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Studies of the affective and developmental domains of psychopathology in psychosis

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CHAPTER 5

Summary

General comments

In this thesis, several studies are described concerning the *developmental* and *affective* aspects of schizophrenia and bipolar disorder, in terms of where they differ and overlap, and how that potentially overlaps in the *prodrome*.

Examination of the developmental and non-developmental risks of affective and non-affective psychotic disorders has important diagnostic implications, which led us to include work focusing on examination of diagnostic likelihood ratios of developmental and non-developmental risks in relation to the diagnoses of schizophrenia and bipolar disorder. This is discussed in Chapters 2 and 3.

The study of the developmental domains of affective and non-affective psychosis was carried out by examining areas where they differ and overlap in genetic and environmental factors shared by these two disorders (Chapter 3). In addition, several aspects of the prodrome, in terms of the distinction between bipolar disorder and schizophrenia, were investigated, examining the view that transition from subclinical states of psychometric risk in the general population to psychotic disorder can be viewed from the perspective of a psychosis continuum. In order to investigate this, aspects of the epidemiology of psychotic experiences in the general population, which may predict transition to various clinical psychotic disorders, was investigated (Chapter 4).

In the above-mentioned studies, data pertaining to both the NEMESIS and the EDSP data were examined. Additionally, we examined evidence from the literature using the methodology of qualitative and quantitative review of both observational and experimental studies.

Our findings

In **Chapter 2**, the developmental domains of affective and non-affective psychosis – in particular schizophrenia and bipolar disorder – were investigated. A common and well accepted position regarding the causes of psychiatric disorders, especially with schizophrenia, is the supposition of a multifactorial component (Johns & Van Os, 2001) similar to chronic physiological disease such as diabetes or cardiovascular disease. In the case of schizophrenia and bipolar disorder, this generally is taken to indicate that apart from the genetic component – with reported heritabilities of around 80% for schizophrenia and bipolar disorder – environmental factors may play a role as well. However, it is unclear what impact genetic and environmental factors have in terms of *attributable fraction* within these highly heritable diagnostic constructs. It is also unclear to what extent genetic factors play in their contribution to domains generally taken to reflect aberrant neurodevelopment, such as brain structural alterations associated with these disorders. Since pathophysiological findings demonstrate that there are brain changes in most psychiatric disorders, we wanted to investigate to what extent there is a genetic contribution to the development of brain structures. We also wanted to see if this genetic influence is also the cause of the brain changes in schizophrenia, because the brain changes in schizophrenia have been investigated more extensively than in any other psychiatric disorder.

In the ***first*** article, '***Heritability of structural brain traits: an endophenotype approach to deconstruct schizophrenia'***, a literature search on the heritability of brain structures in

healthy people, in people with schizophrenia and pedigrees was carried out. In this article, evidence from literature on the heritability of brain structures in healthy monozygotic twins was examined and the heritability rates in studies with monozygotic and dizygotic twins concordant and discordant for schizophrenia were summarised in order to be able to estimate the contribution of genetic and environmental factors to brain structures. Examination of the contribution of genetic and environmental factors was also investigated in pedigree studies, in which the genetic component can be estimated more accurately as environmental factors are assumed to play a minor role in pedigree effects. In addition, the genes that may be involved in these brain structures in the different subgroups were investigated.

The following conclusions were drawn from the studies: the brain structures that were formed earlier in life and also the deeper structures were more genetically influenced than structures formed later in life, which are more environmentally influenced. The findings were similar for most of the brain structures across the different groups. However, there were also conflicting results in different studies on the same brain structures both in healthy people and in patients with schizophrenia. The brain changes in schizophrenia are present in about 50% of the patients that are included in these neuroimaging findings. As for the genes underlying these effects on brain structures, there are not enough studies showing evidence for effects of specific genes on specific brain structures.

The use of brain structures as an endophenotype may be valuable in deconstructing the genetics of brain traits in healthy people, people with schizophrenia and in pedigrees. Taking into account the limitations of neuroimaging as well of genetic epidemiological studies, and considering the problematic assumption that monozygotic twins share the (prenatal and postnatal) environment to the same degree as dizygotic twins, that most studies included rely on, the results of this review can only be described as helpful for further research in defining which brain structures might be more genetically influenced and represent genetic effects underlying the aetiology of schizophrenia. More research is necessary, and it is too early to state to what extent brain structural alterations represent the genetics of schizophrenia, let alone bipolar disorder, in a meaningful way.

In the ***second*** article, '***Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment?'***, the developmental factors in the overlap or non-overlap between the two disorders, i.e. schizophrenia and bipolar disorder, were investigated in a qualitative review. The search was carried out by examining the evidence from the literature in the past ten years and by revisiting the view by Murray et al., who published an article in 2004 which advocated the view that bipolar disorder was identical to schizophrenia without, however, expression of developmental impairment.

Most of the findings by Murray et al. (2004) are still relevant, according to our findings from the literature. An additional finding was that in the past ten years, more evidence has arisen that genetic risk for schizophrenia is expressed in part as neurocognitive impairments, whereas genetic risk for bipolar disorder is only mildly expressed with neurocognitive alterations. General population studies show that both disorders have phenotypes that are associated with psychometric risk states in healthy individuals and that these psychometric states are similarly highly comorbid with each other. One other finding was that exposure to an urban environment impacts on specific developmental associations with schizophrenia which is not observed in bipolar disorder, although we did find in one of our analyses with the NEMESIS data (Chapter 3, first article), that urbanicity specifically impacts on the psychotic

but not on the affective dimension of bipolar disorder, suggesting dimension-specific effects across diagnostic categories.

In the ***third*** article, '***Extended psychosis phenotype – yes: single continuum – unlikely'***, an alternative theory opposing the categorical view of psychiatric disorder, in the sense of ill versus not ill (in contrast to the use of *continuum* as denoting a lack of contrast between disorder categories *within* psychotic illness), e.g. the continuum theory of psychosis, was investigated *conceptually* in an attempt to clarify whether a population psychosis continuum or, perhaps better described as *extended psychosis phenotype* exists and, if so, how this extended psychosis phenotype is distributed fully or quasi-continuous, and what determines whether some people experiencing psychotic experiences develop psychotic disorders later in life whereas others do not. Until recently, research on syndromal clustering of dimensions of psychosis was carried out almost exclusively in the population of people already attending mental health services, based on the assumption that symptoms observed in patients with psychotic disorder naturally did not exist outside mental health services. However, general population studies are showing that syndromal clusters of psychotic and affective symptoms not only exist in populations attending mental health services, but also are expressed as extended phenotypes in the general population (Stip & Letourneau, 2009). In order to be able to make a conceptual shift from studying clusters of psychosis dimensions in mental health services to the general population, it may not be productive to consider populations inside and outside the hospital as different at the level of symptoms *per se*, but at the level of whether or not *need for care* has developed. Not every person with a psychotic symptom will develop a clinical need, resulting in a visit to a general practitioner or to psychiatric services.

This subject is further investigated in the last article of chapter 4. We present in this article the first meta-analysis to ever attempt to estimate which people, given a certain level of expression of the extended psychosis phenotype in the general population (i.e. not in highly selected high-risk samples) will develop need for care, help-seeking behaviour and diagnostic status. Data were extracted from all published longitudinal studies in non-help-seeking general populations. We conclude that there are a number of variables predicting the transition of subclinical symptoms in general populations to clinical disorders. Not only the *load* of psychotic experiences is important, but also what type of coping the person develops, and the degree of persistence of these subclinical psychotic symptoms over time. We further suggested a new model for research across the psychotic spectrum, suggesting that there is a psychosis continuum, but not a single psychosis continuum.

In **Chapter 3**, studies concerning the affective domains of psychosis are presented. In the first two articles, NEMESIS data were analysed, in search for evidence for overlap (or non-overlap) between affective and non-affective psychosis. In the ***first*** article, '***Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder'***, urbanicity as an environmental risk factor for bipolar disorder was investigated, because reports on this issue have been inconsistent, whereas high rates of psychotic disorders have already been shown in numerous studies related to the urban environment. Our hypothesis was that any effect of urbanicity on the bipolar phenotype would be moderated by comorbid psychotic symptoms. The cumulative incidence of bipolar and psychotic symptoms and syndromes – assessed with the CIDI in relation to five levels of population density of place of residence – were examined. In addition, we examined the degree of comorbidity between broadly and narrowly defined bipolar phenotypes on the one hand and

the dichotomous presence of broadly (17.2%) and narrowly (3.8%) defined psychotic symptoms on the other, as a function of population density of place of residence.

Higher rates of bipolar disorder, however defined, were observed in more urbanized areas, as well as a strong interaction between comorbid psychosis and level of urbanicity, indicating that with greater degree of psychotic comorbidity, a greater effect size of the urban environment was observed. For bipolar disorder without psychosis, no effect of urbanicity was apparent. These results suggest differential environmental causal effects on affective and psychotic dimensions of bipolar psychopathology.

Given the fact that associations with urbanicity are thought to reflect the impact of an environmental exposure that interacts with genetic liability to produce illness (Van Os, 2003a, 2003b, 2004), these results should be examined in light of previous work in the field of both molecular genetics and genetic epidemiology that has shown that there is a substantial sharing of genetic risk between bipolar disorder and non-affective psychosis (Cardno et al., 2002; Berrettini W, 2003a, 2003b). This means that when two individuals have a similar amount of shared genetic liability for both bipolar disorder and schizophrenia, the one that becomes exposed to an urban environment may develop a more *psychotic illness*, whereas the one not exposed to an urban environment may develop a more *mania-only illness*, suggesting that within the bipolar spectrum the impact of urban environment on the occurrence of more psychotic illness may be mediated by a different pathway than the rate of more mania-only illness. These mechanisms of gene-environment interaction have also been described for other psychiatric disorders such as depression and anxiety, two conditions that have been shown to share genes that, however, produce differential outcomes depending on subsequent exposure to divergent environmental risk factors, some resulting in anxiety outcomes and other in depression (Kendler et al., 1987, 1992, Kendler, 1996).

In the ***second*** article, '***The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder'*,** the prevalence of subclinical psychotic and manic symptoms was investigated, in terms of how these subclinical population phenotypes co-vary with and impact on each other. Again, NEMESIS data were used and the degree of comorbidity between subclinical mania and subclinical psychosis was investigated. In addition, the impact of subclinical comorbidity on social impairment and on the transition from subclinical mania to onset of bipolar disorder was also investigated.

The lifetime prevalences of at least one manic and one psychotic symptom were 4.1% and 4.2%, respectively, but, after excluding the people with DSM-III-R diagnoses of bipolar disorder or psychotic disorder, these prevalences were 2.3% (subclinical mania) and 2.8% (subclinical psychosis). Regarding the question as to how these phenotypes co-vary with each other, it was found that individuals with subclinical mania had a 17% risk of subclinical psychosis, compared to 2.3% in those without ($p < 0.000$). Subclinical psychosis in individuals with subclinical mania was much more predictive of a future diagnosis of bipolar disorder. As for social impairment, there was a positive interaction between social impairment due to physical and psychological problems and subclinical psychosis, indicating that for a given level of subclinical mania, the coexistence of subclinical psychotic symptoms was more predictive of social impairment, although this statistical interaction was not significant.

Thus, the subclinical phenotypes of mania and psychosis are more prevalent than their clinical counterparts and cluster together. One of the mechanisms by which the clustering of subclinical mania and subclinical psychosis may be relevant for clinical outcomes is that pos-

sibly the formation of more toxic combinations of subclinical mania and subclinical psychosis may facilitate a higher transition to bipolar disorder. A better understanding of this pathway is crucial for the development of early intervention.

The study is important in showing that subclinical symptoms should not be neglected, since they result in higher transition rates from subclinical to clinical disorders; specifically the comorbidity of psychotic symptoms may be toxic in this regard. Subclinical phenotypes can be seen as intermediary phenotypes of a mood continuum that after exposure to additional risk factors may progress to a full-blown disorder (Hanssen et al., 2005), specifically in the presence of psychotic symptoms at the subclinical level.

In the ***third*** article, '***Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials'*,** the focus was on the maintenance treatment of depression, as a paradigm for sensitisation. Antidepressants are effective in the treatment of depression, but also in prevention of relapse after remission from an acute episode. It is unclear though, to what extent the prophylactic effect of antidepressants is moderated by the duration of the continuation phase, level of abruptness of antidepressants discontinuation, or the number of previous episodes. This study attempted to address these questions.

All published randomized, placebo-controlled, double-blind clinical trials available before May 2007 were identified that addressed the efficacy of continuation or maintenance treatment of major depressive disorder with either SSRIs or TCAs and included patients entering a maintenance phase after achieving remission from the acute phase.

The conclusions were that the overall reduction of relapse risk in the maintenance phase was highly significant for both SSRIs and TCAs over one year of follow-up of maintenance treatment. Treatment with an antidepressant results in approximately 70% reduction of risk of relapse, confirming previous findings by Loonen et al. (1991), Geddes et al. (2003) and Viguera et al. (1998). The prophylactic effect appeared to be constant over the length of the continuation phase. The major conclusion in this study was that recurrent episode patients experience less protection from antidepressants over the maintenance phase than single episode patients. This suggests that with increasing number of episodes, patients may develop a relative resistance against prophylactic properties of antidepressant medication. There was no difference between abrupt discontinuation of antidepressants versus gradual discontinuation on relapse rates, except for a particular subgroup of recurrent episode patients, for which the mode of discontinuation was important. In these patients, abrupt discontinuation may lead to a relapse, a problem that has been identified for lithium as well. This finding may be interpreted in the context of sensitisation or a kindling-like process, in which biochemical and physiological processes involved in the illness become progressively more easily triggered by the same circumstances or precipitants.

We develop the hypothesis that sensitisation, as a form of progressive behavioural sensitisation, would be evident in depressive disorder manifested by evidence of decreased response to treatment with an increasing number of depressive relapses. However, the sensitisation model may not only be applicable to depression. There is accumulating evidence that behavioural sensitisation may also be relevant for psychotic disorder and in particular for positive symptoms in psychotic disorders (Collip et al., 2010). In other words, sensitisation may be important for the affective pathway in psychotic disorder (Myin-Germeys & Van Os, 2007). Future studies should take this issue further, possibly focusing on both affective and

psychotic symptoms in psychotic disorder, also in relation to antidepressant treatment in this group.

In **Chapter 4**, we described to what extent findings in the literature and research in psychiatry on developmental and affective domains of psychosis are applicable to the prodrome. Research on the prodrome is important because it is known that disorders such as schizophrenia or bipolar disorder do not have a sudden onset. In many patients, the first episode is preceded by a lengthy pre-phase in which symptoms manifest themselves in attenuated form for prolonged periods, sometimes as long as years. These trajectories may be amenable to early intervention, in order to reduce the psychological, social and possibly biological disruption that can lead to poor outcome (Pantelis et al., 2003).

Although there are many studies on the prodrome, these may be biased to a degree due to the vagaries of the selection processes that underlie the *ultra-high-risk* samples. Moreover, there is considerable confusion about the meaning conveyed by the term *at risk mental state*.

In the ***first*** article, '***DSM-V and the 'Psychosis Risk Syndrome': Babylonic confusion'***, the focus is on whether DSM-V should consider the inclusion of a new category, called the *psychosis risk syndrome* – or possibly the related term *attenuated psychotic symptoms syndrome*. We make the point that this should not occur, since risk is not an appropriate term in this context because subjects already, by definition, have a need for care, and the predictive value in even ultra-high-risk samples is too low for use in clinical practice.

In the ***second*** article, '***The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results'***, a meta-analysis on psychotic experiences in the general population is presented, with a specific focus on unselected general population samples with psychotic experiences that are at risk of making the transition to a clinical disorder. The yearly risk of conversion to a clinical psychotic outcome in exposed individuals (0.56%) was 3.5 times higher than for individuals without psychotic experiences (0.16%). Conversion to a clinical disorder increased with the number, certainty, frequency, persistence and degree of affective dysregulation of psychotic experiences. The major finding in this study was the discrepancy between the 10% conversion rate in the high-risk literature compared to the actual 0.56% conversion rate in unselected population-based samples. The explanation for the discrepancy lies in the sample enrichment strategies through community awareness campaigns and other selective inclusion methods by which people participating in these high-risk studies are selected, creating a very high density of risk. The high conversion rates of the high-risk early intervention studies thus are based on sample enrichment strategies, rather than on clinical high-risk criteria *per se*.

CHAPTER 7

Summary in Dutch
Nederlandse samenvatting

Inleiding

Deze thesis behandelt verschillende onderzoeken naar een mogelijke overlap van schizofrenie en bipolaire stoornis. We zijn uitgegaan van de klassieke diagnoses van schizofrenie (niet-affectieve psychose) en bipolaire stoornis (affectieve psychose), zoals geclassificeerd in de diagnostische handboeken DSM-IV en ICD-9 (**Hoofdstuk 1**). In de affectieve psychose staat de stemmingscomponent op de voorgrond, terwijl in de niet-affectieve psychose de cognitieve component de hoofdrol speelt. We hebben naar een eventuele overlap, of juist een gebrek daaraan, gezocht op een tweetal domeinen van de affectieve en niet-affectieve psychose, nl. het *ontwikkelings- en het affectieve* domein; verder hebben we gekeken hoe deze domeinen van invloed zijn op de *prodromale* fase van de twee stoornissen.

Bevindingen

In **hoofdstuk 2** begonnen we met het ontwikkelingsdomein van de affectieve en niet-affectieve psychoses, in het bijzonder keken we naar de diagnoses bipolaire stoornis en schizofrenie. We deden dit aan de hand van 3 artikelen.

Een theorie met brede consensus over de oorzaken van psychiatrische aandoeningen is, dat het ontstaan kan worden teruggevoerd op een multifactoriële aetiologie, d.w.z. dat er meerdere factoren bijdragen aan het ontstaan van de aandoening. Schizofrenie en bipolaire stoornis kennen een erfelijkheid van rond de 80%, maar onduidelijk is hierin de bijdrage van gen/omgevingsinteracties. De genetische contributie als oorzakelijke factor kan tot expressie komen in de ontwikkeling van het brein en worden onderzocht met beeldvormend onderzoek van de hersenen van patiënten met schizofrenie in vergelijking met (i) hun broers/ zusters/familieleden en (ii) gezonde controlepersonen.

Omdat de ontwikkelingsneurologische breinveranderingen het beste onderzocht zijn in de schizofrenie, hebben we in het **eerste** artikel van hoofdstuk 2, ***Heritability of structural brain traits: an endophenotype approach to deconstruct schizophrenia***, een literatuurstudie gedaan naar de erfelijkheid van breinstructuren in 1) gezonde personen, 2) personen met schizofrenie en 3) niet-menselijke primaten, om zo een conclusie te kunnen trekken over de invloed van genetische en omgevingsfactoren op breinstructuren. Daarnaast hebben we gekeken of er genen zijn die bij de ontwikkeling van specifieke breinstructuren betrokken zijn.

We kwamen tot de volgende conclusies:

1) De breinstructuren die vroeg in het leven ontwikkeld zijn, of die diep in het brein liggen, ondervinden meer invloed van genetische factoren dan breinstructuren die later in het leven gevormd zijn en meer worden beïnvloed door omgevingsfactoren.
2) In de gepubliceerde onderzoeken zijn tot op heden geen specifieke genen gevonden die coderen voor specifieke breinstructuren; er is nog maar weinig onderzoek verricht op dit gebied.
3) Ondanks de beperkingen van neuroimaging en genetisch onderzoek, kunnen de bevindingen tot nu toe als leidraad dienen voor verder onderzoek naar genetische oorzaken die aan de basis van schizofrenie liggen.

In het **tweede** artikel, ***Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment***, hebben we gekeken naar een mogelijke overlap (of juist gebrek daaraan) van ontwikkelingsfactoren bij enerzijds schizofrenie en anderzijds bipolaire stoornis. De volgende conclusies konden worden getrokken:

1) De bipolaire stoornis is in vele opzichten "identiek" aan schizofrenie, maar mist, of vertoont in veel mindere mate, de ontwikkelingsneurologische beperkingen die de schizofrenie kenmerken zoals beschreven door *Murray et al*, 2004.
2) Uit de onderzoeken van de afgelopen 10 jaar komt naar voren dat het genetische risico op schizofrenie onder meer tot expressie komt als neurocognitieve beperking, terwijl dat bij de bipolaire stoornis veel minder het geval is.
3) Urbanisatie (leven in de grote stad) als omgevingsfactor heeft invloed op het voorkomen van de ontwikkelingsneurologische stoornis schizofrenie, maar niet op het voorkomen van bipolaire stoornis.

In het **derde** artikel, ***Extended psychosis phenotype-yes: single continuum-unlikely***, is de zogenaamde continuümtheorie van psychosen onderzocht en is getracht een conceptueel model te maken van een dergelijk psychosecontinuüm (in de zin van overlap met de normale mentale gesteldheid in de algemene populatie; ook wel *extended psychosis continuum* genoemd): wat maakt dat sommige mensen over het continuüm bewegen van lage waarden naar de hogere, klinische relevante expressiewaarden van psychose? Hiertoe werd onder andere een meta-analyse uitgevoerd (zie hieronder).
De conclusies die getrokken werden uit dit onderzoek zijn:

1) Er zijn meerdere variabelen die de overgang van subklinische symptomen in de algemene bevolking naar een klinische stoornis kunnen verklaren.
2) Niet alleen de hoeveelheid psychotische ervaringen, en hun frequentie, zijn belangrijk, maar ook wat voor soort mechanismen iemand ontwikkelt om hiermee om te gaan, alsmede de mate van persistentie (duur) van de klachten over de tijd.
3) Op basis van de huidige gegevens in de literatuur valt nog niet met zekerheid te zeggen of er werkelijk sprake is van een lineair continuüm, of dat er toch mogelijk kwalitatieve verschillen optreden op het uiterste einde van het continuüm.

In **hoofdstuk 3** zijn affectieve (stemmings-) domeinen van psychose onderzocht aan de hand van 3 artikelen. In de eerste twee artikelen zijn data van de NEMESIS-studie geanalyseerd en is er onderzoek gedaan naar evidentie van overlap (of gebrek aan overlap) tussen affectieve en niet-affectieve psychoses.

In het **eerste** artikel, ***Evidence that the urban environment specifically impacts on the psychotic but not on the affective dimension of bipolar disorder***, is onderzoek gedaan naar wonen in de stad als omgevingsrisicofactor bij bipolaire stoornissen.

De conclusie van de analyses was dat urbaniteit invloed heeft op het voorkomen van bipolaire stoornis, maar alleen in samenhang met psychotische comorbiditeit: het voorkomen van bipolaire stoornis zonder psychose is niet afhankelijk van de mate van stedelijkheid van de omgeving. Bij gelijke genetische kwetsbaarheid kan blootstelling aan urbaniteit dus meer schade aanrichten op het ontwikkelingsneurologisch domein.

In het **tweede** artikel, ***The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder*,** is de prevalentie van subklinische psychotische en manische symptomen onderzocht, met name hoe deze subklinische symptomen covariëren en op welke manier ze elkaar beïnvloeden.
De conclusies waren:

1) Subklinische manie in aanwezigheid van subklinische psychotische symptomen is meer voorspellend voor een toekomstige diagnose van bipolaire stoornis (is dus meer "toxisch" voor het beloop).
2) Er is een suggestieve positieve interactie tussen het optreden van sociale beperkingen in het kader van medisch-psychiatrische aandoeningen en subklinische psychose; de aard van de interactie was dat voor een gegeven niveau van subklinische manie, de (co-) aanwezigheid van subklinische psychotische symptomen meer voorspellend is voor het optreden van sociale beperkingen.

In het **derde** artikel, ***Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials***, is via de methode van de meta-analyse het fenomeen van de progressieve sensitisatie bij affectieve dysregulatie nader onder de loep genomen. Het onderzoek richtte zich op de onderhoudsbehandeling van depressies. Antidepressiva zijn effectief in behandeling van acute depressies en in het voorkomen van terugval na een acute fase ('relapse'). De vraag van het onderzoek was met name of de hoeveelheid eerdere depressieve periodes de beschermende effecten van antidepressiva kunnen beïnvloeden, wat compatibel is met het idee van progressieve sensitisatie: de kans om depressief te worden naar aanleiding van een zelfde hoeveelheid stress wordt met het verstrijken van de tijd steeds groter omdat het individu gesensitiseerd is. De conclusie van de meta-analyse was inderdaad dat patiënten die eerdere depressieve periodes achter de rug hebben, minder profiteren van het profylactisch (beschermend) effect van antidepressiva dan patiënten die een eerste periode van depressie doormaken. Dit kan worden verklaard door 'sensitisatie' of '*kindling-like*' processen: door de ontstane gevoeligheid worden de biochemische en fysiologische processen die tot de ziekte leiden gemakkelijker in gang gezet. Gezien het feit dat affectieve dysregulatie een kerncomponent is van psychose, verwachten we dat deze sensitisering ook een rol speelt bij psychose.

In **hoofdstuk 4** wordt aan de hand van 2 artikelen beschreven in welke mate de bevindingen uit de literatuur over de ontwikkelings- en affectieve domeinen van psychoses, toe te passen zijn op de prodromale fase. Onderzoek van de prodromale fase is erg belangrijk, omdat stoornissen als schizofrenie of bipolaire stoornissen meestal niet een plotselinge start of ontstaan kennen, maar vaak een lange prodromale fase hebben, waarin vroege interventie mogelijk is. Er is veel onderzoek gedaan naar deze prodromale fase, maar de onderzoeken geven mogelijk een vertekend beeld (bias) vanwege een idiosyncratische selectie van 'ultra-high risk' populaties, waardoor de voorspellende waarde meer wordt bepaald door de selectieve samenstelling van de onderzochte groep dan door 'ultra high risk'- criteria, met name *attenuated psychotic symptoms*. Echter wat nu de voorspellende waarde van *attenuated psychotic symptoms* in de algemene populatie is, blijft onbekend.

In het **eerste** artikel, ***DSM-5 and the 'Psychosis Risk Syndrome': Babylonic confusion*****,** wordt de DSM-V (in opzet) nader bekeken, met name wat betreft de eventuele inclusie van een *psychosis risk syndrome* (of mogelijk de daaraan verwante term *attenuated psychotic symptoms syndrome).* We tonen aan dat dit mogelijk verkeerd zou zijn, met name vanwege de boven beschreven *selective sampling* in de onderzoeken en het verkeerde gebruik van het woord "risk" in *psychosis risk syndrome*.

In het **tweede** artikel, ***The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results***, wordt een meta-analyse uitgevoerd met betrekking tot psychotische ervaringen in niet-geselecteerde representatieve populaties uit de algemene bevolking, en de voorspellende waarde van deze ervaringen voor het ontstaan van een psychotische stoornis. De conclusies waren dat:

1) het jaarlijkse risico op het ontwikkelen van een psychotische stoornis bij mensen met een of meer subklinische psychotische ervaringen (0,56%) 3,5 keer hoger is dan voor mensen zonder een psychotische ervaring,
2) het risico op transitie van subklinische psychotische ervaring naar psychotische stoornis toeneemt met aantal, frequentie, persistentie en mate van affectieve dysregulatie van de psychotische ervaringen,
3) de hoofdbevinding van de studie is de discrepantie tussen het 10% jaarlijkse transitierisico uit de *ultra high risk*- literatuur en het 0,56% transitierisico in ongeselecteerde algemene bevolkingsonderzoeken. De verklaring voor deze forse discrepantie ligt ons inziens in de manier van *selective sample enrichment* die wordt toegepast in de *ultra-high risk*- onderzoeken maar onterecht wordt toegeschreven aan psychopathologische '*ultra-high risk'* -criteria.

Toekomstige ontwikkelingen

Naar aanleiding van onze publicaties en literatuurgegevens kan geadviseerd worden om de psychotische stoornis, zowel affectieve als niet-affectieve, multidimensioneel te benaderen; dit vanwege de beperkingen die een categorale indeling van psychiatrische stoornissen met zich meebrengt voor de dagelijkse klinische praktijk, voor wetenschappelijk onderzoek in de psychiatrie en voor de hanteerbaarheid van deze diagnoses voor patiënten en familieleden. Daarbij kan worden uitgegaan van verschillende symptoomdimensies, die cross-sectioneel in verschillende mate en in verschillende combinaties aanwezig zijn in verschillende individuen, zoals voorgesteld door Van Os en collega's in een recente publicatie (Nature, 2010). In dit multidimensionele model kan uitgegaan worden van in ieder geval vier symptoomdimensies in het psychosesyndroom: affectieve dysregulatie (depressie, manie, angst), psychose (wanen, hallucinaties), negatieve symptomen (o.a. verminderde motivatie) en cognitieve veranderingen. In de algemene bevolking zijn lage gradaties van deze vier symptoomdimensies ook aanwezig, die beschouwd kunnen worden als de expressie van genetische en niet-genetische kwetsbaarheid voor psychose (prevalentie van rond de 10-20%). In plaats van ons vast te bijten op de erfelijkheid van grote en vage diagnostische entiteiten zoals schizofrenie, waarbij onduidelijk is welk deel van het erfelijkheidspercentage werkelijk door genetische factoren wordt bepaald en welk deel door gen/omgevingsinteractie, is het misschien beter om de

erfelijkheid van deze vier symptoomdimensies apart te bepalen. De symptoomdimensies zelf tonen matig tot hoge erfelijkheidspercentages, variërend van 40% erfelijkheid voor affectieve dimensies tot 40-60% erfelijkheid voor cognitieve dimensies.

Toekomstige onderzoekslijnen zouden de genetische en epidemiologische aspecten van het psychosespectrum moeten integreren; genetische epidemiologie zou het relevante fenotype (of de symptoomdimensie) moeten koppelen aan variabelen van *timing*, ernst en invloed van omgevingsfactoren, in een en dezelfde studieopzet. Dat betekent dat populatiecohortonderzoeken gecombineerd zouden kunnen worden met klinische onderzoeken om zo alle syndromen van het klinische en niet-klinische spectrum bij elkaar te brengen. Op deze manier zou het moleculair genetisch onderzoek (zoals *Genome-wide association studies* [GWAS] en de speurtocht naar zeldzame varianten met grote of kleine effecten) gecombineerd kunnen worden met onderzoek naar omgevingsfactoren, en gen/omgevingsinteracties in kaart kunnen worden gebracht.

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