handle time-dependent phenomena by inherently describing the change in a quantity over

time based on its rate of change[62]. Therefore, employing more flexible and advanced techniques like computational models of differential equations found in complexity science could be essential for capturing the dynamic and intricate interactions between clinical, genetic, and environmental factors, especially when the focus is on prediction and temporal dynamics for better understanding the underlying mechanisms of psychopathological development and progression. These alternative approaches may provide more accurate insights into the complex nature of psychopathology and offer new opportunities for targeted interventions and personalized treatments.

Machine learning models can also improve on the limitations of traditional statistical methods, by allowing for greater flexibility and adaptability in the models used to study complex and individualized phenomena like psychopathology. Machine learning algorithms can continuously learn and adapt according to the data they are given, allowing them to make more accurate predictions[63, 64]. Additionally, by using machine learning algorithms, researchers can analyse larger and more diverse datasets, which can provide a more comprehensive view of the underlying mechanisms of these conditions[64].

Overall, three broad areas of research suggestions can be drawn. **First,** larger sample sizes can be obtained using multicentre cohort studies, allowing for the examination of gene-environment interactions and a wider range of exposure variables. **Second,** the potential of affective regulation networks as intermediate phenotypes and the collection of real-time data on symptoms and experiences should be further explored to improve diagnostic accuracy and treatment efficacy. **Finally,** the integration of cutting-edge methodologies, such as complexity science techniques and machine learning algorithms, could prove advantageous for the analysis and interpretation of large data sets, especially when the assumptions of conventional statistical approaches cannot be fully satisfied without compromising the power of the analysis. This may necessitate the establishment of interdisciplinary research teams composed of specialists from diverse fields, encompassing epidemiology, clinical medicine, biology, computer science, and mathematics.

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Chapter 7

Impact

Chapter 7
Impact

The discoveries presented in this thesis shed light on the intricate causal system behind emerging psychopathology, including psychosis. By demonstrating that this system is multi-layered and involves numerous exposures and dimensions, this research could significantly impact the way mental health disorders are studied and treated.

For instance, the thesis highlights the critical role that affective dysregulation plays in the relationship between psychosis expression and risk factors, such as genetics and environmental exposures. This insight could inspire researchers to explore new ways to address emotional imbalances in their studies, potentially leading to innovative therapeutic approaches.

Furthermore, based on our findings, we conceptualized the emergence of psychopathology as a complex dynamical system. Given that such systems are sensitive to small initial changes[1], this understanding may inspire scientists to explore how early adjustments to specific elements could lead to significantly different mental health outcomes. One possible research direction could involve examining the impact of early interventions targeting various risk factors, not only on multiple levels—such as emotional, environmental, and genetic factors—but also on different layers, both at the entire population and at the individual level. This all-encompassing approach could help us better understand how to support mental health more effectively.

At an individual level regarding the clinical population, the findings of this dissertation, support the development of personalized mental health care. This approach helps patients link their current or past distress with related feelings, thoughts, beliefs, and situations in an open, empathic, and non-judgmental manner. By fostering a non-stigmatizing relationship with the patient, this model bridges the gap between patient and therapist and could be applied from the first contact with mental health facilities.

Chapter 5 demonstrates the feasibility of using the Experience Sampling Method (ESM) self-monitoring in patients with psychotic disorders. This approach allows for the identification of individual patterns that can be beneficial in treatment planning. Future applications of ESM could involve providing patients with immediate, personalized graphs based on recent input. Network analysis reveals the potential for accurately predicting relapse and other prognostic measures, facilitating the development of tailor-made interventions. However, understanding the complex interactions between symptoms in psychotic disorders requires further exploration of how ESM-based clinical network analysis can aid clinical practice2.

In addition to the clinical implications of this research, there may also be broader economic and societal advantages. Enhancing the effectiveness of mental health treatment could potentially mitigate the burden on healthcare systems and reduce the overall costs associated with treatment. Moreover, the positive impacts on individuals struggling with mental health issues could create ripple effects on their families and communities, potentially leading to improved social and economic outcomes. In terms of economic repercussions, it is estimated that the total costs of mental health issues amount to over 4% of GDP (exceeding €600 billion) across the 27 EU countries and the United Kingdom[3].

The need for effective preventive measures are particularly relevant considering that, according to the World Health Organization (WHO), in 2019, 1 in every 8 people, or 970 million people around the world were living with a mental disorder[4]. Similarly, in the United States, it is estimated that about 43.8 million adults (or 18.5% of the adult population) suffer from a mental illness in any given year[5], with only about half receiving treatment[5]. Consequently, mental health disorders remain among the leading causes of disability worldwide and are associated with negative outcomes such as decreased productivity, increased absenteeism, and an increased risk of physical health problems[5].

Given this context, and the prevention paradox principle suggesting that small-scale interventions may have a broader impact on the population compared to treatments focused exclusively on high-risk individuals[6]. Our thesis findings could motivate researchers to develop large-scale prevention strategies that address affective dysregulation and other risk factors in the general population. Potential strategies may include creating mental health awareness campaigns, promoting emotional intelligence education in schools, or integrating mental health support and social workers services into primary care settings[7]. By highlighting the role of risk factors such as stressful life events, economical stress, belonging to an ethnic minority group and others in the emergence of mental suffering, this research supports the suggested added value of incorporating social worker services into primary care settings[7].

Finally, I intend to share my research conclusions with other researchers and plan to present my findings at relevant conferences to engage with professionals in the field. Through various communication channels, I aim to emphasize the significance of my research and its potential impact on clinical practice and on the society on a larger scale. My goal is to continue researching complex dynamical systems, potentially focusing on the development of preventive clinical trials, training programs, and innovative methods for addressing mental health issues more effectively.

In summary, the research carried out in this dissertation holds the potential to make a substantial impact in the field of mental health treatment and prevention. It is my aspiration that these findings will be extensively disseminated and implemented in practice.

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Chapter 8

Summary / Samenvatting

Chapter 8
Summary /Samenvatting

The current comprehension of causality in psychiatric diagnoses has limitations, and there is a growing emphasis on novel techniques and analyses, such as experience sampling methodology (ESM) combined with a network approach, to enhance our understanding of these complex conditions. The all-encompassing goal of my research was to investigate the application of these techniques alongside traditional study and statistical designs to improve our insight into the emergence of psychopathology. Specifically, I examined the interplay between affective dysregulation and various genetic and environmental factors that may contribute to the development of clinical psychosis. Employing ESM and network analysis, I sought to obtain a more refined and comprehensive understanding of the complex factors influencing the emergence of psychopathology, particularly psychosis, and pinpoint potential targets for early intervention and treatment.

To achieve this objective, we conducted four studies, the results of which are presented in this thesis. The first and second studies investigated the utilization of ESM to depict affective dynamics in a network while examining gene and environment effects on it (chapter 2 and 3). The third study explored the application of long-term cohort incidence analysis to predict the probability and identify the factors contributing to the occurrence of clinical psychosis (chapter 4). The fourth study employed ESM in conjunction with network analysis to examine the dynamics of interacting momentary mental states in an individual patient diagnosed with paranoid schizophrenia over a year, aiming to understand the impact of illness severity and pharmacological treatment on symptom dynamics (chapter 5).

Our research has unveiled several key findings and general outcomes with significant implications for understanding the development of psychopathology, particularly psychosis, and for devising interventions to prevent or mitigate its impact. Affective dysregulation plays a crucial role in the relationship between psychosis expression and risk factors, such as genetics and environmental exposures. The causal system of emergent psychopathology, including psychosis, is multi-layered and involves numerous exposures and dimensions. These dimensions and factors interact in a complex, dynamic manner that necessitates an increase in exposure load before transitioning to a pathological mode.

Overall, this research's primary contribution lies in illustrating the potential of incorporating both intensive time series for examining affect dynamics and long-term cohort study techniques to enhance

our comprehension of psychopathology. Future research should not only consider these outcomes but also derive insights from them to further advance our understanding of these intricate conditions. These findings hold significant implications for practitioners, as they may employ ESM techniques to refine their diagnostic accuracy and treatment planning. Moreover, layered interventions targeting risk reduction, such as social welfare measures at the general population level or individualized psychotherapy for the clinical population, may prove effective in preventing the emergence of psychopathology.

Samenvatting

Het huidige begrip van causaliteit in psychiatrische diagnosen heeft beperkingen, en er is een groeiende nadruk op nieuwe technieken en analyses, zoals de experience sampling-methodologie (ESM) gecombineerd met een netwerkaanpak, om ons inzicht in deze complexe aandoeningen te vergroten. Het alomvattende doel van mijn onderzoek was om de toepassing van deze technieken naast traditionele onderzoeksdesigns en statistische technieken te onderzoeken om ons inzicht in het ontstaan van psychopathologie te verbeteren. Ik heb vooral gefocussed de wisselwerking tussen affectieve dysregulatie en verschillende genetische en omgevingsfactoren die kunnen bijdragen aan de ontwikkeling van klinische psychose. Door ESM en netwerkanalyse te gebruiken, heb ik geprobeerd een verfijnder en uitgebreider begrip te krijgen van de complexe factoren die het ontstaan van psychopathologie, in het bijzonder psychose, beïnvloeden en mogelijke aangrijpingspunten voor vroege interventie en behandeling te identificeren.

Om dit doel te bereiken, hebben we vier studies uitgevoerd, waarvan de resultaten in dit proefschrift worden gepresenteerd. De eerste en tweede studie onderzochten het gebruik van ESM om affectieve dynamiek in een netwerk weer te geven, terwijl werd gekeken naar de effecten van genen en omgeving hierop (hoofdstuk 2 en 3). De derde studie verkende de toepassing van langetermijn-cohortincidentieanalyse om de waarschijnlijkheid te voorspellen en de factoren te identificeren die bijdragen aan het optreden van klinische psychose (hoofdstuk 4). De vierde studie gebruikte ESM in combinatie met netwerkanalyse om de dynamiek van interactieve momentane mentale toestanden bij een individuele patiënt met paranoïde schizofrenie gedurende een jaar te onderzoeken, met als doel het effect van de ernst van de ziekte en farmacologische behandeling op symptoomdynamiek te begrijpen (hoofdstuk 5).

Ons onderzoek heeft verschillende belangrijke bevindingen en algemene resultaten opgeleverd met aanzienlijke implicaties voor het begrip van de ontwikkeling van psychopathologie, met name psychose, en voor het bedenken van interventies om de impact ervan te voorkomen of te verminderen. Affectieve dysregulatie speelt een cruciale rol in de relatie tussen psychose-uiting en risicofactoren, zoals genetica en omgevingsblootstellingen. Het causale systeem van opkomende psychopathologie, inclusief psychose, is meerlagig en omvat talrijke blootstellingen en dimensies. Deze dimensies en factoren hebben op een complexe, dynamische manier interactie met elkaar, die een toename van de blootstellingsbelasting vereist voordat wordt overgegaan naar een pathologische modus.

Over het geheel genomen ligt de belangrijkste bijdrage van dit onderzoek in het illustreren van het potentieel om zowel intensieve tijdreeksen voor het onderzoeken van affectdynamiek als langetermijn-cohortstudietechnieken op te nemen om ons begrip van psychopathologie te verbeteren. Toekomstig onderzoek zou niet alleen deze resultaten moeten overwegen, maar ook inzichten daaruit moeten afleiden om ons begrip van deze ingewikkelde aandoeningen verder te bevorderen. Deze bevindingen hebben aanzienlijke implicaties voor professionals, omdat zij ESM-technieken kunnen gebruiken om hun diagnostische nauwkeurigheid en behandelplanning te verfijnen. Bovendien kunnen gelaagde interventies gericht op risicovermindering, zoals sociale welzijnsmaatregelen op het niveau van de algemene bevolking of geïndividualiseerde psychotherapie voor de klinische populatie, effectief zijn bij het voorkomen van het ontstaan van psychopathologie.

Appendix

Acknowledgements
Curriculum Vitae
Published work

Acknowledgements

My journey as a Ph.D. student was not without its challenges. As a foreigner in a European country, I had to adjust to a new culture and learn to navigate the unique academic landscape. In a department where most students had previously been local master students, I faced challenges in building trust and working collaboratively with my peers and supervisors. At times, I found myself in disagreement with my supervisors, but through open communication, compromise, and a willingness to find common ground, we were able to resolve conflicts and continue moving forward. Despite these struggles, I am proud to have persevered and emerged as a stronger and more proficient scientist as a result. It is a testament to the unwavering support and encouragement of my family and the guidance and mentorship of my supervisors and professors.

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Curriculum Vitae

I am a Medical Doctor with a strong background in both clinical practice and research. I began my journey in the field of medicine in 1998 when I enrolled in the Faculty of Medicine and Pharmacy of Casablanca, Morocco. After completing my M.D. in 2007, I became a general practitioner and soon after that pursued a psychiatric residency. During this time, I also earned a Research Master in Neuroscience in 2011. In 2012, I obtained a cognitive and behavioural psychotherapy (CBT) certificate and completed my medical specialty in Psychiatry at the Psychiatric University Center Ibn Rochd in Casablanca.

In 2013, I had the opportunity to participate in a research internship at Maastricht University, where I gained valuable experience and knowledge in the field of research. From 2013 to 2015, I served as the Chief of a Regional Ambulatory Unit of Psychiatry in Morocco, overseeing and providing the care and treatment of patients with mental health conditions.

In 2015, I began my journey as a Ph.D. student and have been dedicated to furthering my education and research in the field of Psychiatry since then. In 2017, I began my psychiatric training in Germany, obtained my German medical license in 2019. and ,in 2022, my german CBT certificate. Concurrently, I continued to work diligently on my Ph.D. research remotely, maintaining a parallel focus on both my clinical and academic development.

Throughout my career, I have been driven by a passion for improving the lives of individuals suffering from mental health conditions. I am dedicated to continuing my education and research in this field and am committed to making a positive impact in the world of medicine.

Published work

Peer-reviewed Publications:

Hasmi, L., Bono, W., Ailal, F., Quessar, A., & Bousfiha, A. (2008). Les déficits immunitaires primitifs de l'adulte: Les déficits immunitaires. Espérance médicale, 15(150), 358-365.

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(2012, January 19). Hasmi, L., Saadouli, A., Monfardini, E., Battas, O., Meunier, M., Boussaoud, D., & Agoub, M. Social learning deficit in patients with schizophrenia. [Oral Communication] 10th Congrès de l'Encéphale, Session: Oral Communications 3 - Psychoses, Paris, France.

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(2012, Marsh 31). Hasmi, L., Kadri, N., & Eddahby, S. Cognitive therapy of bipolar disorder. [Oral Communication] World Regional Congress of Psychotherapy, Marrakech.

(2014, September 18) Hasmi, L., Moustaghfir Z., Layoussifi K. "Perceived Stigma in Families of Suicide Attempters" [Speaker of Regular Workshop] XVI World Congress of Psychiatry, Session: Social and Cultural Aspects of Suicide.

(2022, June 26). Can we really separate non-psychotic disorders from the Clinical High Risk for Psychosis phenotype? [Oral Presentation in a Symposium] The WPA Thematic Congress on Early Intervention in Psychiatry across the Life Span, Athens, Greece, 23-25/06/2022, https://www.erasmus.gr/microsites/1238.

Poster presentations:

Hasmi, L., & El Yazaji, M. (2010, October). What Diagnosis in Front of a Catatonia? 20th Congress of the World Association of Social Psychiatry, Marrakech, Morocco.

Hasmi, L., Manaf, S., Kasmi, F., Majri, N., Saadouli, A., & Kadiri, N. (2010, October). Addictive Behaviors in Hospitalized Adolescents in Psychiatric Settings. 20th Congress of the World of Social Psychiatry, Marrakech, Morocco.

Hasmi, L., & Battas, O. (2011). Simplified Arabic translation and transcultural adaptation of the MATRICS Consensus Cognitive Battery. GDRI Neuroscience School, "Neurobiology of adaptations to the environment", Faculty of Medicine and Pharmacy, Casablanca, Morocco.

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Network Complexity Modelling of Psychopathology

to encompass Symptoms, Genetic, and Environmental Influences

Laila Hasmi

This research delves into the underlying causal system influencing the emergence of psychopathology, with a focus on psychosis. Utilizing a dynamic network approach, the study shines light on the pivotal role of affective dysregulation as a mediator in the complex interplay between the onset of psychosis and its various determinants.

Key Insights:

- The central importance of emotional responses as a linking mechanism between the root causes of psychsis and the need for medical intervention.
- The efficacy of the Experience Sampling Method (ESM) as a valuable asset for individualized clinical care and treatment planning in the realm of psychotic disorders.
- The potential for breaking the cycle and preventing psychopathology through comprehensive, multi-layered strategies, including interventions focused on emotional regulation.

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