Beyond classification

Clinical studies into psychosis spectrum disorders

Noortje van de Kerkhof

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Beyond Classification

Clinical Studies into Psychosis Spectrum Disorders

Classificatie en verder. Klinische studies naar psychosespectrumstoornissen

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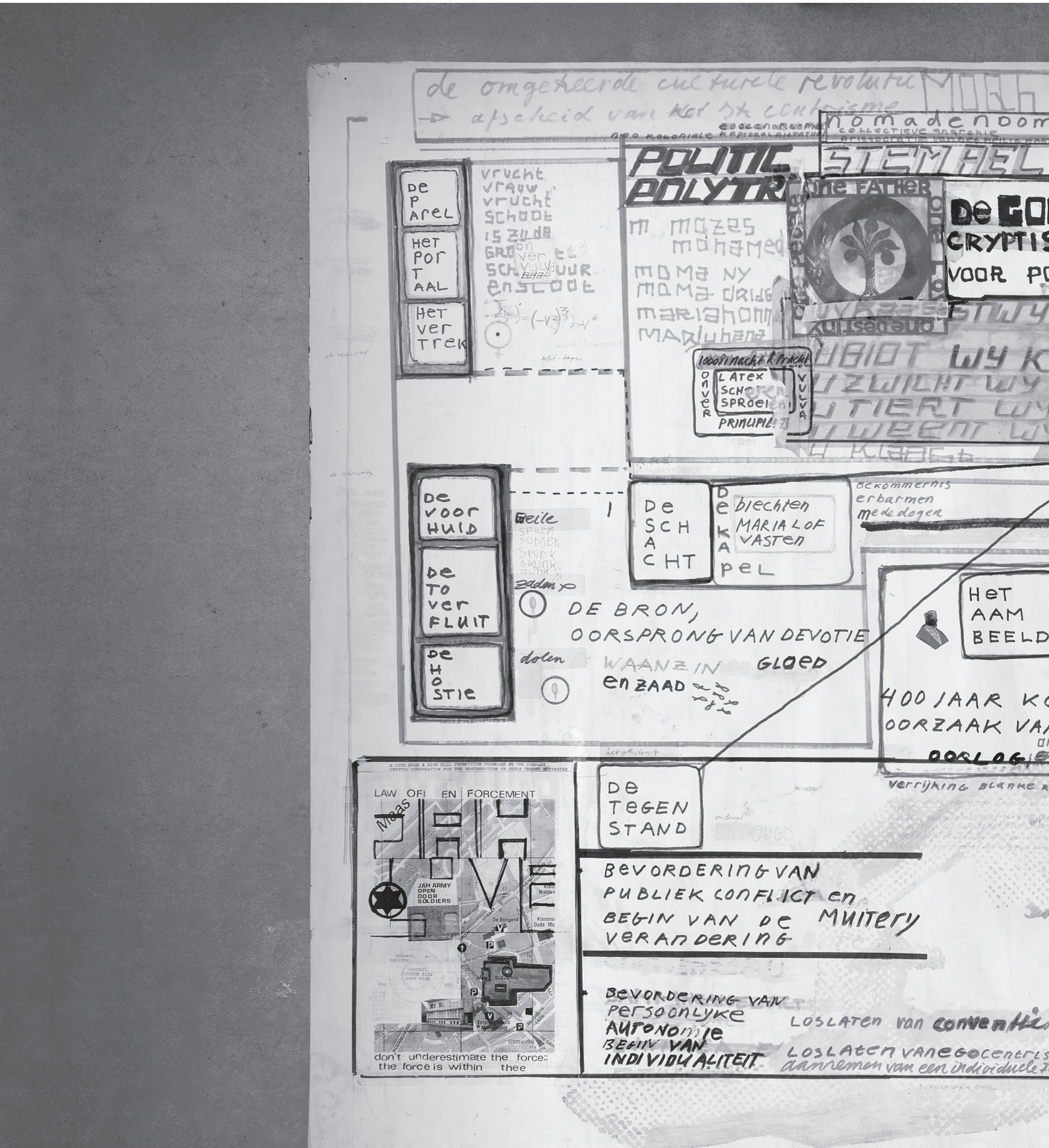
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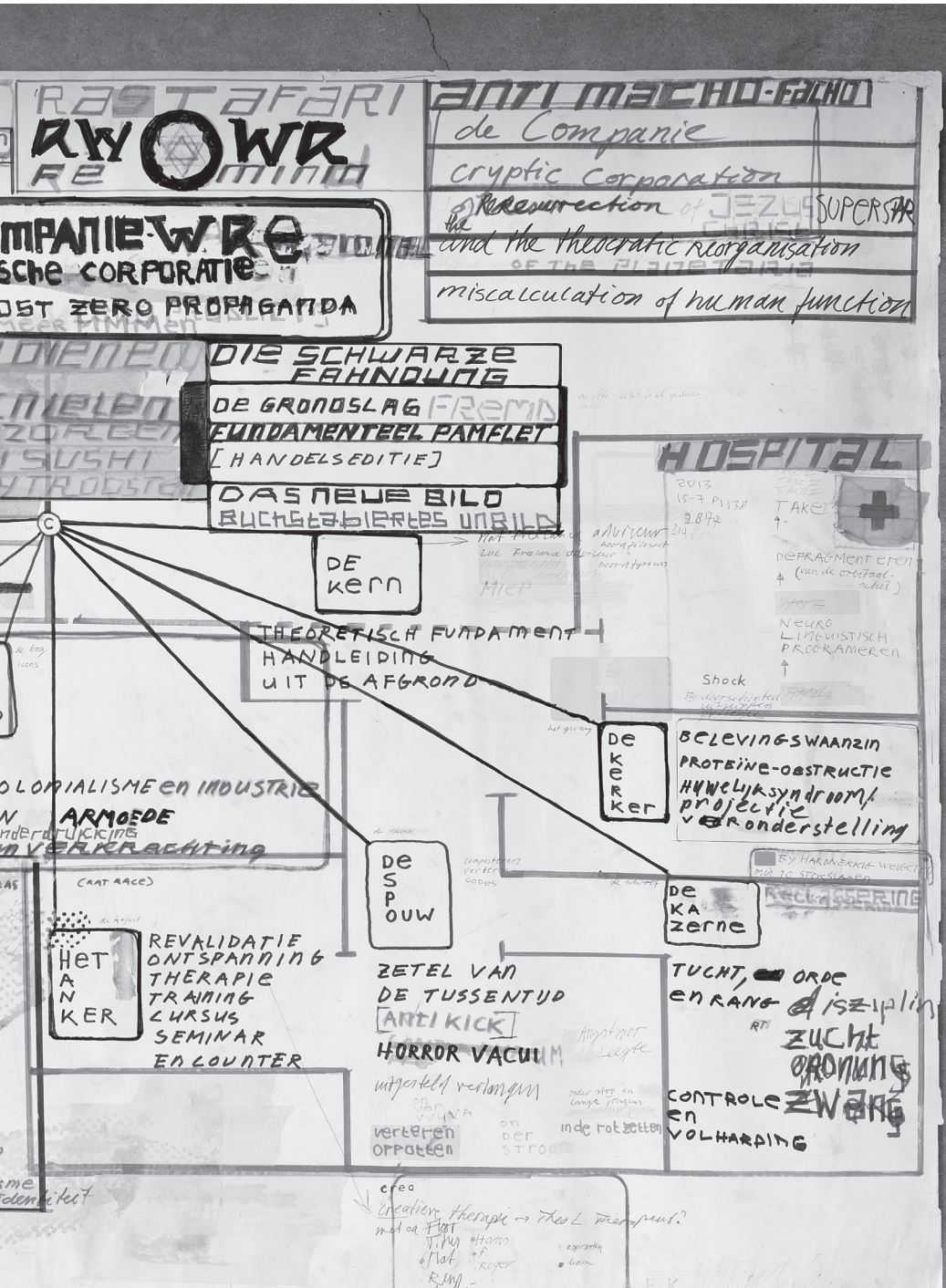
Chapter 1

General introduction



Psychotic disorders probably are the most impressive and disruptive disorders in psychiatry among those who suffer from them as well as friends, relatives or other people that come across subtle or striking symptoms like delusions or hallucinations. It is therefore not surprising that schizophrenia, the 'prototypic' psychotic disorder, is the subject of numerous books, movies and artwork. Many of these are informative and rightly illustrate symptomatology, course and impact of the illness. Many, however, comprise several incorrect prejudices about patients with psychotic disorders, such as split personalities, bizarre aggressive behaviours or lack of social skills. Nonetheless, they illustrate the complex and enigmatic character of psychoses and stress the need for a framework to evaluate and understand psychotic disorders.

1. Psychosis spectrum disorders

Psychosis spectrum disorders are characterized by (a combination of) delusions, hallucinations, disorganization, abnormal psychomotor activity and negative symptoms. These five dimensions are the backbone of classification of psychosis spectrum disorders in the widely used international classification systems and are used in most scientific research into psychotic disorders. The first four dimensions (1.1-1.4) are usually referred to as "positive symptoms".

1.1 *Delusions* are fixed ideas that do not correspond with reality and are held on to as absolutely true, even in the presence of contradictory evidence. Delusions can be persecutory, but also of reference or grandiosity. Delusions are called 'bizarre' when impossible and not corresponding with cultural background, such as insertion of thoughts or the idea of being controlled by an external power.

1.2 *Hallucinations* are sensory experiences in the absence of an external stimulus and can emerge in every modality (e.g. hearing or taste). Hallucinations occur independent of will and are vivid and emotion-loaded. To be of psychopathological significance, the sensory experiences should occur in the presence of clear conscience.

1.3 *Disorganization* of thought and speech can be noticed in or deferred from conversation. A dialogue can be complicated by e.g. frequent changes of subject, responses beyond the actual question or mere incoherence. Formal thought disorder is diagnosed when severe enough to seriously hamper normal communication and should be distinguished from language differences.

1.4 Thoroughly disorganized or *abnormal psychomotor activity* (including catatonia) interferes with goal-directed behavior. In catatonia, striking loss of reactivity to the environment is seen. It varies from posturing and mutism to smirking and motor excitement. Although catatonia is often associated with schizophrenia, it also occurs in severe mood disorders or somatic conditions.

1.5 Negative symptoms are most frequent in schizophrenia and less in other psychosis spectrum disorders. Most striking examples of negative symptoms are affective flattening and loss of volition. Other examples are social withdrawal, anhedonia and alogia.

2. Classification of psychotic disorders in DSM-5

In 2013, the fifth edition of the Diagnostic and Statistical Manual (DSM)[1] was published, although its predecessor DSM-IV (1994)[2] is still widely used. The chapter *Schizophrenia spectrum and other psychotic disorders* comprises clusters of the above mentioned symptom dimensions. In Table 1, psychotic disorders are listed according to DSM-5. Contrary to DSM-IV, in DSM-5 schizophrenia is not the opening act of the chapter, though it is still considered the most severe illness in the psychosis spectrum.

Table 1. Classification of psychotic disorders according to DSM-5

Code[1]	Classification[2]	Symptomatology[3]
301.22	Schizotypal personality disorder	Included in the chapter since it is considered part of the schizophrenia spectrum, although elaborated in the chapter *Personality disorders*.
297.1	Delusional disorder	Delusions in the absence of other psychotic symptomatology during at least one month.
298.8	Brief psychotic disorder	One or more positive symptoms, that do not meet criteria for schizophrenia and have a duration between 1 day and 1 month until full remission.
295.40	Schizophreniform disorder	Two or more positive symptoms during at least 1 month, but shorter than 6 months. Good prognostic features (e.g. acute onset and perplexity) are included as specifier and resemble the Leonhardian description of the cycloid psychoses.
295.90	Schizophrenia	Symptoms from the schizophreniform disorder with a duration of at least 1 month, but with significant functional decline before or since the onset of psychotic symptoms during at least 6 months. Specifiers included to classify course after one year or more. The subtypes from DSM-IV were abandoned, since they were of no prognostic value.
295.70	Schizoaffective disorder	Can be classified when both criteria for a depressive or manic episode and criterion A from schizophrenia are met simultaneously during a large part of the index episode, also including a period of at least 2 weeks in which delusions or hallucinations are present in the absence of mood symptoms. Whereas in DSM-IV the schizoaffective disorder was diagnosed cross-sectional, in DSM-5 the longitudinal character has been given more emphasis to avoid unsustainable classification.
291.9/ 292.9	Substance- or medication-induced psychotic disorders	Delusions or hallucinations caused by use of abuse of alcohol, drugs or medication.

Code[1]	Classification[2]	Symptomatology[3]
293.81/ 293.82	Psychotic disorders due to another medical condition	Prominent delusions or hallucinations that are the direct pathophysiological consequence of a somatic disease.
293.89	Catatonia	Contrary to DSM-IV, where it was considered a schizophrenia subtype, it is included in DSM-5 as both a specifier (associated with another mental disorder) and as a disorder due to another medical condition. Catatonia should comprise 3 or more symptoms from a total of 12.
298.8	Other specified schizophrenia spectrum and other psychotic disorder	Clinical presentations that resemble schizophrenia spectrum disorders, but do not meet criteria for any of the specific disorders, and in which the clinician chooses to specify the reasons why (not).
298.9	Unspecified schizophrenia and other psychotic disorder	Comprises presentations that resemble schizophrenia spectrum disorders and do not meet criteria for specific disorders, but in which the clinician chooses not to specify the reasons why (not), because of too little information (e.g. in an emergency room setting).

Note. [1] Diagnostic code derived from ICD, [2] Diagnostic category according to DSM-5, [3] Summary of core symptoms, inclusion and exclusion criteria

3. Advantages and disadvantages of classification

The development of classification systems, of which DSM is best known and most widely used, has worldwide been of great importance for psychiatry. The use of operational criteria to establish diagnoses has improved communication between psychiatrists and other (mental) health workers, since consensus was established on the basic elements of the disorder. Furthermore, by providing a nosological framework, it has promoted research into illness concepts across the boundaries of countries, making it possible to share and combine skills and knowledge of different countries and settings. For patients, the establishment of certain diagnostic classes (e.g., post-traumatic stress disorder, PTSD) has legitimated the burden of their mental problems by delineating these as psychiatric disorder, invoking proper use of mental health care facilities and/or social services. In the case of PTSD, but also with respect to other disorders, evidence based treatment guidelines have been developed to improve efficacy of treatment and outcome of disease. Moreover, in a domain as complex as psychiatry, a classification system provides a global summary to those who have to deal with known, possible or probable mental disorders in other than health care settings, such as policemen, lawyers, politicians and welfare workers.

A proper diagnosis should be informative about present and expected symptomatology ("what is going on?"), prognosis and expected course ("where are we going?"), but also on etiology and pathophysiology ("how and why did we get here?"). Most of the categorical labels from psychiatric classification systems such as DSM are at best informative about clusters of symptoms at the time of establishing a "diagnosis", since the categories are based

on symptomatology instead of etiology. Despite the fact that many risk factors for psychiatric disorders in general have been identified, expectations on course in the short and in the long run are hard to establish for individual patients. Diagnoses may alter during the course of the disease because of either their limited stability over time or change of definition of the diagnostic criteria in subsequent versions of the applied classification system.[3] Psychiatrists in general accept that classification, though helpful in many ways, is not the same as diagnosing. However, the "D" in DSM has led to reification of the categories which in turn has been abundantly applied by many authorities responsible for health care costs, insurance, legislation and jurisdiction.[4,5] Thus, a diagnosis has become not only important for choosing the right treatment, but also in many other ways, e.g., to use welfare, to avoid prison or to control (mental) health care costs.

4. Schizophrenia spectrum disorders

With respect to psychotic disorders, the general classification divides the spectrum into affective and non-affective psychosis, of which the latter are usually divided into schizophrenic and non-schizophrenic psychoses. The schizophrenic psychoses are considered to show an unfavourable course and prognosis, with gradual but steady decline in cognitive and social functioning.

The lifetime incidence of schizophrenia is estimated to be ~1% in developed countries.[6] Genetic studies have shown a heritability varying from 40-70% and a family history of schizophrenia has been demonstrated to be the most important risk factor.[7] Over the past years, substantial evidence has emerged concerning the relevance of gene-environment interactions for the onset and course of disease.[8,9] Schizophrenia spectrum disorders are reported in a variety of genetic disorders associated with copy number variations (CNVs; chromosomal microdeletions and microduplications). Best known in this respect are Prader-Willi syndrome[10,11] and 22q11 microdeletion syndrome.[12-14]

Dopamine is a central neurotransmitter involved in the pathophysiology of hallucinations and delusions, whereas glutamate has received special attention in relationship to negative and cognitive symptomatology.[15-17]

Risk factors for schizophrenia and related psychoses are, apart from genetic burden, among others urbanicity, structural brain damage (either hereditary or acquired), abuse of cannabis and obstetrical complications.[18] Schizophrenia-like psychoses are also observed in a variety of organic syndromes, like epilepsy.[19-21]

Outcome may vary dramatically between patients and it is thought that in ~20% the course of the illness is favourable, with full remission of symptoms and preservation of social and occupational functioning.[1] The remaining patients show a relapsing-remitting or chronic

course of disease. The presence of so-called atypical symptoms or negative symptomatology and the level of social and occupational functioning prior to first psychosis, are thought to be indicative for prognosis[22] but there are, to date, no objective parameters to predict disease course in individual patients. Some propose that the concept of schizophrenia should be conceptualized in different dimensions, to prevent aforementioned heterogeneity in patients with the same initial diagnosis (that mostly remains unchanged during follow-up). On the one hand, it is generally accepted that course and outcome vary between patients with similar diagnoses. On the other hand, given the way psychiatric diagnoses are established, it could also be argued that patients with different outcomes should instead be regarded as representatives of distinct illness entities.

5. Diagnosis in clinical practice

Psychiatrists are trained in establishing psychiatric diagnoses applying DSM (or other classification systems) using all available information in a longitudinal fashion. Since there are multiple sources of information, this can be a time consuming process. What makes it even more challenging in times of evidence based medicine, is the absence of objective individual conclusive tests (e.g., X-ray, blood test). Research into underpinnings of psychiatric illness is performed with emphasis on existing classifications, resulting in a great deal of information on categorical groups of patients. However, these findings cannot yet be translated into guidelines for individual patients. Moreover, since new concepts can only be accepted when "proven", this inward bound research practice seriously hampers innovative research across the current boundaries of classification. Schizophrenia might be the best known psychotic disorder, but psychoses emerge in many other psychiatric diagnoses. Many questions have remained unanswered to date. Where exactly do psychoses emerge? Does structural brain damage result in psychosis or vice versa? And how can findings in groups of patients be translated into information for individual patients in everyday clinical practice?

Research into psychotic disorders should be focused on further understanding of putative pathophysiological mechanisms in order to improve diagnosis and treatment. Neurotrophic proteins such as Brain Derived Neurotrophic Protein (BDNF) have been an area of interest because of associations of these proteins with neuroplasticity and disease severity.[23-25] The glutamate hypothesis has gained attention as a valuable extension for the dopamine hypothesis to understand the emergence of cognitive symptomatology.[26-28] Many biochemical parameters have been shown to be altered not only in schizophrenia, but in other psychiatric disorders as well. Hypotheses about altered neuroplasticity are not exclusive for DSM-categories, but appear to cut across diagnostic boundaries.[29-31] Furthermore, not all psychosis concepts to date have been incorporated in current classifications. Atypical psychoses, such as the cycloid psychoses

as described by Leonhard (1957)[32], differ from schizophrenia with respect to symptom profile, course and prognosis, but are not included *as such* in DSM or ICD.[33-35]

In times of scarce financial resources in general and mental health care, time to establish a diagnosis is limited and the focus lies on quick assessment of symptoms in order to achieve a categorical diagnosis initiating the corresponding treatment protocol. Diagnostic re-evaluation is time consuming and considered not to be cost-effective in the short run. However, in the long run, ineffective treatments and long-term use of medication might be prevented when re-evaluation would have been done on a regular basis. In general, patients do not present with an established DSM label but with psychosis, agitation, mania, anxiety or a combination of these. Objective, easily applicable tests that are independent from categorical diagnostic labels could be helpful in improving and facilitating the diagnostic process from the first visit on, thus providing individual patients with more accurate and personally applicable information on what to expect in weeks, months or even years to come.

6. Outline of the thesis

The present studies aim at contributing to the search for individual diagnostic tests for patients with psychotic disorders across diagnostic boundaries, that are both informative and easily applicable in everyday practice. In subsequent studies patients are assessed by different diagnostic methods always also including DSM and/or ICD in order to build upon previous research.

In **chapter 2**, the value of routine screening for CNVs by means of micro-array in patients with psychotic disorders is investigated. **Chapter 3** introduces a symptom checklist for cycloid psychoses according to Leonhard with focus on specific symptomatology. The concept of the cycloid psychoses is evaluated for prevalence, discriminating symptoms and concordance with current classification systems in a cohort of admitted patients with psychoses.

The next two chapters describe studies in which the associations between biochemical parameters, neuroplasticity and treatment responsiveness in patients with psychosis spectrum disorders are determined. **Chapter 4** deals with the neurotrophic proteins BDNF and S100B, and in **chapter 5**, the dopamine metabolite homovanillic acid (HVA) is addressed. In **chapter 6**, the concept of cycloid psychoses according to Leonhard is elaborated by means of direct comparison with DSM-IV schizophrenia on the level of biochemical parameters related to neuroplasticity, dopaminergic and glutamatergic neurotransmission.

Finally, in **chapter 7**, the most important findings of the presented studies are discussed in terms of other concepts regarding psychosis spectrum disorders and clinical management. Suggestions for future research are proposed.

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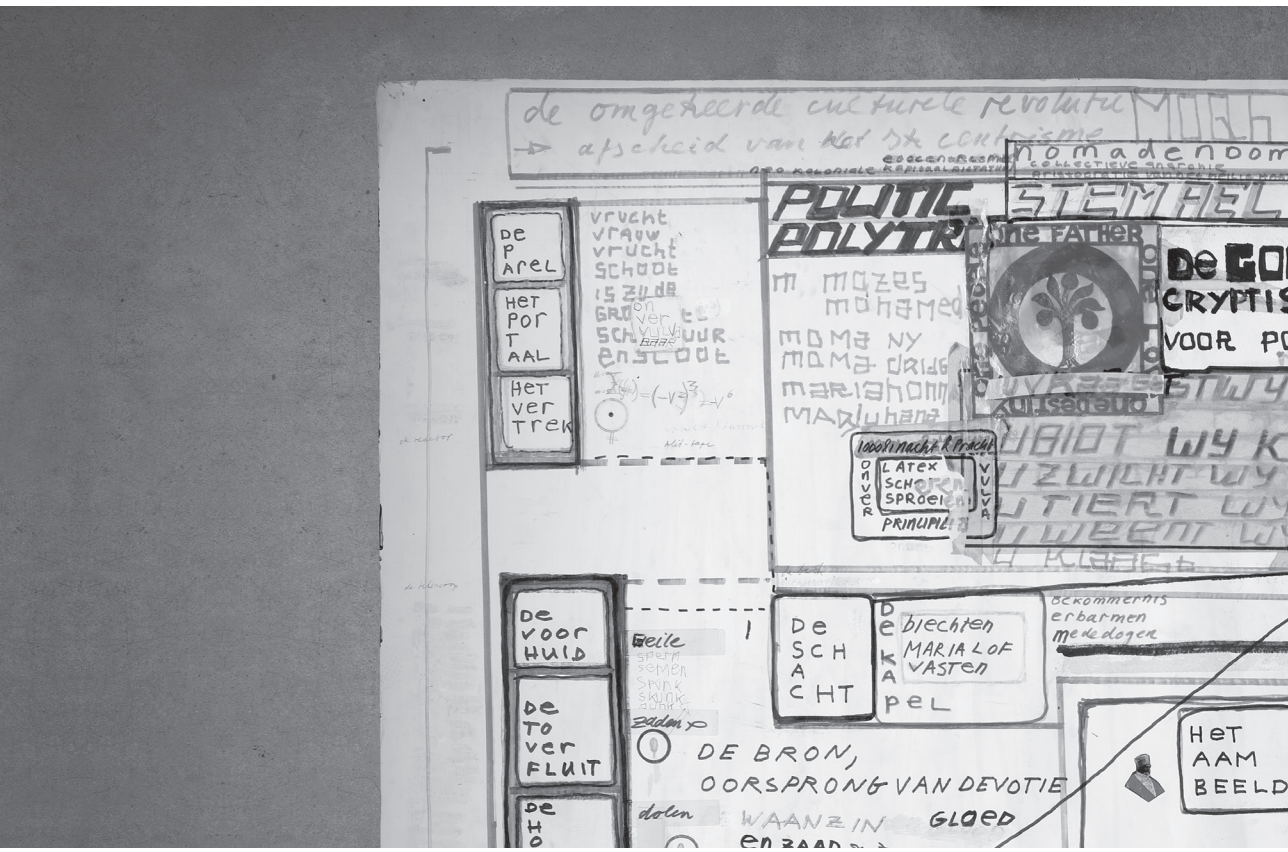
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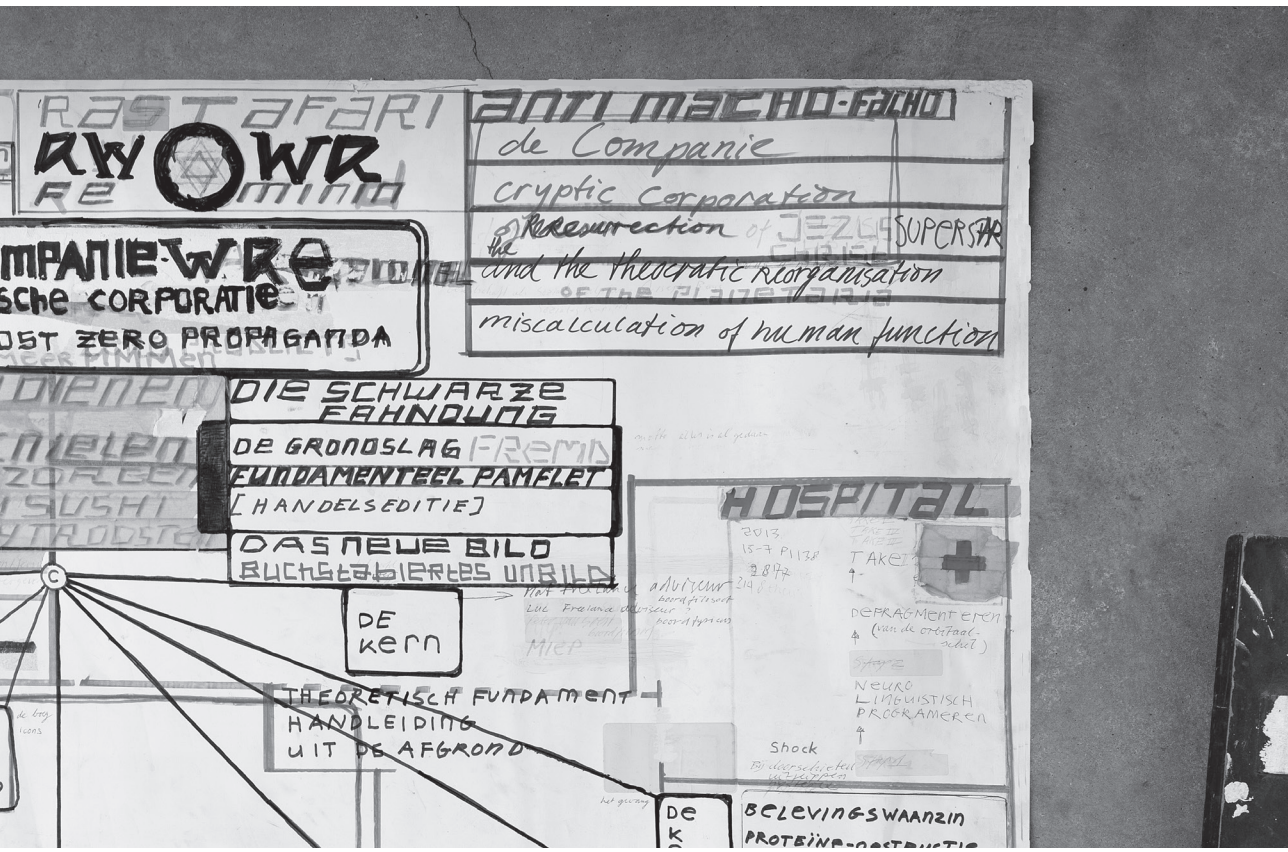
Chapter 2

Copy number variants in a sample of patients with psychotic disorders: Is standard screening relevant for actual clinical practice?



Noortje W.A. van de Kerkhof[1], Ilse Feenstra[2], Jos I.M. Egger[1,3,4], Nicole de Leeuw[2], Rolph Pfundt[2], Gerald Stöber[5], Frank M.M.A. van der Heijden[1], Willem M.A. Verhoeven[1,6]

[1]Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, the Netherlands
[2]Radboud University Nijmegen Medical Centre, Department of Human Genetics, Nijmegen, the Netherlands
[3]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, the Netherlands
[4]Behavioural Science Institute, Radboud University Nijmegen, the Netherlands
[5]University of Würzburg, Department of Psychiatry, Psychosomatics and Psychotherapy, Würzburg, Germany
[6] Erasmus University Medical Centre, Department of Psychiatry, Rotterdam, the Netherlands

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Abstract

With the introduction of new genetic techniques such as genome-wide array comparative genomic hybridization, studies on the putative genetic etiology of schizophrenia have focused on the detection of copy number variants (CNVs), i.e., microdeletions and/or microduplications, that are estimated to be present in up to 3% of patients with schizophrenia.

In this study, out of a sample of 100 patients with psychotic disorders, 80 were investigated by array for the presence of CNVs. The assessment of the severity of psychiatric symptoms was performed using standardized instruments and ICD-10 was applied for diagnostic classification. In three patients, a submicroscopic CNV was demonstrated, one with a loss in 1q21.1 and two with a gain in 1p13.3 and 7q11.2, respectively.

The association between these or other CNVs and schizophrenia or schizophrenia-like psychoses and their clinical implications still remain equivocal. While the CNV affected genes may enhance the vulnerability for psychiatric disorders via effects on neuronal architecture, these insights have not resulted in major changes in clinical practice as yet. Therefore, genome-wide array analysis should presently be restricted to those patients in whom psychotic symptoms are paired with other signs, particularly dysmorphisms and intellectual impairment.

Introduction

It has become obvious that the phenotypical presentation of psychotic disorders such as schizophrenia is extremely heterogeneous and that their symptoms may comprise the entire spectrum of psychopathology with a high interindividual variation.[1,2] Although the diagnostic boundaries of schizophrenia still remain unclear, the worldwide lifetime prevalence of this psychotic disorder is estimated to be 0.5-1%.[3] Previous studies have shown a heritability varying from 40-70%[4], and a family history of schizophrenia has been demonstrated to be the far most important risk factor.[5,6] Over the past years, substantial evidence has emerged concerning the relevance of gene-environment interactions for the onset and course of schizophrenia.[7,8]

With the ongoing developments in genetic techniques, particularly array-based comparative genomic hybridization analysis, it has become possible to investigate the human genome in far greater detail than is possible with routine cytogenetic analysis, leading to the discovery of previously undetectable defects.[9] These so-called copy number variants (CNVs) are deletions or duplications ranging in size from 1 kb to 3 Mb resulting in loss or gain of a DNA segment. *De novo* microdeletions are generally considered of clinical significance and are frequently associated with intellectual disability.[10] Of these patients, a substantial percentage develops symptoms from the affective and/or psychotic cluster after adolescence. Microdeletions and duplications may also be causatively involved in patients with normal intelligence and psychiatric disorders like schizophrenia[11,12] or autism.[13,14] In his review, Kirov[15] calculated a collective rate of 3% of patients with schizophrenia in whom rare deletions in 1q42, 22q11 and 1q21 and duplications in 16p are found. In the general population, this percentage is estimated to be 0.1-1%.[16] The explanatory power of CNVs for the pathophysiology of psychiatric disorders in general and for their phenotypical presentation, however, still needs to be clarified.[17,18]

In the present study, genome-wide array analysis was performed in a group of patients with carefully diagnosed psychotic disorders in order to detect possible pathogenic CNVs. If present, their phenotypical relevance was explored and discussed.

Methods

Patients and assessments

Over a period of 30 months, 100 patients referred to the Vincent van Gogh Institute for Psychiatry for treatment of psychotic symptomatology were investigated. Patients with previously demonstrated cytogenetic aberrations and/or intellectual disability (IQ <70) were excluded. According to the medical ethical guidelines, 80 patients gave written informed consent and 20 refused further participation (CCMO registration number: NL20469.097.07). Assessment of symptomatology and collection of data from history was performed using Comprehensive Assessment of Symptoms and History (CASH[19]), Positive and Negative

Syndrome Scale (PANSS[20]), and Clinical Global Impression Scale (CGI[21]). Final clinical diagnoses were made in a so called LEAD conference.[22] Subsequently, patients were classified according to ICD-10 criteria.[23] The main characteristics of the patients including the classification of their psychotic disorders are presented in Table 1. Pictures were taken of all patients for evaluation of dysmorphisms by an experienced clinical geneticist (IF). In case CNVs were found by array, the patient was examined in detail by the clinical geneticist.

Genetic analyses

DNA was isolated from an EDTA blood sample and genome-wide array analysis was performed with an average resolution of 200 kb using the Affymetrix 250k SNP array platform (Affymetrix, Santa Clara, CA, USA) as described previously.[24]

Table 1. Main characteristics of the patients (n=80)

	n	%
Male / female	53 / 27	66 / 34
Mean age / range (years)	35.0 / 18-62	
Mean age at onset of psychosis / range (years)	27.1 / 9-61	
Mean number of episodes / range	2.8 / 1-15	
Diagnoses (ICD-10)	n	%
- schizophrenia	50	62.5
- schizoaffective disorder	6	7.5
- acute and transient psychotic disorder	11	13.8
- bipolar disorder (psychotic)	6	7.5
- other psychotic disorders	7	8.8
PANSS scores (range) at inclusion		
- total score	86.1 (46-138)	
- positive subscale	23.1 (11-37)	
- negative subscale	19.9 (7-40)	
- global subscale	43.0 (22-67)	
Mean CGI score (range)		
- severity	4.5 (2-7)	

Results

As Table 1 shows, 50 patients fulfilled the criteria for schizophrenia (F20) and in 11 patients, a diagnosis of acute and transient psychotic disorder was made (F23). A diagnosis of schizoaffective disorder (F25) was established in six patients whereas in another six, bipolar affective disorder, current episode manic with psychotic symptoms, was present (F31.2). In the remaining seven patients, various diagnoses were made (F29: n=1; F28: n=2; F22: n=3; F21: n=1). All patients received antipsychotic medication according to the hospital standards.

If screening for dysmorphic features suggested a particular monogenetic disorder, specific genetic tests were performed. However, no abnormalities were disclosed. In 77 patients, microarray analysis did not reveal any abnormalities. In three patients, a submicroscopic chromosome imbalance was detected.

Table 2. Phenotype of the three patients with a potentially pathogenic CNV

patient	psychiatric phenotype	somatic phenotype	ICD-10 diagnosis	CNV
A (♀ 61)	pananxiety, religious delusions, delusions of influence, catastrophic thoughts, olfactory and auditory hallucinations	dysplastic ear helices, length and head circumference <2.5 SD	acute polymorphic psychotic disorder without symptoms of schizophrenia	3.5 Mb loss in 1q21.1
B (♂ 36)	pressure of speech, misrecognition of persons, thought incoherence, transient visual misinterpretations	no dysmorphisms	schizoaffective disorder, manic type	375 kb gain in 1p13.3
C (♂ 22)	delusions of persecution and grandiose identity, non-affective verbal hallucinations about himself	no dysmorphisms	acute schizophrenia-like psychotic disorder	1.1 Mb gain in 7q11.21q11.22

Patient A presented with a subacute onset of psychotic symptoms (total scores on PANSS and CGI-S: 79 and 4, respectively) that remitted within one month after treatment with 2.5mg haloperidol. Her history disclosed no major somatic or psychiatric diseases and there was no family load with neuropsychiatric or genetic disorders. In her, an interstitial loss of 3.5 Mb in 1q21.1 comprising 45 genes was found (Figure 1a). *Patient B* had a history of a mild and short lasting psychotic episode one year before admission and did not use any psychotropics. Apart from atypical psychotic symptoms, there were mild manic symptoms (total scores on PANSS and CGI-S: 78 and 5, respectively). With a treatment regimen comprising risperidone (4mg daily) and lithium (1600mg daily), all symptoms gradually resolved within three months. Here, a 375 kb interstitial gain was found in band p13 of chromosome 1 encompassing two genes (Figure 1b). *Patient C* had neither a history of any psychiatric or somatic disease nor a family load with neuropsychiatric or genetic disorders. Shortly prior to admission he developed paranoid psychotic symptoms (total scores on PANSS and CGI-S: 63 and 2, respectively) which fully remitted after one month of treatment with risperidone 4mg daily. He had a 1.1 Mb interstitial gain in 7q11.21q11.22 containing 11 genes (Figures 1c).

It remained unclear whether these CNVs had occurred *de novo* since in none of the patients blood samples of the parents were available for carrier testing. A concise description of psychiatric and somatic phenotypes as well as ICD-10 classification is presented in Table 2.

Figure 1a

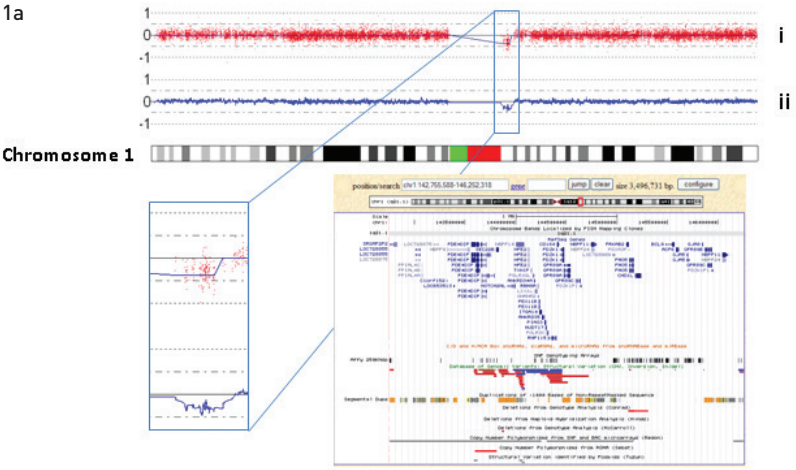


Figure 1b

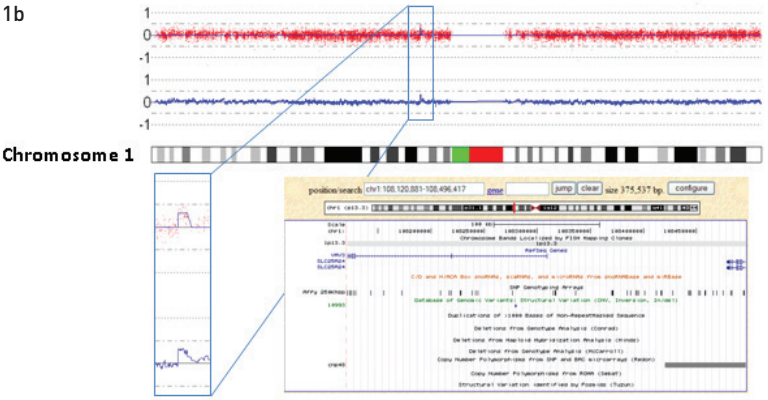
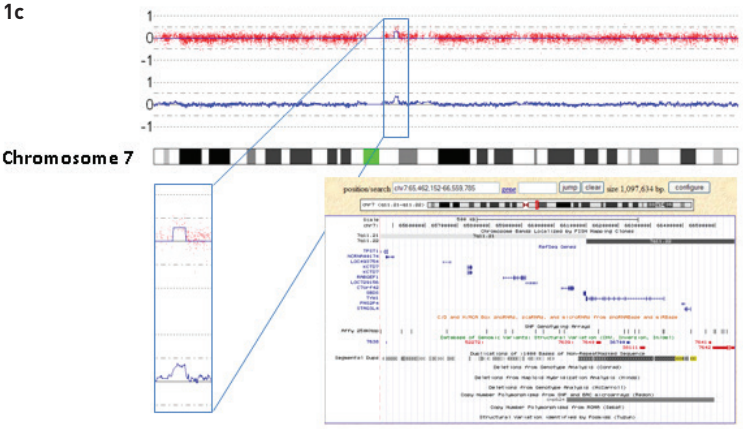


Figure 1c



Legend to Figure 1

In the upper panel (i) of each plot (A-C), the log2 test over reference ratio is plotted on the y-axis against the genomic Mb position from pter to qter on the respective chromosome represented by the idiogram on the x-axis in the lower part of each figure. Each red dot represents the average value for a certain SNP probe. The normal ratio with value 0 is indicated by the solid, horizontal blue line. Values for normal ratios range between -0.38 and +0.3. Values outside this range are considered abnormal.[39] In panel ii, the thick blue line represents the average of ten neighbouring SNP probe values. In each figure, the aberrant chromosomal region is indicated by a rectangle that is enlarged in the lower left side of that figure. The gene content, 250k SNP array probe coverage, structural variation and segmental duplications of the aberrant chromosomal region is shown in the lower right side of the figure (screen shot of the Human March 2006 (hg18) Assembly of the UCSC genome browser, http://genome.ucsc.edu/).

In 1a, the interstitial 3.5 Mb loss in 1q21.1 of patient A is shown. In 1b, the interstitial gain in 1p13.3 (375 kb) detected in patient B is shown, and in 1c, the 1.1 Mb interstitial gain in 7q11.21q11.22 of patient C is shown.

Discussion

In three out of the 80 patients with psychotic disorders (3.75%), one loss and two gains >250 kb were detected which is in accordance with the report by Kirov who calculated a collective percentage of 3% CNVs in schizophrenia.[15]

Apart from the recent report by Maiti et al,[25] who found three *de novo* CNVs (two gains and one loss) in 7q11.21 in two families with monozygotic twins discordant for schizophrenia in which, however, the breakpoints of these CNVs do not overlap with those in patient C, there is virtually no literature on the clinical significance. We recently detected a larger, completely overlapping gain of 2.4 Mb in 7q11.21 in a prenatal sample and the healthy father of this foetus with congenital diaphragmatic hernia. This makes it less likely that this gain is of clinical relevance.

With respect to 1p13.3, only Ohtsuki et al. reported on a possible association with the *netrin G1* (*NTNG1*) gene, located at 1p13.3, in Japanese families.[26] This does not, however, apply to patient B, nor does it clarify his symptom profile. Its relevance is further challenged by the detection of an exact similar gain in 1p13.3 (in addition to a pathogenic, *de novo* duplication in 10q) in an intellectually disabled patient without any psychiatric symptoms who inherited this gain from his healthy father (unpublished data).

Microdeletions in the 1q21 region have been reported in several genome-wide analyses in large populations.[27,28] A possible relationship between 1q21 and psychotic symptoms was reported by three research groups.[29-31] Maiti et al. reported on two *de novo* CNVs in families with monozygotic twins discordant for schizophrenia.[25] Several genes are mapped on 1q21, such as the *KCNN3*[32], *NOTCH2NL*[25], and *Connexin 40/50*.[33] Associations of these specific genes with schizophrenia in affected patients so far remain equivocal.

The results from this relatively small study using genome wide array analysis do not differ essentially from the reported large scale studies. It has to be stressed that the commonly applied diagnostic categories, derived from the ICD or DSM systems, show no relationship

to a specific genetic aetiology. Moreover, a single gene defect never codes for a categorical psychiatric disorder, but may lead to a biological dysfunction that has a certain probability to be associated with the development of an array of psychiatric symptoms.[14,17,18] This can best be illustrated by the discovery of the *DISC1* gene in one family that was originally thought to be causally related to schizophrenia[34], but later appeared to be involved in a biochemical cascade with consequences for neuronal functions predisposing for psychiatric symptoms across diagnostic boundaries.[35,36]

Although the CNVs detected in three out of 80 patients are not likely to be primarily involved in the evolution of their psychotic disorders, systematic genetic analysis in patients may reveal novel recurrent microdeletion syndromes that, however, are nearly always accompanied with developmental delay and dysmorphisms, and do not seem to correlate with psychiatric symptoms.[37,38] The counterpart microduplications in these regions often cause a much milder phenotype.

In conclusion, the results of this and other studies on the presence of CNVs in patients with psychotic disorders have not yet lead to a further specification of their pathophysiology nor to breakthroughs in clinical strategies. Therefore, while genetic analysis should always be considered as part of the diagnostic equipment in neuropsychiatry, the application of genome-wide array analysis in patients with psychotic disorders is mandatory only in the presence of other clinical signs such as facial dysmorphisms or developmental delay,

Acknowledgment

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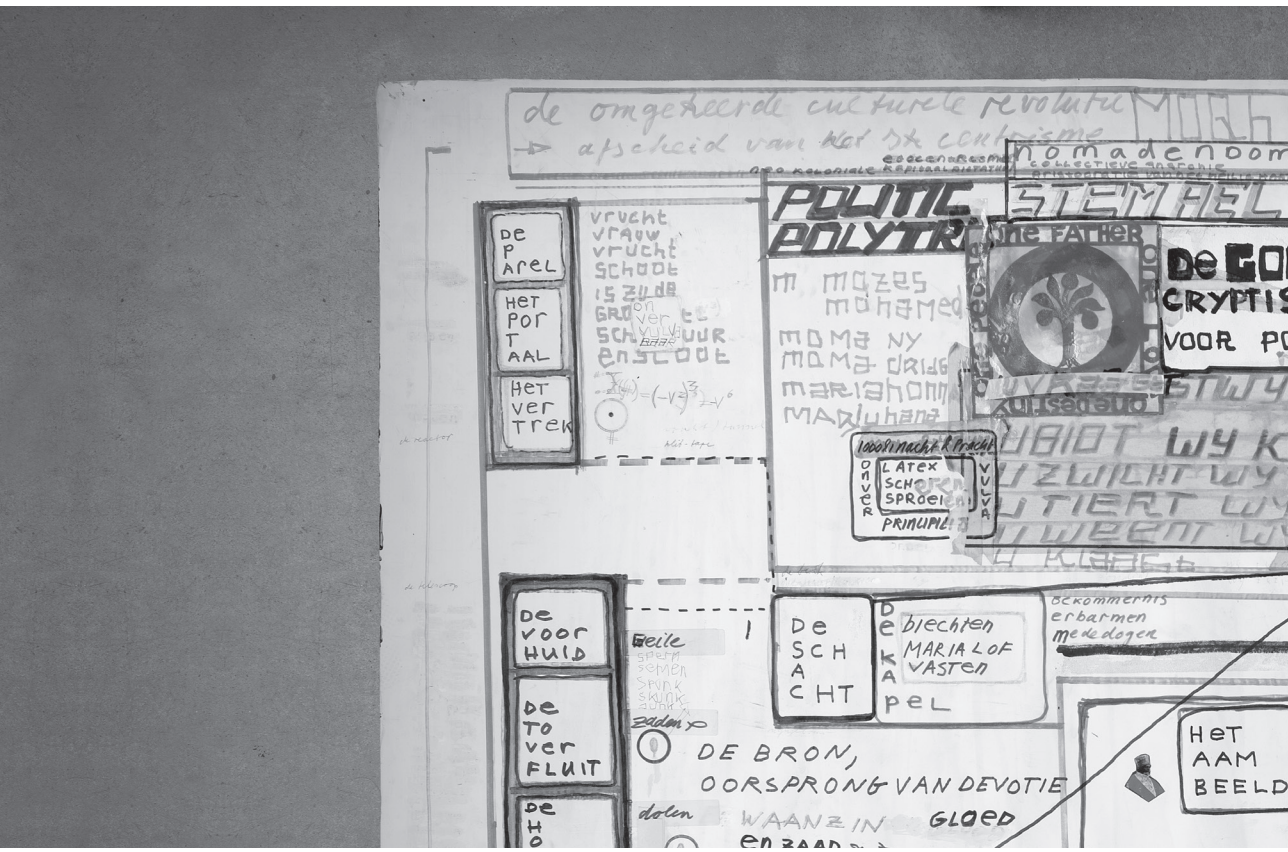
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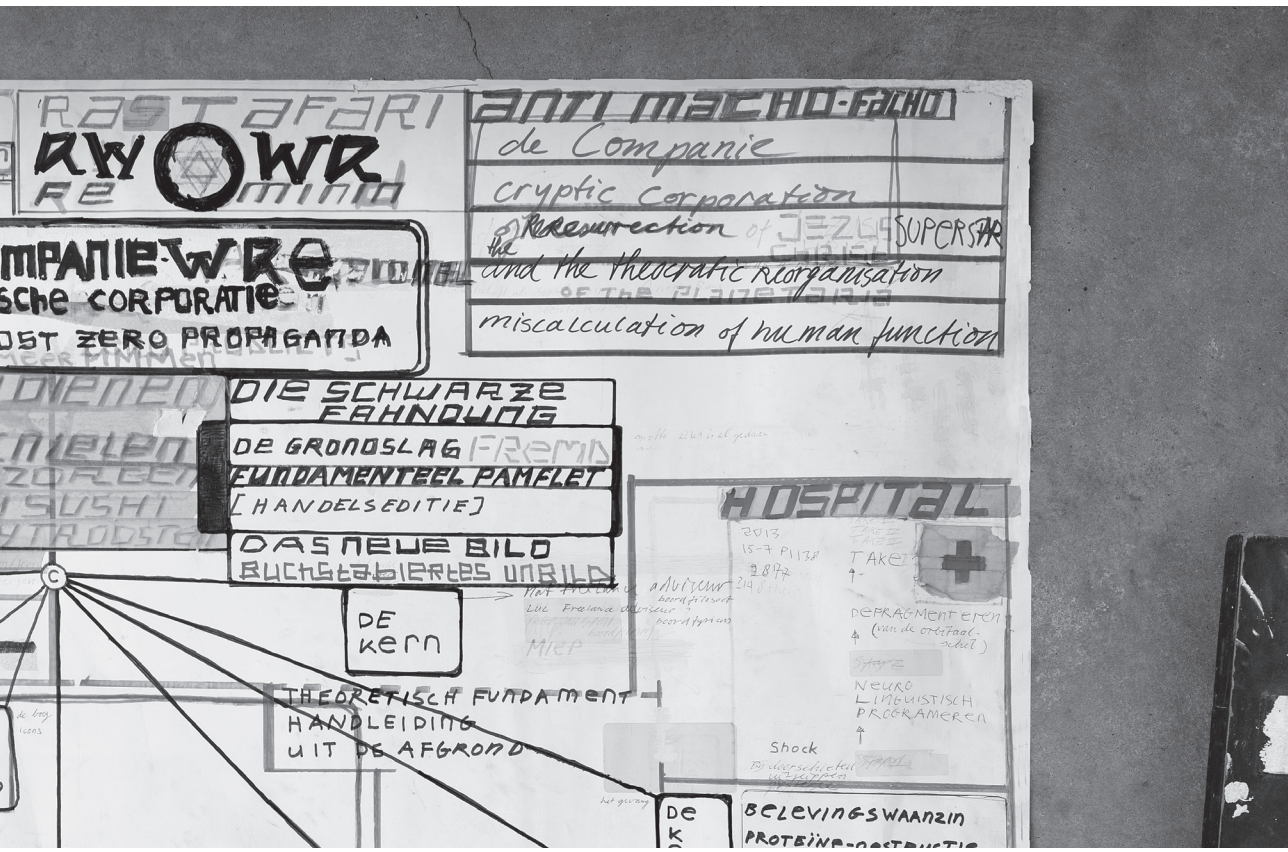
Chapter 3

Cycloid psychoses: Leonhard's descriptions revisited



Noortje W.A. van de Kerkhof[1,2], Frank M.M.A. van der Heijden[1], Marc K.F. Schneider[1], Bruno Pfuhlmann[3],Gerald Stöber[3], Jos I.M. Egger[1,4,5], Willem M.A. Verhoeven[1,2]

[1] Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, The Netherlands
[2] Erasmus Medical Centre, Department of Psychiatry, Rotterdam, The Netherlands
[3] University of Würzburg, Department of Psychiatry, Psychosomatics and Psychotherapy, Würzburg, Germany
[4] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands
[5] Behavioural Science Institute, Radboud University, Nijmegen, The Netherlands

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Abstract

Objectives: Cycloid psychoses are characterized by pleiomorphic symptomatology with intraphasic bipolarity, a remitting and recurrent course and favourable prognosis. Perris and Brockington (P&B, 1981) described the first set of operational criteria that were partly incorporated in ICD-10. The present study investigates psychopathological profiles according to the original descriptions by Leonhard, against the background of the criteria from the prevailing international classification systems.

Methods: Eighty patients with psychotic disorders were recruited and assessed with various psychometric instruments at baseline and after six weeks of antipsychotic treatment in order to investigate the presence of cycloid psychoses according to Leonhard (LCP) and the effect of treatment with antipsychotics. The overlap between LCP and DSM-IV Brief Psychotic Disorder (BPD), ICD Acute Polymorphic Psychotic Disorder (APP) and P&B criteria was calculated.

Results: Using P&B criteria and a symptom checklist adapted from the original descriptions by Leonhard, 14 and 12 cases of cycloid psychosis were identified respectively, reflecting a prevalence of 15-18%. Small though significant concordance rates were found between LCP and both DSM-BPD and ICD-APP. Concordance between LCP and P&B criteria was also significant, but modest.

Conclusions: This study demonstrates that LCP can be identified in a substantial number of patients with psychotic disorders. Cycloid psychoses are not adequately covered in current classification systems and criteria. Since they are demonstrated to have a specific psychopathological profile, relapsing course and favourable prognosis, it is advocated to include these psychoses in daily differential diagnostic procedures.

Introduction

As an independent group, the term "cycloid psychoses" was first coined by Kleist in 1926.[1] Psychoses with atypical symptoms had been described from the turn of the nineteenth century and were termed e.g., 'bouffées délirantes des dégenerées'[2], 'Degenerationspsychose'[3], acute schizoaffective psychosis[4], 'degeneratiepsychose'[5] and atypical psychosis.[6] About two decades ago, the psychopathological concepts about this type of psychoses were reviewed in detail by Tappe.[7]

In general, cycloid psychoses present with a (sub)acute onset and a polymorphic and shifting symptomatology comprising symptoms from both the schizophrenic and affective spectrum. Depending on the subtype, most typical symptoms are rapid mood swings, severe anxiety and/or ecstasy, confusional states and psychomotor disturbances.[8-11] In the fifties, based on the detailed longitudinal analysis of symptom profiles, Leonhard delineated three subtypes: anxiety-happiness psychosis, confusion psychosis and motility psychosis.[12] Later, Pfuhlmann and coworkers found high interrater reliability (Cohen's kappa: 0.82-0.89) of Leonhard's classification system.[13]

As to prognosis, cycloid psychoses show a remitting and recurrent course with a favourable outcome.[14-16] The only study on the pharmacological treatment of cycloid psychoses has demonstrated beneficial effects of lithium.[17] More recently, some evidence has been obtained that, in the acute phase, atypical antipsychotics may be useful.[18]

Although in 1952 the first edition of the DSM comprised a psychotic disorder with atypical symptoms resembling some features of the cycloid psychosis (termed schizophrenic reaction, acute undifferentiated type), later versions did not cover this diagnostic category. In fact, Kraepelin's dichotomy increasingly dominated the categorical structure in the consecutive editions of the DSM so that in DSM-IV[19], only Brief Psychotic Disorder (BPD) and Schizophreniform Disorder with specifier 'With Good Prognostic Features' partially cover the cycloid concept. This development and the increase of the clinical diagnosis of schizoaffective disorders resulted in a gradual loss of scientific and clinical interest for the cycloid psychoses. Recently, in their scholarly review, Jäger and coworkers stipulated the problematic reliability and validity of schizoaffective disorder and hinted at a fundamental reconsideration of the current diagnostic concepts of psychosis.[20] Similar suggestions were made by the research group of García-Andrade.[21] Therefore, the cycloid psychosis postulate needs to be revisited, particularly given its relevance for clinical practice.

The first set of operational criteria for cycloid psychoses in general was formulated by Perris and Brockington[22] and subsequently incorporated in the 'Diagnostic Criteria for Functional Psychoses' of the World Psychiatric Association.[23] Starting with the ICD-10[24], the category acute polymorphic psychotic disorder without/with symptoms of schizophrenia (APP) is included that was derived from the Perris and Brockington (P&B) criteria. This

category comprises, apart from cycloid psychosis, also the psychotic disorder bouffée délirante, used in France as a separate diagnostic category.

Clinical studies in patients with Leonhard's cycloid psychoses (LCP), using brain imaging[25] and event related potentials[26,27], have demonstrated that, in addition to variability in symptomatology, course and prognosis, this class of psychoses is etiologically distinct from schizophrenia and bipolar affective disorders.[28,29] In rare cases of cycloid psychosis, disturbances in amino acid metabolism were observed.[30,31] Hereditary factors have been demonstrated to play a minor role[32,33], whereas environmental factors like maternal first-trimester gestational infection and obstetrical complications seem to be of etiological importance.[34,35] Cycloid psychoses predominate in postpartum psychotic disorders.[36,37]

The present study aims at delineating cycloid psychoses according to Leonhard's original descriptions and analyses the diagnostic overlap with P&B as well as with ICD-10 and DSM-IV criteria.

Methods

Patient recruitment

All patients were recruited at the Vincent van Gogh Institute for Psychiatry, a large psychiatric teaching hospital in the southern part of The Netherlands with a catchment area of ~510.000 inhabitants. The recruitment period comprised 2.5 years (March 2008-September 2010).

Included were adult patients of both sexes (age range: 18-65 yrs) admitted for psychotic symptomatology that warranted treatment with psychotropics. Patients were included before the start or in the first week of treatment with psychotropics. In all cases, psychopharmacological treatment was performed according to the hospital standards by the responsible ward psychiatrist. Excluded were patients with proven genetic syndromes or intellectual disability. For this reason, a genetic work-up was performed by a registered clinical geneticist. Also excluded were patients with relevant somatic or neurologic diseases and females with post-partum psychopathology. All patients gave written informed consent following the Dutch medical ethical guidelines (CCMO registration number NL20469.097.07).

Table 1. Symptom checklist for cycloid psychosis (translated by Pfuhlmann [adapted from Leonhard, 1990])

	Original checklist symptom description	Translation
1.	Ängstliche Stimmung	Anxious mood
2.	Angstvorstellungen (Bedrohungsideen, ängstliche Beziehungsideen)	Anxious beliefs and delusions (ideas of threat, anxious ideas of (self-) reference)
3.	Ängstlich hypochondrische Ideen	Anxious hypochondriacal ideas
4.	Pathetisch-euphorische Stimmung	Ecstatic elation
5.	Beglückungsideen (altruistischer Charakter)	Altruistic ideas of happiness
6.	Angst und Euphorie im raschen Wechsel	Rapidly changing anxiety and euphoria
7.	Selbstopferungsideen	Ideas of self-sacrifice
8.	Affektkongruente optische Sinnestäuschungen (aus Angst oder Ekstase)	Mood congruent optical illusions or hallucinations (driven by anxiety or ecstasy)
9.	Affektkongruente Stimmen (aus Angst oder Ekstase heraus)	Mood congruent voices (driven by anxiety or ecstasy)
10.	Rededrang mit Inköhärenz der Themenwahl	Pressure of speech with incoherence of thematic choice
11.	Beziehungsideen mit Ratlosigkeit und Hemmung	Ideas of reference with perplexity and thought inhibition
12.	Bedeutungsideen bei Ratlosigkeit	Ideas of significance in association with perplexity
13.	Stimmen aus Ratlosigkeit	Voices in association with perplexity
14.	Denkhemmung	Inhibition of thought
15.	Ratloser Stupor	Confused stupor
16.	Flüchtige Personenverkennungen	Fleeting misrecognition of persons
17.	Psychomotorische Erregung mit vermehrter Ausdrucks- u. Reaktivmotorik	Psychomotor excitement with increased expressive and reactive movements
18.	Starke Ablenkbarkeit durch äußere Gegebenheiten	Strong distractability by environmental stimuli
19.	Sinnlose ("leerlaufende") motorische Aktivität (keine Vielgeschäftigkeit!)	Senseless motor activity (not general overactiveness!)
20.	Sinnlose motorische Sprachentäusserungen (Schreien, Johlen, Wortfetzen)	Senseless motor speech expressions (screaming, yelling, syllables)
21.	Psychomotorische Verlangsamung	Psychomotor slowing
22.	Stupor mit starrer Motorik	Stupor with stiff posture

Note:
Symptom 1-9: *Anxiety-happiness psychosis*
Symptom 10-16: *Confusion psychosis (inhibited/excited pole)*
Symptom 17-22: *Motility psychosis (akinetic/hyperkinetic pole)*

During the study period, a total of 194 patients were admitted for evaluation and treatment of psychotic symptoms of whom 100 were judged to be eligible for inclusion. Twenty patients refused to participate yielding a study group of 80 patients of whom 63 were available for follow-up assessment (i.e., 63% of the initial selected group).

Diagnostic procedures and scoring instruments

Baseline diagnostic instruments comprised Comprehensive Assessment of Symptoms and History (CASH)[38], Positive and Negative Syndrome Scale (PANSS)[39], and Clinical Global Impression scales for Severity and Improvement (CGI-S/CGI-I).[40] The CASH was specifically developed for research in the schizophrenia and affective spectrum conditions and is not uniquely connected to a classification system. PANSS and CGI were re-assessed at week 6. These assessments were performed by a well-trained PhD resident in psychiatry (NvdK).

Subsequently, classification was performed according to DSM-IV[19] and ICD-10[24] by NvdK and FvdH. Independently, the criteria for cycloid psychoses as advanced by Perris and Brockington[23] were applied to all subjects by a psychiatrist specifically trained in the diagnosis of cycloid psychosis (MS). In addition, using the symptom checklist of Leonhard[12,41] (Table1), an internationally recognized psychiatrist (GS) delineated patients with LCP. Accordingly, a division into the three subtypes of cycloid psychosis was performed.

Analogous to a so called LEAD consensus conference[42], in a final meeting with all investigators chaired by an independent experienced psychiatrist (WV), all available classificatory data were discussed to analyse the differential application of the various sets of criteria.

Statistics

For all statistic procedures, SPSS 14.0 software was used. Group differences were tested using the Student's t-test for continuous variables and Chi-square test for nominal variables. Cohen's kappa was used to test the concordance between the different categorical diagnostic groups. Significance was tested against $p<0.05$.

Results

1. Total patient sample and symptomatic reduction after 6 weeks

The total group comprised 53 males and 27 females (mean age ± SD: 35 ± 11.5). Mean age at first episode and mean duration of psychotic disease were 27.4 ± 10.7 and 7.6 ± 7.9 years respectively. According to DSM-IV, 48 patients met the criteria for Schizophrenia. The remaining 32 patients fulfilled diagnostic criteria for Brief Psychotic Disorder: n=10, Psychotic Disorder NOS: n=7; Bipolar Disorder: n=7; Schizoaffective Disorder: n=5; Delusional Disorder: n=2; and Schizotypal Disorder: n=1.

Patients were treated with classical/first generation (n=27) and atypical/second generation (n=61) antipsychotics, either as monotherapy (n=72) or in combination (n=8). After six weeks of treatment, scores on the PANSS total, positive, negative and global scales decreased from 86 to 69 (20%), 23 to 17 (26%), 20 to 17 (15%) and 43 to 35 (19%) respectively. The CGI-S improved from 4.5 to 3.4 (23%). All comparisons were statistically significant ($p<0.001$).

Table 2. Core symptomatology in patients with cycloid psychosis (Leonhard, 2003)

no	sex/age	signs and symptoms	Leonhard diagnosis
1	♀, 27	fear of death, suspicion, suspicious anxiety, mood congruent imperative voices with aggressive behaviour towards mother	anxiety psychosis
2	♂, 39	mutism, stupor, no spontaneous action, bad self-care, severe akinetic symptoms, reduced thinking	motility psychosis, akinetic pole
3	♀, 35	moving and removing things, elated mood, non-goal directed psychomotor activity, sleep disturbances, paranoid ideation, angry outbursts	motility psychosis, hyperkinetic pole
4	♂, 36	pananxiety, religious delusions, anxious stupor, perseveration, verbigeration	anxiety psychosis
5	♀, 53	anxiety and dysphoria, behaviour driven by suspicion, mood congruent delusions of guilt, mood swings, transient auditory, tactile and olfactory hallucinations	anxiety psychosis
6	♂, 39	illogical thinking, higher awareness of meaning, visual misinterpretations, delusions of reference	confusion psychosis
7	♂, 36	delusion of grandiosity, pressure of speech, poor concentration, visual misinterpretations, psychomotor agitation, chaotic behaviour	confusion psychosis
8	♂, 47	anxiety, religious delusions, pressure of speech, emotionally driven behaviour, illogical thinking	anxiety-happiness psychosis
9	♀, 33	chaotic thinking, auditory hallucinations, mood swings, inadequate behaviour	confusion psychosis (inhibited pole)
10	♀, 61	anxiety-driven behaviour, catastrophic thinking, illogical speech, delusions of persecution and control, mood swings	anxiety-happiness psychosis
11	♀, 46	chaotic and inhibited, confusion, ritualistic behaviour, perseveration, disorganised speech, paranoia	motility psychosis
12	♀, 56	psychomotor agitation, sleep disturbances, delusions of reference and grandiosity, chaotic thinking	motility psychosis

2. Diagnosis of cycloid psychoses according to Leonhard and P&B criteria

Concerning cycloid psychosis according to P&B, 14 patients (18%) met the criteria. According to Leonhard's descriptions, in 12 patients a cycloid psychosis was present reflecting a prevalence of 15%. Leonhard's cycloid psychoses could further be specified as anxiety-happiness psychosis (n=5), confusion psychosis (n=3) or motility psychosis (n=4). Brief case vignettes are depicted in Table 2. Of the 14 patients with P&B cycloid psychoses, 9 also accorded with Leonhard's descriptions (Table 2: no 1-4, 6-9, and 11).

Table 3. Clinical characteristics of the sample (n=80); Leonhard cycloid psychosis (LCP) versus non-cycloid psychosis (Non-CP)

	LCP (n=12)	Non-CP (n=68)
Demographics		
Male/female ratio	5/7	48/20
Age, years (mean ±SD)*	42.8 (±10.5)	33.1 (±11.2)
Age at onset general symptoms (mean ±SD)**	31.8 (±12.6)	20.9 (±10.8)
Age at onset psychosis (mean ±SD)**	38.2 (±11.2)	25.5 (±9.5)
Number of episodes (mean ±SD)	2.2 (±1.5)	2.9 (±2.8)
PANSS total score baseline	77	88
PANSS total score after 6 weeks**	55	72
DSM-IV diagnoses		
- Schizophrenia	0	48
- Schizoaffective disorder	2	3
- Bipolar disorder	2	5
- Brief psychotic disorder	7	3
- Psychotic disorder NOS	1	6
- Delusional disorder	0	2
- Schizotypal disorder	0	1
ICD-10 diagnoses		
- Schizophrenia	0	50
- Schizoaffective disorder	4	2
- Bipolar disorder	1	5
- Acute and transient psychotic disorder [1]	7 (4)	4 (3)
- Psychotic disorder NOS	0	3
- Persistent delusional disorder	0	3
- Schizotypal disorder	0	1
Meeting Perris & Brockington criteria for cycloid psychosis	9	5
Antipsychotic treatment		
- Classical agents	2	17
- Atypical agents	10	43
- Combination of antipsychotic agents	0	8

** Difference between LCP and Non-CP cases, p<0.05. ** Difference between LCP and Non-CP cases, p<0.01. 1 Any F23 diagnosis, including acute schizophrenia-like disorder. The numbers of patients meeting criteria for Acute Polymorphic Psychosis (APP; F23.0/F23.1) are inserted between brackets.*

In Table 3, the main characteristics of the non-cycloid (n=68) and LCP (n=12) patient groups with their corresponding DSM-IV, ICD-10 and P&B diagnoses are presented. As can be inferred, the LCP subgroup has a higher age at onset of both psychosis and general psychiatric symptoms. LCP as well as non-CP groups show diagnostic heterogeneity, albeit that a diagnosis of schizophrenia, according to ICD and DSM, is exclusively made in the non-CP group. In the LCP group, diagnoses of DSM-IV Brief Psychotic Disorder or ICD-10 Acute and Transient Psychotic Disorder are represented more often.

With respect to severity of symptomatology as assessed with the PANSS, total scores at baseline did not reveal differences between the two groups. After 6 weeks of treatment with antipsychotics in a naturalistic setting, however, the symptomatic decrease was more pronounced in the cycloid group ($p<0.01$).

3. Psychopathology

Detailed analysis of the individual symptomatology of the LCP patients (n=12) and those who met the P&B criteria (n=14), revealed that the seven symptoms 'ecstatic elation', 'altruistic ideas of happiness', 'rapidly changing anxiety and euphoria', 'pressure of speech with incoherence of thematic choice', 'confused stupor', 'psychomotor excitement with increased expressive and reactive movements' and 'stupor with stiff posture' (Table 1, symptom checklist items 4-6, 10, 15, 17 and 22) are most prevalent in both or either group of patients, indicating that bipolarity of mood, thought and locomotion, frequently occurring also intraphasic, are key symptoms of cycloid psychosis. Moreover, these key symptoms are virtually identical to those from the extreme poles as originally described by Leonhard.

Table 4. Frequency distribution of Perris & Brockington criteria in Leonhard cycloid psychosis (LCP) and non-cycloid psychosis (Non-CP)

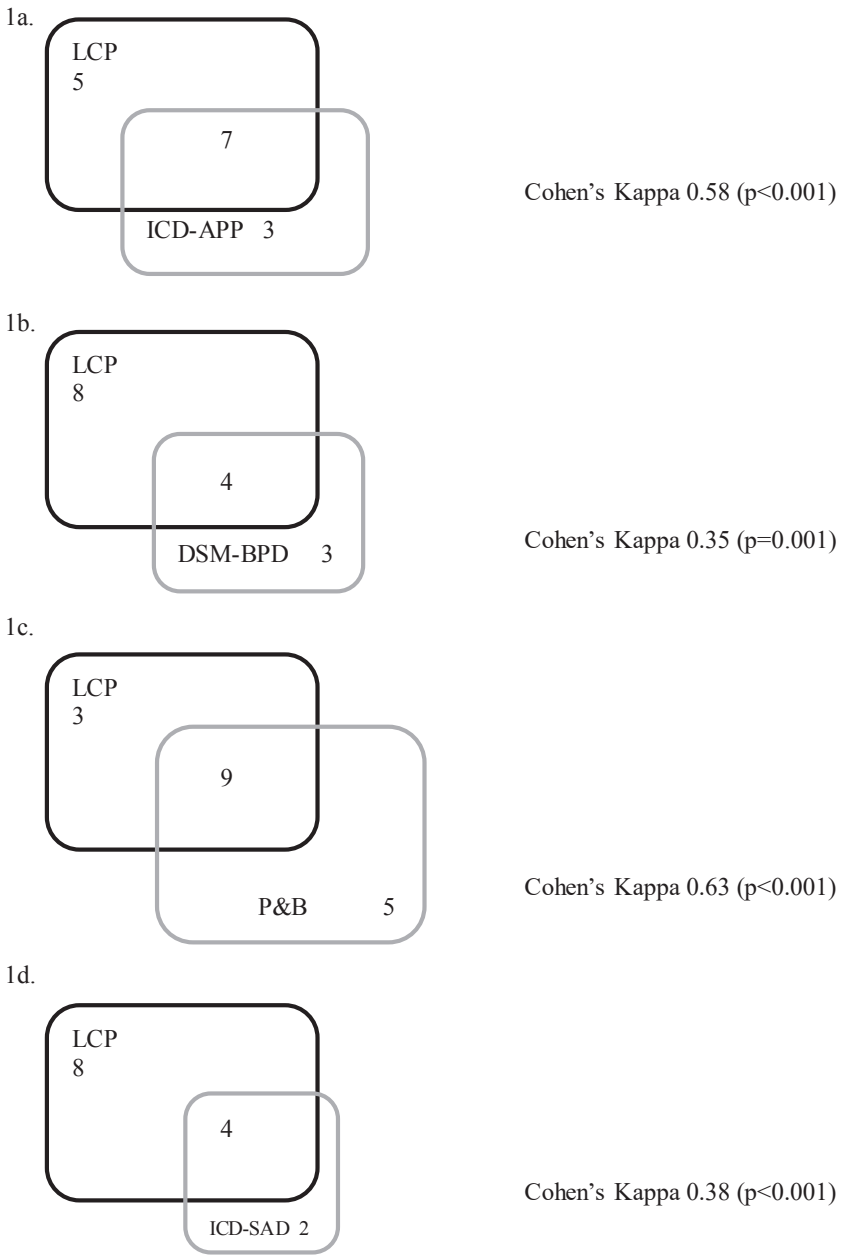
	LCP (n=12)		Non-CP (n=68)		p
Perris & Brockington criteria	*n*	*%*	*n*	*%*	χ^2
Perplexity	11	91.7	12	17.6	<0.001
Ecstatic feelings	6	50.0	14	20.6	0.030
Akinesia or hyperkinesia	8	66.7	15	22.1	0.002
Mood-incongruent delusions	12	100	64	94.1	n.s.
Hallucinations	12	100	56	82.4	n.s.
Pananxiety	9	75.0	20	29.4	0.002
Concern with death	4	33.3	10	14.7	n.s.
Mood swings	6	50.0	20	29.4	n.s.
Acute onset	12	100	8	11.8	<0.001

Table 4 illustrates the symptom profile of the 12 patients with LCP as compared to the group of non-cycloid psychosis (n=68) by applying the P&B criteria. Whereas delusions and hallucinations are present in most of the patients in both groups, the atypical symptoms (perplexity, ecstatic feelings, motility disorders and pananxiety) are overrepresented in the LCP subgroup.

4. Cycloid psychosis: representation in ICD/DSM and concordance rates

Concordance rates were calculated for LCP (n= 12) and the most frequent DSM-IV and ICD-10 diagnoses in this group (see: Table 3). Between LCP on the one hand and DSM-BPD and ICD-APP on the other hand a concordance rate of 0.58 and 0.35 (both $p \leq 0.001$) was present respectively (Figure 1a,b). A concordance rate of 0.63 ($p<0.001$) was calculated between LCP diagnosis according to Leonhard's symptom checklist and P&B criteria whereas a rate of 0.38 ($p<0.001$) was found between LCP and ICD schizoaffective disorder (SAD) (Figure 1c,d). The concordance between LCP and DSM-SAD did not reach statistical significance.

Figure 1a-1d. Concordance rates



Legend to Figure 1.
Concordance between Leonhard's cycloid psychosis (LCP, n=12) and a: DSM-IV Brief Psychotic Disorder (DSM-BPD, n=10), b: ICD-10 acute polymorphic psychotic disorder (APP, n=7), c: Perris and Brockington criteria (P&B, n=14) and d: ICD-10 schizoaffective disorder (ICD-SAD, n=6).

Discussion

In this observational study with a group of patients admitted for psychotic disorders, the presence of cycloid psychoses according to both Leonhard's descriptions and the criteria as established by Perris and Brockington, was investigated. A prevalence rate of 15% was found for Leonhard's cycloid psychoses (LCP). It appeared that cycloid psychosis can also be diagnosed according to the P&B criteria, whereas application of Leonhard's descriptions additionally provides differentiation in the three subtypes

The highest concordance was calculated between LCP and P&B, whereas lower concordance rates emerged between LCP and the different ICD-10 (APP and SAD) and DSM-IV (BPD) categories (Figure 1a-d).

With respect to the prevalence of cycloid psychosis, the here observed frequency of 15% is in accordance with that reported by other investigators (8-24%).[14,43-46] The prevalence from this study may, however, be biased negatively since female patients with postpartum psychopathology were a priori excluded and the sample size was limited due to the strict inclusion criteria as defined by the Dutch ethical rules for genetic work-up and for patients admitted under a legal act. Still, the overrepresentation of female patients in our cycloid group is in line with the results from other studies.[11,14,47]

Since the majority of the patients who were diagnosed as LCP were classified as ICD-10 APP or DSM-IV BPD, the concordance rates between these categories are most relevant (Figure 1a,b). Albeit that the observed values are higher than those reported by Pillmann and coworkers[47] with ICD-10 Acute and Transient Psychotic Disorders (including APP) of 0.36 and by Van der Heijden and coworkers[46] with 0.24 for BPD and 0.31 for APP, it has to be underlined that in the latter studies, patients were classified according to P&B criteria only. This suggests that the criteria for DSM-BPD and ICD-APP do neither cover sufficiently the descriptions by Leonhard nor the P&B criteria and that particularly Leonhard's symptom checklist is most promising for clinical practice. It has to be stressed, however, that this study is the first to systematically investigate this checklist in its relation to classification systems and thus needs further scientific evaluation.

The observed discrepancies in overlap between LCP and both ICD-APP and DSM-BPD may be explained by the duration criterion. In DSM-IV as well as ICD-10, a maximum duration of 1 to 3 months is required which excludes a priori the cycloid psychoses that are characterized by highly variable duration and frequently relapsing course.[18,35,48-51]

As can be inferred from Figure 1c, the concordance rate between LCP and P&B is also rather moderate which may be due to the onset and age criteria, in that the onset criterion in P&B comprises a time interval of hours to days, while in LCP this is not quantified. Moreover, in P&B the criterion age is restricted to the range 15-50 years, while according to the original monograph, LCP does not comprise any age limitation. That three LCP cases are discordant

with P&B cycloid psychosis, is explained by the age criterion (>50 years old at first presentation; n=2) or the required number of symptoms (≥4; n=1). With respect to the overlap between LCP and SAD, it has to be stressed that this finding is rather irrelevant since the SAD as included in the ICD-10 and DSM-IV cannot be compared with the acute schizoaffective psychosis as originally described by Kasanin[4] and is not clearly demarcated from schizophrenia and affective disorders.[20]

As demonstrated in the present study, the three subtypes of cycloid psychosis can clearly be discriminated from other psychotic disorders by their pronounced symptomatological presentation and intraphasic bipolarity (Table 1). Key features of their core syndromes include perplexity, pananxiety, motor disturbances, mood swings and transient hallucinatory experiences of any kind.

Interestingly, in the cycloid psychosis group a higher symptom reduction was found after 6 weeks on antipsychotics from various classes. Although not the main target of the present investigation, the pharmacological maintenance treatment of cycloid psychoses is suggested to be primarily with mood stabilizers[17,52] whereas in the acute phase atypical antipsychotics may be beneficial.[18] Generally, these psychoses have a good prognosis[15,35,48,53] and their diagnostic stability is high.[54,55]

In conclusion, the results demonstrate that the concept of cycloid psychosis is still clinically useful and valid. It would therefore be wise to include a separate group of nonaffective acute psychoses in the future editions of current international classification systems. Such a proposal was recently also formulated by Nugent and coworkers.[56] Given the rather high prevalence of this kind of psychosis, further clinical studies with differential assessment methods such as Leonhard's symptom checklist are warranted and should particularly focus on treatment strategies and long term outcome.

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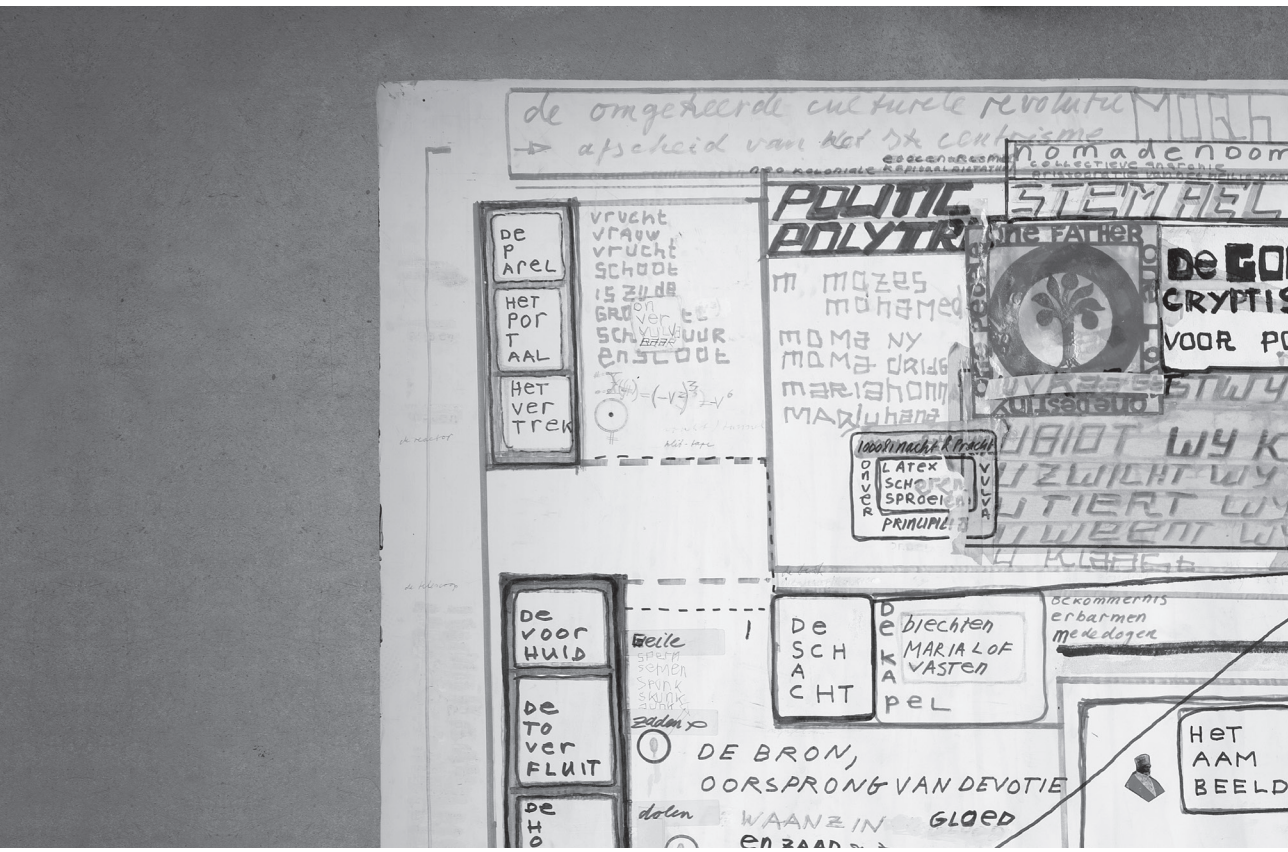
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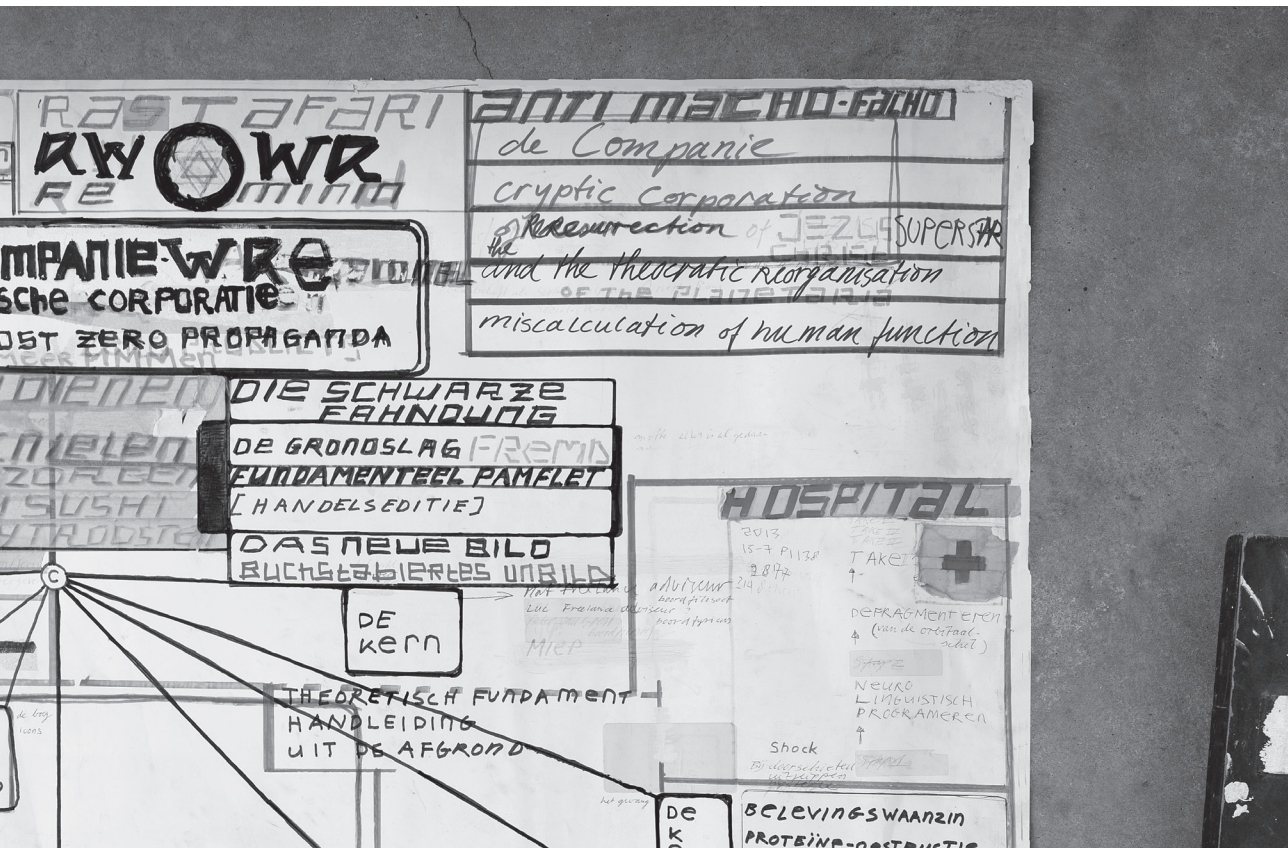
Chapter 4

BDNF and S100B in psychotic disorders: Evidence for and association with treatment responsiveness



Noortje W.A. van de Kerkhof[1,2], Durk Fekkes[2], Frank M.M.A. van der Heijden[1], Willem M.A. Verhoeven[1,2]

[1] Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, The Netherlands
[2] Erasmus Medical Centre, Departments of Psychiatry and Clinical Chemistry, Rotterdam, The Netherlands

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Abstract

Objective: Brain-derived Neurotrophic Factor (BDNF) and S100B are involved in brain plasticity processes and their serum levels have been demonstrated to be altered in patients with psychoses. This study aimed to identify subgroups of patients with psychotic disorders across diagnostic boundaries that show a specific symptom profile or response to treatment with antipsychotics, by measuring serum levels of BDNF and S100B.

Methods: The study sample consisted of 58 patients with DSM-IV psychotic disorders. CASH, PANSS and CGI-S/CGI-I were applied at baseline and after 6 weeks of antipsychotic treatment. At both time points, serum levels of BDNF and S100B were measured and compared to a matched control sample.

Results: Baseline BDNF and S100B levels were significantly lower in patients as compared to controls and did not change significantly during treatment. Dividing the patient sample according to baseline biochemical parameters (low and high 25% and middle 50%), no differences in symptom profiles or outcome were found with respect to BDNF. However, the subgroups with low and high S100B levels had higher PANSS scores than the middle subgroup. In addition, the high subgroup still showed significantly more negative symptoms after treatment, while the low subgroup showed more positive symptoms compared to the other subgroups.

Conclusion: Serum levels of BDNF and S100B are lowered in patients with psychotic disorders across diagnostic boundaries. The differences between high and low S100B subgroups suggest a relationship between S100B, symptom dimensions and treatment response, irrespective of diagnostic categories.

Introduction

Since the concept of schizophrenia was formulated by Kraepelin and Bleuler, there is an ongoing debate on the etiological and pathophysiological factors of psychoses. Over the past decades, increasing evidence has emerged that the prototypic psychotic disorder, schizophrenia, has to be considered as a progressive, neurodevelopmental disorder.[1,2]

The neurodevelopmental trajectory of the human brain is characterised by an increase in grey matter during early childhood and a subsequent decrease during puberty, which can be attributed to a process called 'synaptic pruning'.[3,4] Exaggerated synaptic pruning has been associated with very early onset of first psychotic symptoms.[5] Accordingly, adult patients with schizophrenic psychoses show excessive grey matter loss that is paralleled by white matter increase in the first and second decade of their illness.[6] It has been postulated, that this excessive synaptic pruning leads to reduced synaptic connectedness ('connectivity') which enhances the susceptibility to develop schizophrenia and related psychoses.[7] Connectivity can be established indirectly by measuring neurotrophic factors involved in the development and maintenance ('plasticity') of the central nervous system (CNS).[8] Some of these neurotrophic factors like Brain Derived Neurotrophic Factor (BDNF) and S100B, that both pass the blood brain barrier[9,10] and of which the peripheral levels correlate well with those in the CNS, have been extensively investigated in psychotic disorders.[11-14]

BDNF is the most abundant neurotrophic factor in the brain and plays a crucial role in development, proliferation, regeneration, survival and maintenance of neuronal function of the CNS.[15,16] Serum BDNF levels have repeatedly been reported to be decreased in first-episode and chronic schizophrenia.[17,18] Consistent associations between BDNF levels and symptom profile of psychotic disorders, however, have not been found as yet[19,20], whereas the results about the effects of class or dosage of antipsychotics on the serum concentration of BDNF are very contradictory.[21,22]

S100B is a calcium-binding protein involved in intracellular energy metabolism in the CNS. Depending on the concentration, its extracellular effect is either trophic or toxic. In nanomolar concentrations, S100B stimulates neurite outgrowth and enhances survival of neurons during development and after injury. In micromolar concentrations, however, it induces apoptosis.[23,24] With respect to schizophrenia, enhanced levels of S100B and a positive correlation with negative symptoms are repeatedly reported.[25-27] Treatment with antipsychotics over a relatively short period of time has been shown to normalize S100B serum levels.[28,29] In addition, some evidence is available suggesting a relationship between S100B levels and neurocognitive parameters[30] as well as severity of symptoms.[13]

Thus, serum concentrations of these two neurotrophic proteins express to some extent the functional status of the brain, particularly its neuroplasticity. Moreover, circumstantial evidence is available that their concentrations correlate with either severity of symptomatology or symptomatic changes during antipsychotic treatment.

Aims of the study: The present study was designed to investigate whether the neurotrophic proteins BDNF and S100B may be biomarkers for the identification of a specific symptom profile or responsiveness to treatment in patients with psychotic disorders irrespective of their classificatory status.

Materials and methods

Patient recruitment

Patients were recruited over a period of 30 months at the Vincent van Gogh Institute for Psychiatry, a large psychiatric teaching hospital in the South of the Netherlands. The study was performed according to the Dutch medical ethical guidelines (CCMO registration number NL20469.097.07), approved by the Board of Directors of the hospital and in full accordance with the Helsinki Declaration.

All patients provided written informed consent before entering the study. Included were adult patients (male/female, age range 18-65 years) admitted for psychotic symptomatology, for which pharmacological intervention with antipsychotics was warranted. As exclusion criteria served: proven genetic syndrome, intellectual disabilities and relevant somatic or neurologic diseases. Patients unable to provide informed consent were also excluded.

During the study period, a total of 194 patients were admitted and subsequently screened for eligibility. Because of severity of psychotic illness, 71 patients had to be excluded for informed consent whereas 23 did not meet the inclusion criteria. From the remaining 100 patients, 20 refused to participate, yielding a study population of 80 subjects of whom 58 completed the study period of 6 weeks. The latter group (n=58) was included in the analyses.

Treatment process and diagnostic procedures

All patients were treated with first- or second-generation antipsychotic agents during the study period. Pharmacological interventions were performed by the treating psychiatrist according to hospital standards. At baseline, the Comprehensive Assessment of Symptoms and History (CASH)[31] was applied from which classification according to DSM-IV was done. Severity and distribution of symptomatology were assessed at baseline and after 6 weeks of treatment by means of the Positive and Negative Syndrome Scale (PANSS)[32] and the Clinical Global Impression scale for severity and improvement (CGI-S/CGI-I).[33]

Biochemical assessments

Patients: At both time points of clinical assessment, blood samples were collected to measure serum levels of BDNF and S100B. Sampling was performed between 8 and 10 a.m. and serum was stored at -80°C until analysis. BDNF was measured by a double antibody sandwich enzyme

linked immunosorbent assay (ELISA; Promega, Madison, Wisconsin, USA) and S100B levels by a two-site one step ELISA (Sangtec, Bromma, Sweden).

Controls: BDNF and S100B levels of control subjects were extracted from a database of the neuropsychiatric laboratory of Erasmus Medical Centre (EMC) comprising data from staff members and students of the EMC and subjects from the general community. None of the control subjects neither their first degree relatives had a history of psychiatric illness. For the S100B assay, control subjects were matched for both age and gender. Since we could not find any correlation between BDNF and age in our control group (50 men and 25 women, age 27.5 ± 6.8 years; p=0.908), for the BDNF assay control subjects were matched for gender only. Consequently, separate control groups were created for BDNF (n=75) and S100B (n=77).

Statistics

The Student's t-test was used for normally distributed variables (PANSS scores), the Mann-Whitney U test was used for non-normally distributed variables (BDNF/S100B serum levels) and a Chi-square test was used for binary variables. A paired t-test (PANSS total and subscales) or Wilcoxon's Signed Rank test (BDNF/S100B serum levels) was used to analyse changes between time points. The Kendall tau test was used to establish correlations between BDNF/S100B serum levels and clinical variables. Between-group differences were determined by univariate analysis of (co)variance (AN(C)OVA). All analyses were two-tailed. Significance was set at $p<0.05$. Data are presented as mean +/-SD, unless stated otherwise.

Results

Patient characteristics

The main characteristics of the 58 patients that completed the study are outlined in Table 1. Mean duration of psychotic illness was 8.1 (±8.4) years. According to DSM-IV, 33 patients were classified as schizophrenia whereas in the remaining 25 patients various diagnoses from the schizophrenia spectrum were made. Eighteen patients were free from psychotropics at least 2 weeks prior to study entry. Duration of treatment in the medicated patients varied from 2 weeks to >10 years.

Table 1. Patient characteristics at baseline (n=58)

Gender (male/female) Age (mean ±SD)	38/20 (66/34%) 36.7 ± 11.7 years
Age at first psychosis, years (mean ±SD) Duration of psychotic illness, years (mean ±SD)	28.5 ± 11.1 8.1 ± 8.4
Diagnosis (DSM-IV)	Schizophrenia (n=33) Schizoaffective disorder(n=2) Brief psychotic disorder (n=8) Bipolar disorder (n=7) * Psychotic disorder NOS (n=6) Delusional disorder (n=1) Schizotypal personality disorder (n=1)
Smoking yes/no Hard drugs in month prior to study entry yes/no Soft drugs in month prior to study entry yes/no	38/20 (66/34%) 2/56 (3/97%) 10/48 (17/83%)
Medication status at study entry	Naïve (n=10) Free >2 weeks (n=8) Using medication (n=40)
Medication used at study entry **	1 AP (n=15) 1 MS (n=5) 2 AP (n=6) AP + AD (n=6) AP+MS+AD (n=2) AP+MS (n=2) 2 AP + AD (n=2)

** manic episode with psychotic features*
*** AP: antipsychotic agent (any), MS: mood stabilizer (any), AD: antidepressant (any)*

Clinical and biochemical treatment effects

Clinical and biochemical parameters of the patients are outlined in Table 2. As reflected by the score on the CGI-S the study group was 'moderately to markedly ill' (score 4.4). Concerning treatment efficacy, a mean reduction of 20% ($p<0.001$) on the PANSS total score was noted, corresponding with the generally used definition of 'response'. Reductions on PANSS positive, negative and global scores were 24%, 14% and 18%, respectively (all $p<0.001$). On the CGI-S, a mean reduction of 23% was noticed.

The mean serum levels of BDNF and S100B were significantly lower as compared to controls (BDNF: 20.3 ± 6.6 versus 24.4 ± 6.7 μg/l, $p\leq0.001$; S100B: 0.063 ± 0.032 versus 0.069 ± 0.029 μg/l, $p<0.05$). With respect to BDNF, mean age of the patients was higher compared to control subjects (36.7 ± 11.7 and 27.5 ± 6.8 years, $p<0.001$). However, this age difference did not result in differences in serum BDNF levels, since there was no correlation between age and BDNF levels in the study sample at both time points (the non-parametric Kendall's Tau test showed p-values of 0.143 and 0.323, respectively). Moreover, the laboratory involved found no correlation between age and BDNF levels in healthy subjects (n=75, $p=0.908$). Serum levels of BDNF and S100B did not change significantly during 6 weeks of treatment with antipsychotics.

Possible confounding factors

Since several factors could possibly influence serum levels of neurotrophic proteins, data were scrutinized for effects of smoking, body mass index, abuse of soft or hard drugs, medication status (naïve, free >2 weeks or medicated), antipsychotic class (first- or second-generation agent), co-medication (antidepressants or mood stabilizers), diagnostic category (schizophrenic or non-schizophrenic psychoses), gender and age.

Baseline BDNF levels were significantly lower in medication naïve patients as compared to medication-free and medicated patients (15.4 ± 6.6, 20.6 ± 5.6 and 21.5 ± 6.5 μg/L respectively, p=0.022). In addition, serum levels of S100B were positively correlated with age at both time points (Kendall's Tau 0.197 and 0.212 respectively, $p<0.05$). Moreover, patients who had used soft drugs before study entry (n=10) had significantly lower levels of S100B after six weeks of treatment (0.067 ± 0.033 versus 0.042 ± 0.015). Finally, neither of the other parameters, especially gender, diagnostic category and co-medication, were found to have any influence on serum levels of either neurotrophic protein. For all analyses of BDNF and S100B values, medication status respectively age and use of soft drugs, were used as covariates.

Sample division according to baseline biochemical parameters

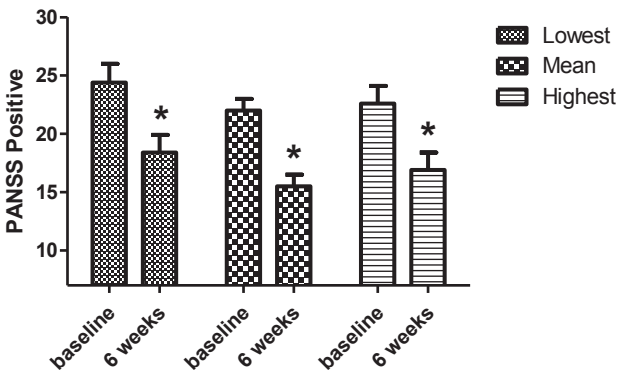
No correlations were established between BDNF and S100B levels on one hand and PANSS scores on the other hand at both time points in the total patient sample (Kendall's Tau, all $p>0.05$). In order to detect possible differences in symptom profile or symptomatic improvement between patients with high and low levels of neurotrophic proteins, the sample was divided into three subgroups (lowest quarter [L-BDNF/S100B], highest quarter [H-BDNF/S100B], and middle group [M-BDNF/S100B]). After analysis, all factors that might influence PANSS scores (see: possible confounding factors) appeared to be equally distributed between the BDNF and S100B subgroups demonstrating that they could not have influenced any of the outcome measures. At baseline, mean levels of BDNF and S100B varied significantly from each other. All differences remained significant during the study period (BDNF: 12.9 ± 2.3 (at baseline) and 12.8 ± 4.9 (after treatment) [L: n=14], 19.4 ± 2.5 and 19.9 ± 4.6 [M: n=30], 29.7 ± 4.1 and 25.5 ± 6.3 μg/L [H: n=14]; S100B: 0.034 ± 0.005 and 0.044 ± 0.011 [L: n=14], 0.054 ± 0.009 and 0.058 ± 0.025 [M: n=29], 0.107 ± 0.030 and 0.088 ± 0.041 μg/L [H: n=15], all $p\leq0.001$).

As to BDNF levels, no differences concerning psychopathological profile, symptom severity and symptomatic improvement were found between the three subgroups.

As compared to M-S100B, PANSS scores in H-S100B and L-S100B were significantly higher at baseline (p=0.003; data not shown). After 6 weeks of treatment, L-, M- and H-S100B subgroups showed a significant decrease on the various PANSS scores, except for the score on the PANSS negative subscale in H-S100B (p=0.347). Thus, negative symptoms did not improve in the subgroup with high baseline S100B levels. As can be seen in Figures 1 and 2, in the

L-S100B subgroup, the reduction in positive symptoms was less pronounced as compared to the H- and M-subgroups, reflected by a significantly higher mean PANSS positive score in the L-S100B subgroup after six weeks (between-group differences p=0.001). In contrast, as could be expected, mean PANSS negative score after six weeks was significantly higher in the H-S100B subgroup (between-group differences p=0.009).

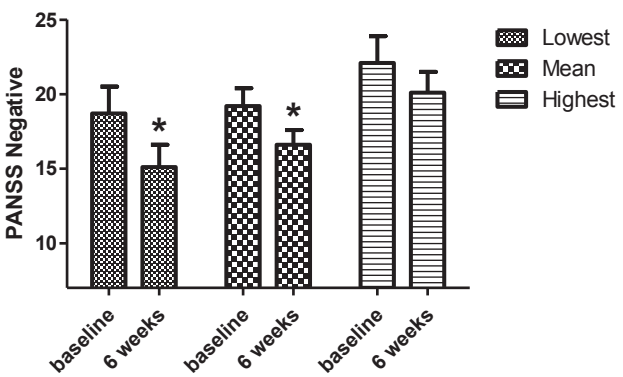
Figure 1. PANSS Positive scores in S100B subgroups



Legend to figure 1

*PANSS positive scores at baseline and after 6 weeks of treatment of the low (n=14), middle (n=29) and high (n=15) subgroups, according to their baseline serum levels of S100B. Between-group differences: univariate analysis of variance, corrected for age and soft drugs, baseline p=0.003, 6 weeks p=0.001. *Within-group differences: paired t-test, all p≤0.001.*

Figure 2. PANSS Negative scores in S100B subgroups.



Legend to figure 2

PANSS negative scores at baseline and after 6 weeks of treatment of the low (n=14), middle (n=29) and high (n=15) subgroups, according to their baseline serum levels of S100B.

*Between-group differences: univariate analysis of variance, corrected for age and soft drugs, baseline p=0.011, 6 weeks p=0.009. *Within-group differences: paired t-test, p≤0.006 in L- and M-S100B, H-S100B p=0.347.*

Discussion

In the present study serum levels of the neurotrophic proteins BDNF and S100B were measured in a group of patients with psychotic disorders before and after 6 weeks of treatment with antipsychotics. It was found that levels of BDNF are lowered in patients with an acute psychotic episode irrespective of diagnostic category, psychopathological profile or treatment effectiveness. Furthermore, no effects were found for age or gender.

Interestingly, reduction of positive symptoms was less pronounced in patients with a relatively low S100B level, whereas virtually no effect of treatment on negative symptoms was found in patients with a relatively high S100B level. The observation of lower serum levels of BDNF is in agreement with the findings by several other investigators[15,17,20,21] and supports the hypothesis that psychotic disorders, of which schizophrenia is most widespread, may be considered as neurodevelopmental disorders indeed. Comparable observations have been made in patients with uni- and bipolar affective disorders.[18,34,35] These observations indicate that BDNF may have pathophysiological implications across diagnostic boundaries. With respect to the effect of psychotropics on BDNF levels, equivocal results have been reported.[15,22,36]

Nearly all literature mentions enhanced serum levels of S100B in schizophrenia.[25,27,37] The present observation of subnormal S100B concentrations can therefore not easily be explained. This finding should be considered cautiously, especially since the difference between patients and controls was present at baseline only and the size of the study sample was modest. However, since S100B has neurotoxic as well as neurotrophic effects, it could be that this lower S100B level at baseline reflects deficiencies in neuroprotective mechanisms.

Comparable considerations have to be taken into account for the observation that, in this study, more severe positive psychotic symptoms are associated with lower S100B levels. It could be speculated that subnormal levels of this neurotrophic protein might initially induce positive symptoms while during the course of disease S100B levels might rise, resulting in the development of negative symptoms due to a neurotoxic effect of the higher S100B levels in the brain.

The present observation that severity of negative psychotic symptoms is associated with higher S100B levels is in agreement with other reports[26,28,29] and is suggestive for either a neurotoxic effect or a compensatory mechanism for damage already done. It should be stressed, however, that the H-S100B subgroup consisted of 15 patients only.

Although all potentially confounding factors have been included in the analyses[14], interpretation of the here presented data still has to be done carefully since the study comprised a relatively small sample size with many differences between individual patients. The sample size, however, can be considered moderate when compared to other studies on BDNF or S100B, with study numbers varying between 18 and 88 patients with respect to BDNF[16,19] and 12 and 98 patients with respect to S100B.[14,26]

Given the diagnostic uncertainties in psychiatry in general[38,39], instead of focusing on a particular category of psychoses (e.g. DSM-IV schizophrenia), the here chosen approach of including psychotic disorders irrespective of their classification may disclose a psychopathological phenotype that is associated with the functional status of one of the investigated neurotrophic proteins. This, in turn, may have consequences for either treatment or course of disease. It is therefore suggested that studies on pathophysiological determinants, e.g. neurotrophic proteins, of major psychiatric diseases like psychoses and affective disorders, should preferably follow a so-called dimensional approach searching for endophenotypes.[40-42]

In conclusion, this study, for the first time, demonstrates that patients with a relatively low serum level of S100B show less reduction in severity of positive psychotic symptoms after treatment with antipsychotics, whereas those with a relatively high S100B level hardly show any improvement of negative symptoms. Further studies are warranted to elucidate the pathophysiological significance and potential clinical implications of these observations.

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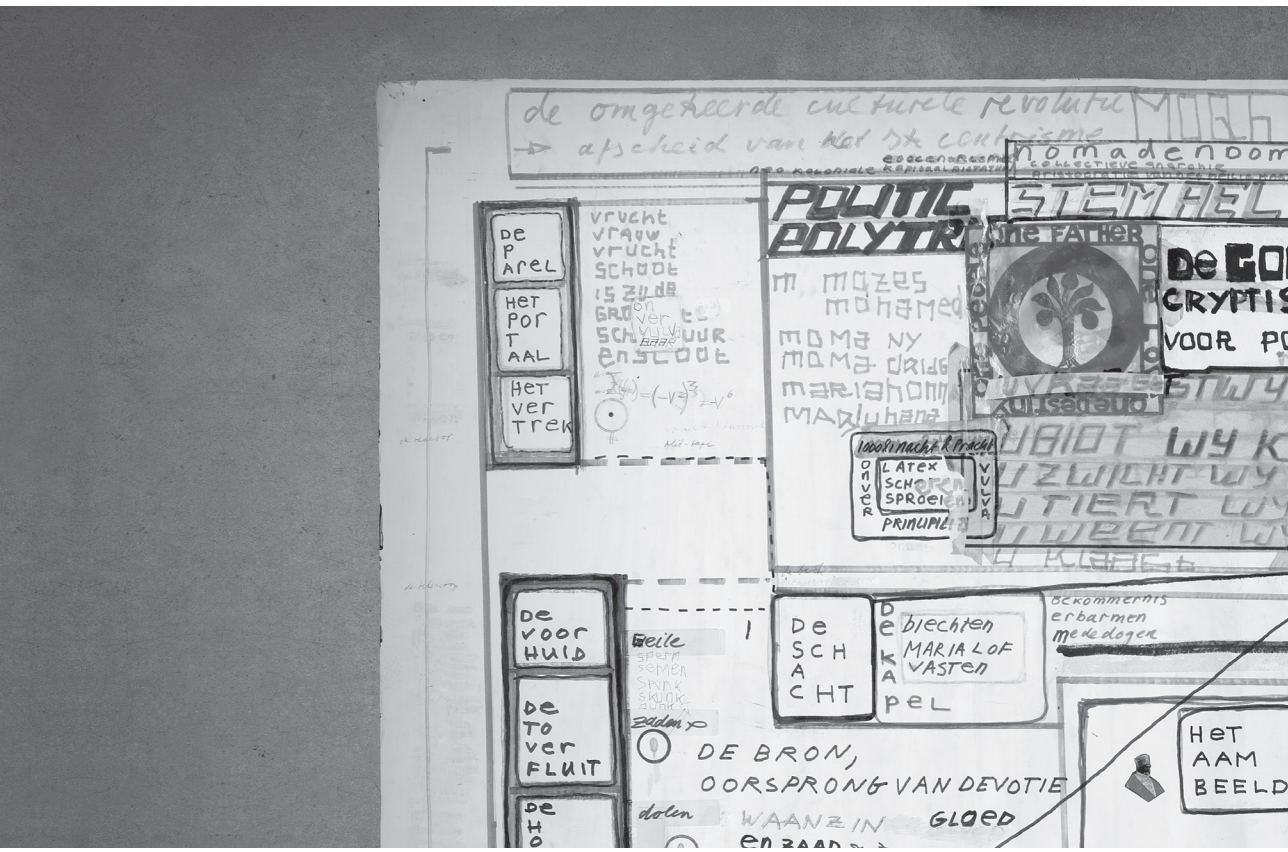
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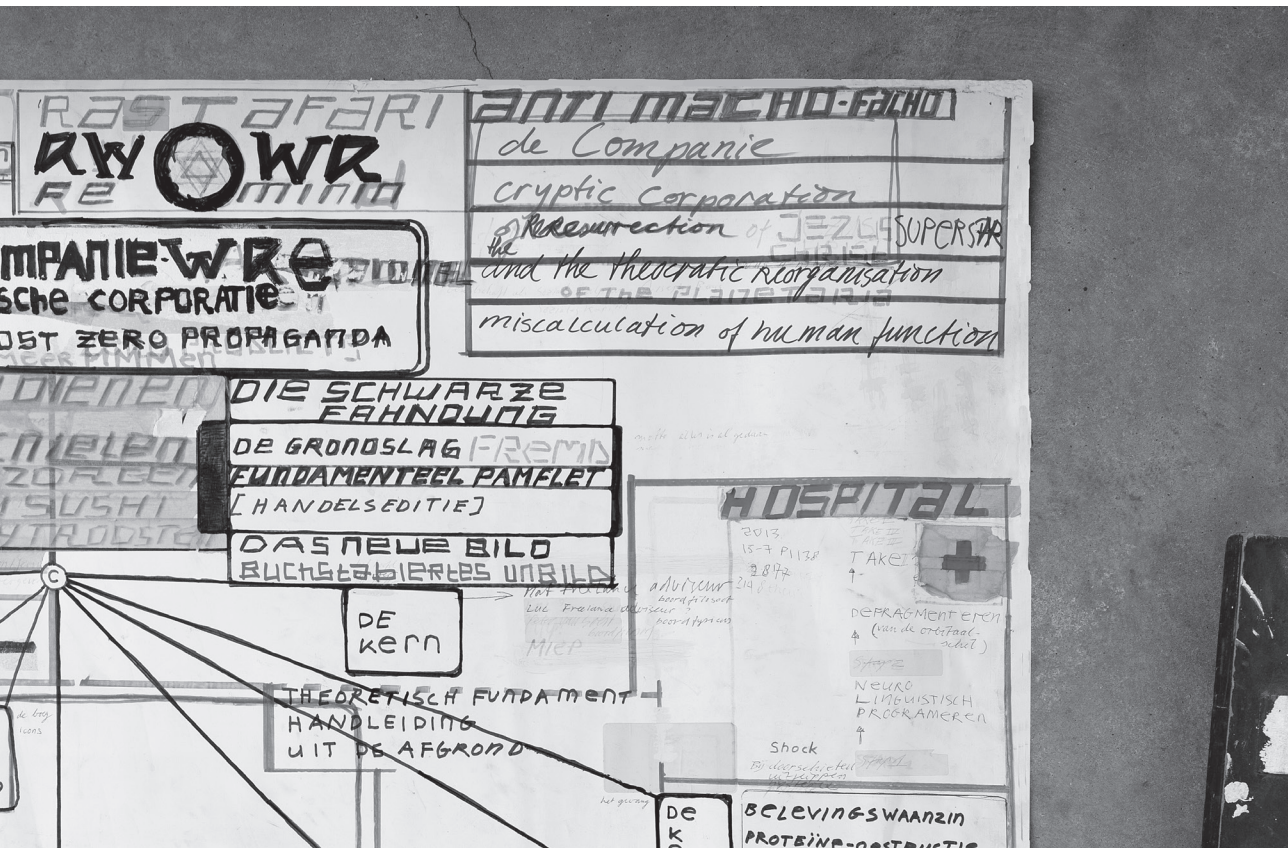
Chapter 5

Relationship between plasma homovanillic acid and outcome in patients with psychosis spectrum disorders



Noortje W.A. van de Kerkhof[1,2], Durk Fekkes[3], Frank M.M.A. van der Heijden[1], Jos I.M. Egger[1,4,5], Willem M.A. Verhoeven[1,2]

[1]Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, the Netherlands
[2]Erasmus University Medical Centre, Department of Psychiatry, Rotterdam, the Netherlands
[3]Erasmus University Medical Centre, Departments of Clinical Chemistry and Psychiatry, Rotterdam, the Netherlands
[4]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, the Netherlands
[5]Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, the Netherlands.

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Abstract

Background: Psychosis spectrum disorders, especially schizophrenia, have been linked to disturbed dopaminergic activity in the brain. Plasma homovanillic acid (pHVA) levels partly represent dopaminergic metabolism in the central nervous system. In the present study associations between (changes in) pHVA levels, symptom severity and symptomatic improvement in patients with psychoses were investigated.

Methods: From a total of 80 patients, 58 fulfilled all inclusion criteria and their symptom profile and severity were assessed by means of the Comprehensive Assessment of Symptoms and History (CASH), the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression Scale for Severity and Improvement (CGI-S/CGI-I) at baseline and after six weeks of antipsychotic treatment. After inclusion, all patients were prescribed first- or second-generation antipsychotics by their treating psychiatrist. A total of twelve patients had first-episode psychosis (FEP). At both time points, pHVA levels were measured. Subsequently, pHVA levels were compared to an age-matched control sample and changes in pHVA levels (ΔpHVA) after treatment were associated with clinical parameters.

Results: Before analyses, data were scrutinized for possible confounders, partcicularly gender, smoking, medication status (including antipsychotic class) and recent drug use. The pHVA levels in patients were not different from those in controls. Treatment resulted in a significant decrease of all parameters. Symptomatic improvement as well as ΔpHVA was most pronounced in FEP patients.

Conclusion: These findings show that patients with FEP have a more favourable outcome than non-FEP-patients and that greater ΔpHVA also suggests that FEP patients still have the capacity to adjust dopaminergic neurotransmission.

Introduction

Psychosis spectrum disorders, particularly schizophrenia, have been linked to dysregulated dopamine (DA) neurotransmission in the central nervous system. It has been demonstrated that DA hyperactivity in subcortical areas results in positive psychotic symptoms, whereas DA-hypoactivity in the frontal cortex is assumed to be involved in the evolution of negative symptoms.[1] Although criticized by several investigators, the dopamine hypothesis is still the most comprehensive model for schizophrenia and related psychoses.[2,3]

Homovanillic acid (HVA) is the main metabolite of DA, and 30-60% of plasma HVA (pHVA) is estimated to originate from DA neurons in the central nervous system. As a consequence, alterations in central DA activity are reflected by changes in plasma HVA levels (ΔpHVA).[4] pHVA levels are widely used to study the function of central dopaminergic activity in psychiatric disorders and it has been shown that, following antipsychotic treatment, levels initially rise and later on return to normal or lowered values.[5]

As to pHVA in schizophrenia and related psychoses, both lowered and elevated levels have been reported, whereas some authors found no differences at all between patients and healthy controls.[6,7] Low pHVA levels have been associated with deficit states[8], whereas high baseline pHVA levels have been reported to be related with improvement of positive psychotic symptoms after treatment with antipsychotics.[9] Elevated pHVA levels have been shown to be correlated with severity of psychotic symptoms during acute relapse[10] and appeared to be present already in the prodromal phase of schizophrenia.[11] Furthermore, some authors have reported differences in pHVA between patients with first episode psychosis (FEP) and those with relapsing or chronic psychoses, calling for further investigation.[12]

Associations have been established between baseline pHVA levels and overall improvement of psychotic symptoms or rapidity of response to antipsychotics in schizophrenia.[13,14] In general, the results of studies about the effect of antipsychotic treatment on pHVA in patients with psychotic disorders are equivocal in that, depending on the antipsychotic agent, lowered (risperidone, olanzapine and aripiprazole)[15,16], unchanged (clozapine)[17], or elevated (haloperidol and olanzapine)[18,19] levels have been reported. With respect to treatment response, comparable associations have been found in other psychosis spectrum disorders, such as schizoaffective disorder[20], bipolar disorder[21] and delusional disorder.[22]

Based on the hypothesis that pHVA reflects nature and severity of symptoms as well as treatment response, the present study was designed to investigate baseline pHVA and ΔpHVA in patients with both first episode and chronic relapsing psychosis spectrum disorders prior to and after 6 weeks of antipsychotic treatment.

Methods

Patients

Patients were recruited from the Vincent van Gogh Institute for Psychiatry, a large teaching hospital in the south of the Netherlands, over a period of 2.5 years. Included were male and female patients (aged 18-65 years) hospitalized for psychotic symptoms necessitating psychopharmacological intervention and meeting the criteria for DSM-IV psychotic disorders. Intervention was defined as start or switch of antipsychotic agent or use of augmentation strategies. Excluded were patients with proven genetic syndromes, intellectual disability, or relevant somatic and neurologic disease as well as those who were unable to provide consent. All patients provided informed consent following Dutch medical ethical guidelines (CCMO registration number NL20469.097.07). The study was performed in accordance with the Declaration of Helsinki.

Out of a total of 194 patients who were admitted during the study period, 100 met the inclusion criteria (71 were unable to provide informed consent, and in 23 the intended antipsychotic intervention was not implemented). Twenty patients refrained from participation for various reasons. Eventually, the study group comprised 80 patients of whom 58 completed the study period of 6 weeks. Relevant patient characteristics are summarized in Table 1.

Diagnostic procedures and treatment process

All assessments at baseline and after six weeks of treatment were performed by the same psychiatrist (first author). The Comprehensive Assessment of Symptoms and History (CASH)[23] was applied at baseline as a diagnostic instrument and data were subsequently used for classification according to DSM-IV. To assess symptom profile and overall symptom severity, the Positive and Negative Syndrome Scale (PANSS)[24] and Clinical Global Impression scale for severity and improvement (CGI-S/CGI-I)[25] were used at both time points. All patients were prescribed first- or second-generation antipsychotic agents by the treating psychiatrist according to hospital standards.

Response to antipsychotic treatment was defined as a reduction of at least 20% on the PANSS total score[26] whereas for symptomatic remission the internationally accepted criteria were applied that comprise a selection of PANSS items with a cut-off score of ≤3 per item.[27]

Biochemical assessments

Patients: At both assessment dates, blood sampling to measure plasma HVA levels (nmol/l) was performed between 8 and 10 a.m. under fasting and resting conditions; plasma was stored at -80°C until analysis. All biochemical analyses were performed at the Neuropsychiatric Laboratory of the Erasmus Medical Centre (EMC). The technician was blinded to the clinical situation or diagnosis of the patients. HVA levels were measured by high performance liquid

chromatography using a Zorbax Eclipse XDB-C8 column (5 µm particle size, 250 x 3 mm; Agilent Technologies, Waldbronn, Germany) for separation. For the detection of HVA, we used an electrochemical detector (oxidation potential was set to 0.7 V) and the Intro controller (Antec Leyden, Leiden, The Netherlands). Quantification was done by measuring peak heights relative to two internal standards (isoprenaline and 5-methylserotonin). The mean recovery (± SD) of HVA added to the plasma samples was 95 ± 7%.

Table 1. Patient characteristics (n=58)

Gender (male/female) Age (mean ±SD)	38/20 (66/34%) 36.7 ± 11.7 years
Age at first psychosis, years (mean ±SD) Duration of psychotic illness, years (mean ±SD) First episode psychosis yes/no	28.5 ± 11.1 8.1 ± 8.4 12/46 (21/79%)
Diagnosis (DSM-IV)	Schizophrenia (n=33) Schizoaffective disorder(n=2) Brief psychotic disorder (n=8) Bipolar disorder (n=7) * Psychotic disorder NOS (n=6) Delusional disorder (n=1) Schizotypal personality disorder (n=1)
Smoking yes/no Hard drugs in month prior to study entry yes/no Soft drugs in month prior to study entry yes/no	38/20 (66/34%) 2/56 (3/97%) 10/48 (17/83%)
Medication status at study entry	Naïve (n=10) Free >2 weeks (n=8) Using medication (n=40)
Medication used at study entry (n=40)	1 AP (n=15) 1 MS (n=5) 2 AP (n=6) AP + AD (n=6) AP+MS+AD (n=2) AP+MS (n=4) 2 AP + AD (n=2)
Type of intervention (n=58)	(Re)start AP (n=23) Switch AP (n=26) Augmentation of AP (n=2) Switch + augmentation (n=1) Significant dose increase (n=4) Discontinuation of 1 AP (n=2)
Medication used after 6 weeks (n=58)	1 AP (n=35) 2 AP (n=4) AP+AD (n=6) AP+MS+AD (n=3) AP+MS (9) 2 AP + AD (n=1)

Notes: values are n(%) or means ±SD. NOS= not otherwise specified; AP= antipsychotic agent (any), MS= mood stabilizer (any), AD= antidepressant (any)

** manic episode with psychotic features*

Controls: HVA levels of age-matched control subjects (n=75), sampled under similar conditions, were extracted from a large database of the Neuropsychiatric Laboratory of the EMC, consisting of staff members and students of the EMC and subjects from the general community, all without a personal or family history of psychiatric illness. Since no gender effects for HVA (p=0.98) were found in the control group and recent literature equally reports so[28], control subjects were collected by age only.

Statistics

For statistical analyses, the 58 completers were included. In the case of normally distributed variables, parametric tests were applied, otherwise non-parametric tests were used. For nominal variables, Chi-square test was used. Mean comparisons were performed with Mann-Whitney U (HVA levels) or Student's t-test (PANSS scores), changes between time points with Wilcoxon signed-rank test (HVA) or paired t-test (PANSS scores) and correlations with Kendall's Tau test. Between-group differences were calculated by means of a Kruskal-Wallis analysis of variance. Significance was set at $p<0.05$. All data are presented as mean ±SD, unless stated otherwise.

Results

Clinical data

Main characteristics of the patients, including diagnostic breakdown and medication status at relevant time points are presented in Table 1. As can be inferred, 18 out of 58 were free of medication at study entry, including 6 patients with relapsing psychosis. The remaining patients displayed psychotic symptoms despite treatment with various antipsychotic, mood stabilizing, or antidepressant agents. Of the total group, 19 patients, including all 12 FEP-patients, were admitted for the first time and 39 patients were re-admitted or permanently institutionalized.

As presented in Table 2, decreases in PANSS and CGI scores were all significant. Symptomatic reduction using the 20% response criterion was most pronounced on the PANSS positive subscale and illness severity decreased from marked to mild. As to FEP and non-FEP patients, at baseline, no differences were found with respect to severity of illness or remission status. After 6 weeks, both groups did not differ regarding their response while, as might be expected, significantly more patients in the FEP-group met the remission criterion.

Biochemical data

The pHVA levels in the patient group (n=58) at both time points (63.3 ± 25.9 and 55.0 ± 19.1 nmol/l, respectively) were not significantly different from those in controls (53.4 ± 13.7 nmol/l). The mean decrease in pHVA after six weeks (ΔpHVA) in the patient sample, however,

was significant (z = -2.45, p=0.014). In the total patient group, no correlations between ΔpHVA and changes in PANSS scores could be established.

Since several factors are known to influence DA activity in the brain, pHVA and ΔpHVA data were scrutinized for possible confounding effects of age, gender, smoking, recent drug use, medication status (naïve, free for at least two weeks, medicated), use of comedication (antidepressant, mood stabilizer or any), diagnosis (schizophrenic vs. non-schizophrenic psychosis), and antipsychotic class (first- vs. second-generation). At both time points, no associations were found between pHVA levels and any of these factors.

As to ΔpHVA, a significant higher change rate was found for FEP-patients (n=12) compared to those with (chronic) relapsing (n=46) psychoses (p=0.012). Data on the distribution of pHVA levels in FEP-patients are depicted in Figure 1.

Table 2. Clinical and biochemical parameters in total group, FEP patients, and non-FEP patients at baseline and after 6 weeks of treatment

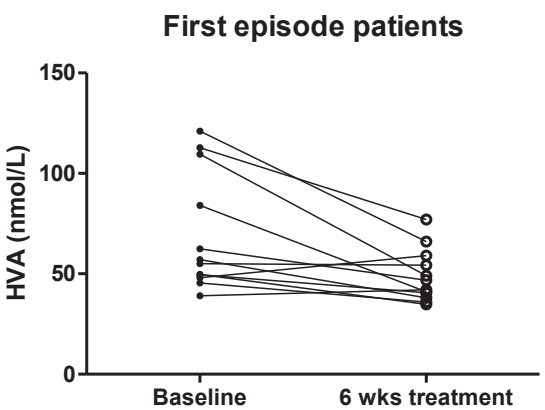
	Total group (n=58)	FEP (n=12)	Non-FEP (n=46)
PANSS baseline			
- total	84.9±19.4	73.9±12.3 [c]	87.8±20.0
- positive	22.7±6.3	21.8±4.3	22.9±6.8
- negative	19.8±7.2	15.3±4.6 [c]	21.0±7.2
- global	42.3±9.5	36.8±7.9 [c]	43.8±9.5
PANSS 6 weeks			
- total	68.4±17.7 [a]	54.6±12.4 [e]	72.0±17.2
- positive	16.6±6.4 [a]	12.8±4.1 [c]	17.5±6.6
- negative	17.2±5.8 [a]	13.7±5.8 [c]	18.1±5.6
- global	34.7±8.5 [a]	28.1±5.6 [e]	36.4±8.4
Mean CGI-Severity			
- baseline	4.4±1.2	4.0±0.7	4.5±1.3
- 6 weeks	3.4±1.4 [a]	2.4±0.9 [d]	3.7±1.4
Number of patients			
- response	30/58	8/12	22/46
- remission baseline	8/58	1/12	7/46
- remission 6 weeks	21/58	8/12 [c]	13/46
pHVA (nmol/l)			
- baseline	63.3±25.9	69.5±29.4	61.6±25.0
- 6 weeks	55.0±19.1 [b]	48.7±13.1	56.7±20.2
ΔpHVA	-8.2±23.7	-20.7±22.9 [c]	-4.9±23.1

Note.

a: difference treatment versus baseline, p<0.001
b: difference treatment versus baseline, p=0.014
c: difference between FEP and non-FEP group p<0.05
d: difference between FEP and non-FEP, p<0.01
e: difference between FEP and non-FEP, p≤0.001

The difference between FEP and non-FEP patients was further analysed in terms of the aforementioned confounding factors. Only diagnosis and medication status were unevenly distributed (X^2, p=0.020 and p=0.003, respectively), with diagnosis of schizophrenia being more dominant in the non-FEP group and antipsychotic medication less present in the FEP-group. Concerning the latter, six patients were medication naïve and one had been treated previously with a non-antipsychotic agent. In addition, both subgroups were analysed on the relation between changes in pHVA and PANSS (subscale) scores. No significant correlations were found for any of the subgroups (FEP group: all p>0.273; non-FEP: all p>0.489).

Figure 1. Plasma HVA levels in FEP (n=12)



Legend to Figure 1
Distribution of pHVA levels in FEP at baseline and after six weeks of treatment. Each dot represents an individual patient.

Discussion

In the present study, pHVA levels were investigated in 58 patients with psychosis spectrum disorders before and after 6 weeks of treatment with antipsychotics. Overall, mean pHVA levels did not differ from a matched control sample, which is in line with the existing literature reporting inconclusive results.[29]

Baseline pHVA levels were not correlated with PANSS scores at both time points, indicating that this parameter has little prognostic value, as was already suggested in the nineties by other investigators.[30] In contrast, data from the present study suggest that ΔpHVA may have a predictive value for responsiveness and possibly outcome in individual patients, as has also been suggested by others.[31]

With respect to FEP-patients and patients with (chronic) relapsing psychoses, a significant difference in decrease of pHVA was found. Symptomatic improvement and reaching remission status was most pronounced in FEP-patients as repeatedly reported by other investigators.[10,32] These observations may be related to the individual's state of neuroplasticity, as reflected by the ability to alter pHVA levels, especially since lack of plasticity is hypothesized to be related to loss of antipsychotic efficacy[33,34], poor prognosis, and chronic course of disease.[12,35]

The observation of significant differences in ΔpHVA and remission status between FEP and non-FEP patients, irrespective of initial categorical diagnosis, stresses the importance of investigating psychoses across strict diagnostic boundaries of current classification systems. This idea is supported by the observation that, within the psychosis spectrum, multiple clinical phenotypes exist with different responses to treatment.[7,9,36] The same holds for the association between ΔpHVA and antipsychotic responsivity in other psychosis spectrum disorders such as bipolar disorder[21,37], schizoaffective disorder[20] and delusional disorder.[22]

Several limitations can be identified that may have influenced the here reported results such as heterogeneity with respect to diagnostic classifications and antipsychotic treatment regimens. Concerning the latter, it is known that different antipsychotics may have a differential effect on pHVA levels[15,38], albeit that in a recent study of Nishimura and coworkers, no association between pHVA and dose of antipsychotics could be established.[39]

Nonetheless, in spite of the relatively small number of included patients, the observations on pHVA changes and responsiveness, remission status and outcome in FEP-patients can be considered rather robust.

In conclusion, the results from this study suggest that neuronal plasticity, expressed as ΔpHVA and reflecting the capacity to alter dopamine status, may be crucially involved in the individual responsiveness to antipsychotic treatment, especially in reaching the remission status.

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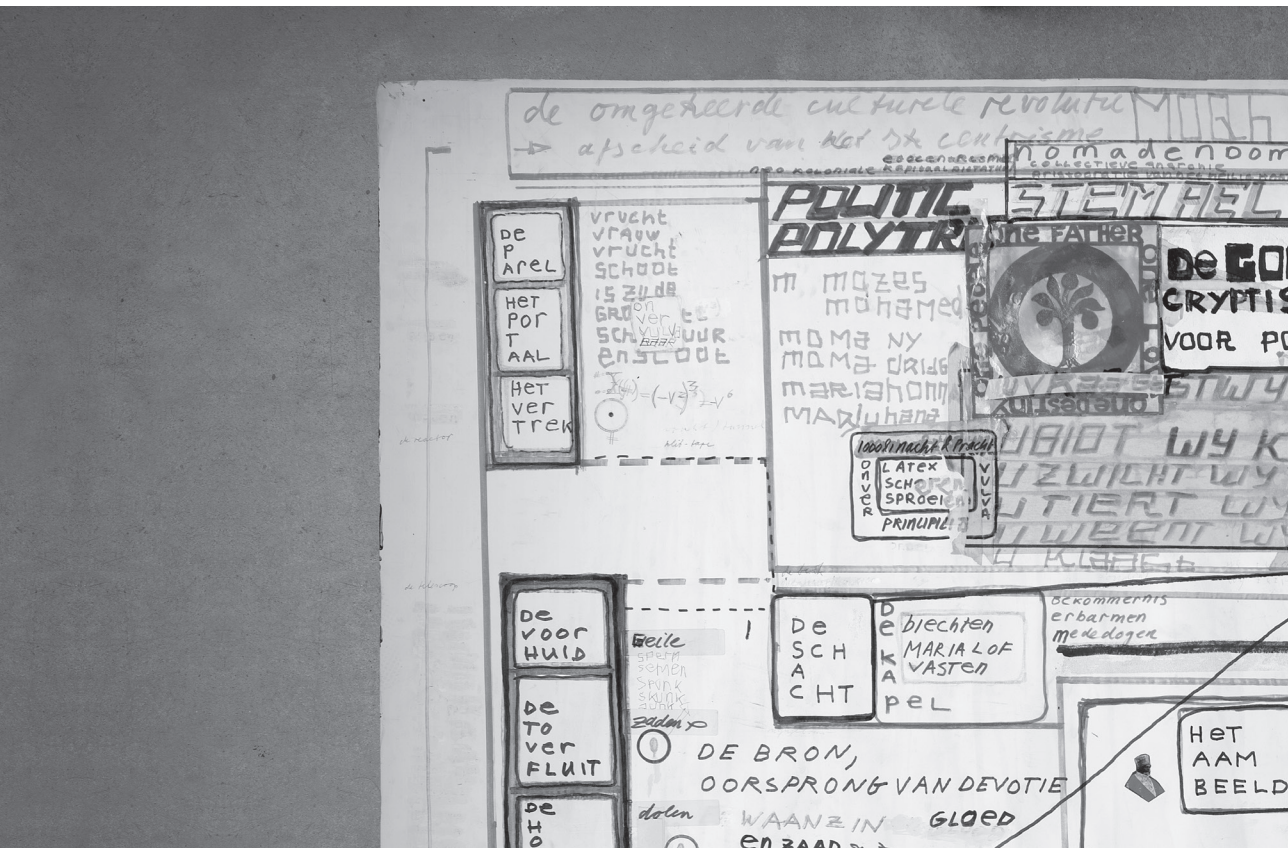
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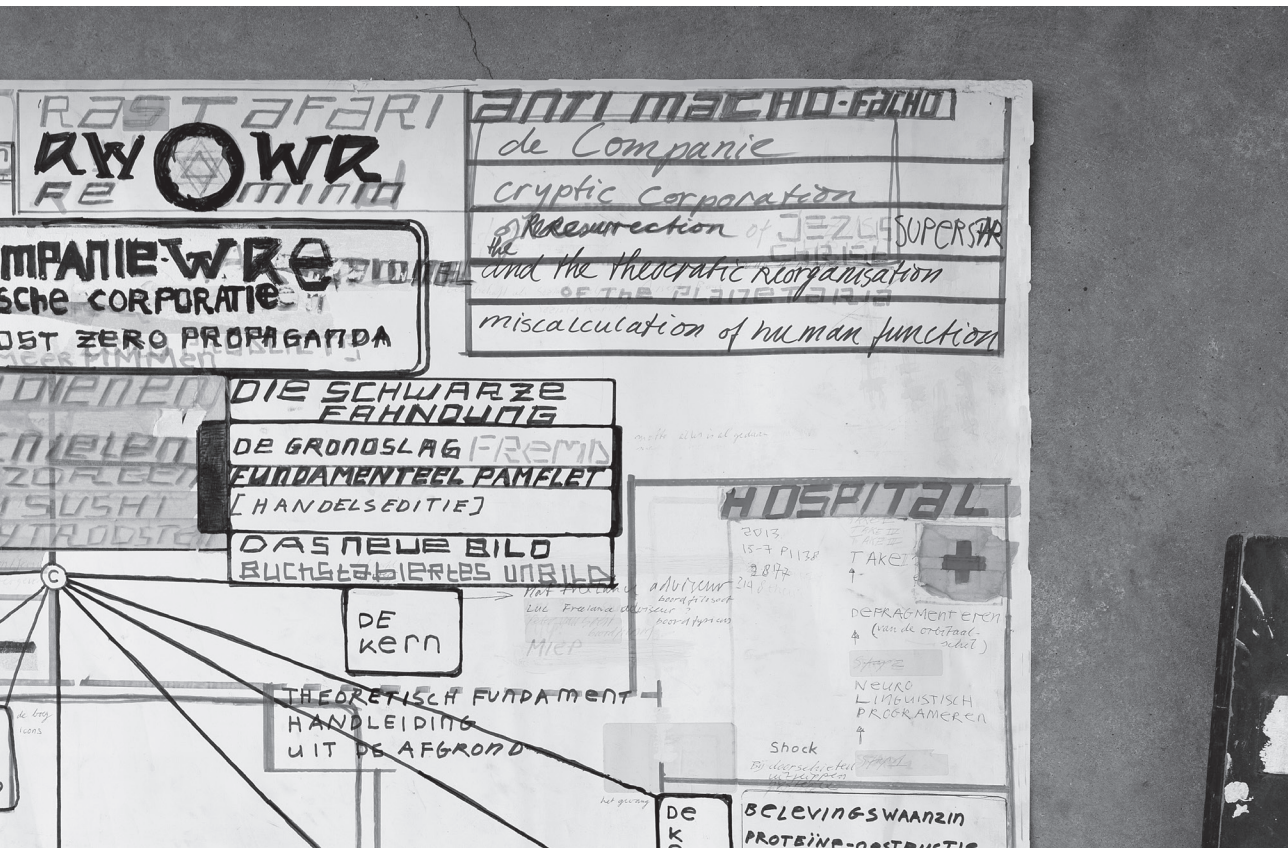
Chapter 6

Cycloid psychoses in the psychosis spectrum: Evidence for biochemical differences with schizophrenia



Noortje W.A. van de Kerkhof[1,2], Durk Fekkes[2,3], Frank M.M.A. van der Heijden[1], Witte J.G. Hoogendijk[2], Gerald Stöber[4], Jos I.M. Egger[1,5,6], Willem M.A. Verhoeven[1,2]

[1]Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, The Netherlands
[2]Erasmus Medical Centre, Department of Psychiatry, Rotterdam, The Netherlands
[3]Erasmus Medical Centre, Department of Clinical Chemistry, Rotterdam, The Netherlands
[4]University of Würzburg, Department of Psychiatry, Psychosomatics and Psychotherapy, Würzburg, Germany.
[5]Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, the Netherlands
[6]Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, the Netherlands

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Abstract

Cycloid psychoses (CP) differ from schizophrenia regarding symptom profile, course, and prognosis and over many decades they are thought to be a separate entity within the psychosis spectrum. As to schizophrenia, research into the pathophysiology has focused at dopamine, Brain-derived Neurotrophic Factor (BDNF), and glutamate signaling in which, concerning the latter, the N-methyl-D-aspartate receptor plays a crucial role. The present study aims to determine whether CP can biochemically be delineated from schizophrenia.

Eighty patients referred for psychotic disorders were assessed with the Comprehensive Assessment of Symptoms and History, and (both at inclusion and after 6 weeks of antipsychotic treatment) with the Positive and Negative Syndrome Scale and Clinical Global Impression. From 58 completers, 33 patients were diagnosed with schizophrenia and 10 with CP psychoses according to DSM-IV and Leonhard criteria, respectively. Fifteen patients were diagnosed with other disorders within the psychosis spectrum. At both time points, blood levels of the dopamine metabolite homovanillic acid, BDNF, and amino acids related to glutamate neurotransmission were measured and compared with a matched control sample.

Patients with CP showed a significantly better response to antipsychotic treatment as compared to patients with schizophrenia. In CP, glycine levels were elevated and tryptophan levels were lowered as compared to schizophrenia. Glutamate levels were increased in both patient groups as compared to controls.

These results, showing marked differences in both treatment outcome and glutamate-related variable parameters, may point at better neuroplasticity in CP, necessitating demarcation of this subgroup within the psychosis spectrum.

Introduction

Over many decades, dopamine (DA) neurotransmission has been thought to be the main mechanism in the pathophysiology of psychotic disorders, and DA-receptor antagonists have been demonstrated to be effective in reducing -mainly positive- psychotic symptoms.[1] Subsequent research has disclosed that other neurotransmitter systems, particularly that of glutamate, are associated with negative symptoms and cognitive dysfunctions via the N-methyl-D-aspartate (NMDA) receptor [2-5]

Glutamate is the most abundant excitatory neurotransmitter in the human brain and glutamatergic receptors are involved in regulating neuronal migration, growth and pruning (i.e. neuroplasticity).[6,7] Glutamate acts at different types of receptors, of which the NMDA receptor is the most investigated.[8,9] Glycine acts as a co-agonist at the NMDA receptor and can potentiate glutamatergic neurotransmission.[10] In contrast, antagonizing the NMDA receptor by means of phencyclidine (PCP) or ketamine induces schizophrenia-like symptoms.[11,12]

These observations have led to the hypothesis that the pathophysiology of schizophrenia is at least partly related to impairment in NMDA neurotransmission.[13,14] Hence, it seems likely that enhancing NMDA activity might benefit patients with schizophrenia, which could possibly be achieved by administration of components targeting at the glutamate system.[8,10,15,16]

Cycloid psychoses (CP) as described by Leonhard in the 1950s, partly operationalized by Perris and Brockington and included in ICD-10 as acute polymorphic psychotic disorder, differs from schizophrenia with respect to symptom profile, course and prognosis.[17-20] According to Leonhard, three subtypes can be delineated: anxiety-happiness psychosis, confusion psychosis and motility psychosis, all showing a pleiomorphic symptom profile with intraphasic bipolarity. In general, full recovery is reached without residual negative symptoms or cognitive decline.[21-23] CP, as such, are not included in DSM-IV, although key symptoms like pananxiety, perplexity and motility disorders have been demonstrated in a substantial percentage of patients.[24-30] An overview of the characteristics of schizophrenia and CP is presented in Table 1.

Since CP differ significantly from schizophrenia, the hypothesis was formulated that they could also be distinct on their biochemical profile, especially regarding glutamatergic transmission. Therefore, in the present study, peripheral levels of amino acids related to glutamate signaling (i.e. glutamate, glycine, and tryptophan) were measured in a group of patients with psychosis spectrum disorders. In addition, levels of Brain-derived Neurotrophic Factor (BDNF) and the dopamine metabolite homovanillic acid (HVA) were determined, reflecting neuroplasticity and dopaminergic activity, respectively.

Table 1. Characteristic differences between schizophrenia and cycloid psychoses

	Schizophrenia	Cycloid psychoses
Onset	Slow and insidious (weeks to months)	Often acute (hours to days)
Age at onset	Adolescence / young adulthood	Any age
Symptomatology	Delusions, hallucinations, disorganization, negative symptoms	Perplexity, confusion, mood swings, motility disorders, hallucinations, ideas of self sacrifice
Course	Relapsing and remitting, chronic, gradual functional and cognitive decline	Full remission, relapsing course without negative or cognitive decline
Prognosis	Unfavourable	Favourable
Treatment	Antipsychotic agents	Low potent antipsychotic agents in acute phase, limited evidence for maintenance treatment (lithium carbonate)
Gender distribution	Male ≈ female	Male < female

Methods

Patients

Patients were recruited over a 2.5 year period at the Vincent van Gogh Institute for Psychiatry. Included were adult male and female patients meeting DSM-IV criteria for psychosis spectrum disorders, who required antipsychotic treatment intervention. Intervention was defined as start or switch of antipsychotic agent or use of augmentation strategies. Exclusion criteria were known genetic syndromes or intellectual disability, and somatic or neurologic disorders interfering with treatment as usual. Research was performed in accordance with the Declaration of Helsinki and was approved by the regional ethics committee (METiGG) and board of directors of Vincent van Gogh Institute. Written informed consent was obtained following Dutch ethical guidelines (CCMO registration number NL20469.097.07). After inclusion, all patients were prescribed first- or second-generation antipsychotic agents (FGA/SGA) by their treating psychiatrist following standard professional guidelines. Concomitant treatment with two antipsychotic agents, mood stabilizer and/or antidepressant was allowed and documented.

During the study period, 194 patients were identified as eligible for inclusion. However, from these 194 patients, 71 were considered unable to provide informed consent because of severity of illness. In another 23 patients the intended pharmacological intervention was not performed, yielding 100 patients who were eligible for inclusion. Twenty patients refused to participate, mostly because of the need for venipuncture, resulting in a study group of 80 patients. Of them, 58 completed all clinical and biochemical assessments at baseline and after 6 weeks.

Diagnostic procedures

All patients were assessed by the first author (NvdK) before or within one week after start of treatment with antipsychotics. At baseline, the Comprehensive Assessment of Symptoms and History (CASH) was applied to establish diagnoses according to DSM-IV.[31] The Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression of Severity and Improvement (CGI-S/I) were used to measure symptom profile and overall disease severity at baseline and after 6 weeks.[32,33] PANSS cognitive score was calculated according to the procedure as described by Lindenmayer et al.[34] To establish diagnoses of CP, a symptom checklist according to Leonhard was completed by NvdK and a clinician trained in establishing diagnoses according to Leonhard (MS).[26,30,35] Final diagnoses were made in a so-called LEAD conference, in which all possible and probable cases of CP were discussed with two experts in the field of CP (GS and WV).[36]

Biochemical analyses

Patients: Blood samples were collected by means of venipuncture between 8 and 10 a.m. at both assessment dates to determine BDNF, HVA, the amino acids glutamate, glycine and tryptophan, and the ratio between tryptophan and the 5 large neutral amino acids (LNAA) competing for the same transport system, being leucine, isoleucine, valine, phenylalanine and tyrosine (Trp/LNAA ratio).

Plasma was prepared after centrifugation of EDTA blood for 20 min at 2650 g and 20°C, and stored at -80°C until analysis. All biochemical analyses were performed at the Neuropsychiatric Laboratory of Erasmus University Medical Center (EMC), Rotterdam, and the technician was blinded to the clinical situation and diagnosis of the patients.

Plasma was deproteinized and amino acids were separated by high performance liquid chromatography and detected by fluorescence after derivatization with ortho-phthaldialdehyde as described previously.[37] HVA levels were measured after deproteinization of plasma by high performance liquid chromatography using a Zorbax Eclipse XDB-C8 column (5 µm particle size, 250 x 3 mm; Agilent Technologies, Santa Clara, CA, USA) for separation. For the detection of HVA, an electrochemical detector (oxidation potential was set to 0.7 V) and the Intro controller (Antec Leyden, Zoeterwoude, The Netherlands) were used. Quantification was done by measuring peak heights relative to two internal standards (isoprenaline and 5-methylserotonin). The mean recovery (± SD) of HVA added to the plasma samples was 95 ± 7%. BDNF was measured in serum by a double antibody sandwich enzyme linked immunosorbent assay (ELISA) (Promega Corporation, Madison, WI, USA).

Controls: Biochemical parameters from age-matched controls were taken from a large database of the aforementioned Neuropsychiatric Laboratory. Age-matched controls were taken from a large database, consisting of hospital staff and students and subjects from the general community, all without a personal or family history of psychiatric illness. Mean age of the control group (n=75) was 37.9 ± 10.1 years.

Statistics

From the 58 completers, only patients with a diagnosis of schizophrenia (n=33) or CP (n=10) were included in the statistical analyses. To compare means, the non-parametric Mann-Whitney U test was used for non-normally distributed data (biochemical parameters) whereas the Student's t-test was applied for normally distributed data. To investigate changes between time points, Wilcoxon Signed rank test (biochemical parameters) or paired t-test (PANSS scores) was used. For binary variables, a Chi-square test was done. Significance was set at $p<0.05$. All data are presented as mean ± SD, unless stated otherwise.

Results

Patients:

By excluding patients diagnosed with other psychotic disorders (n=15), the study sample (n=43) consisted of 30 males and 13 females with a mean age of 34.8 ± 11.3 years. Thirty-three patients received a diagnosis of schizophrenia and in ten, a diagnosis of CP according to Leonhard was made (anxiety-happiness: n=5; confusion: n=2; motility: n=3). Mean age at first psychosis was 26.5 ± 9.8 years and mean duration of psychotic illness was 8.3 ± 8.1 years. Fourteen patients (CP: n=5; schizophrenia: n=9) did not receive psychotropic medication prior to inclusion in the study (referred to as "at baseline"), of which 8 were antipsychotic naïve (CP: n=3; schizophrenia: n=5). Eight out of the total of 43 patients were first-episode psychosis (FEP) patients. Five patients were classified as both medication naïve and having FEP (CP: n=3; schizophrenia: n=5). Details on symptom clusters, effect of antipsychotic treatment and severity of illness are summarized in Table 2.

Since each patient received an individually targeted treatment, data were scrutinized for possible confounding effects of psychopharmacological heterogeneity. With respect to the two patient groups (CP: n=10; schizophrenia: n=33), no differences were found as to medication status (naïve, free >2 weeks, or medicated), use of co-medication (antidepressant or mood stabilizers), and antipsychotic class (FGA or SGA). Regarding the latter, in the CP group, none of the patients was treated with clozapine, whereas nine patients in the schizophrenia group did receive this agent. The CP group comprised significantly more females, who had higher ages at first presentation of psychotic illness as well as at time of inclusion. Finally, five patients with CP were defined as FEP patients.

As can be inferred from Table 2, CP patients had significantly lower scores on the PANSS total, positive and negative scale at both time points. Symptomatic improvement was most marked in the positive symptom cluster. While both groups showed symptomatic improvement after 6 weeks of treatment, a significant difference was found between the groups in PANSS cognitive score and CGI-S in favour of the CP group.

Table 2. Demographic and clinical parameters in patients with cycloid psychosis (CP, n=10) and schizophrenia (n=33)

	CP (n=10)	Schizophrenia (n=33)
Male/female *	4/6	26/7
Age *	42.3 ± 10.3	32.6 ± 10.8
Age at onset *	36.7 ± 10.8	23.4 ± 7.1
FEP yes/no **	5/5	3/30
Smoking yes/no[1] *	3/7	25/8
Caffeine yes/no[1]	9/1	29/4
Softdrugs yes/no[1]	1/9	7/26
Harddrugs yes/no[1]	0/10	2/31
PANSS baseline		
- Total score *	77.2 ± 19.1	92.9 ± 17.4
- Positive subscale *	20.2 ± 5.8	25.0 ± 5.5
- Negative subscale **	16.6 ± 5.8	22.9 ± 6.8
- Global subscale	40.4 ± 11.7	45.1 ± 9.1
- Cognitive subscale	13.1 ± 4.4	15.3 ± 3.9
PANSS 6 weeks		
- Total score *	55.4 ± 22.2	75.3 ± 13.3
- Positive subscale **	11.5 ± 6.5	18.9 ± 5.2
- Negative subscale *	13.8 ± 6.1	19.4 ± 5.1
- Global subscale	30.1 ± 11.7	37.0 ± 6.9
- Cognitive subscale *	9.8 ± 4.5	13.1 ± 3.4
Mean CGI Severity (CGI-S)		
- baseline	4.0 ± 1.2	4.9 ± 1.1
- 6 weeks *	2.5 ± 1.4	4.0 ± 1.1
Mean CGI Improvement (CGI-I)	2.4 ± 1.0	2.9 ± 0.9

Abbreviations: FEP = first episode psychosis; PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impression

[1] Smoking and use of caffeine/ softdrugs/ harddrugs were defined as any use ≠ 0 in the past month, as reported by the patient.

All within-group differences between PANSS and CGI scores at baseline and after six weeks are significant (p≤0.001) except for PANSS negative score in the CP group (p=0.062)

** difference between CP and schizophrenia, Mann Whitney U, p<0.05*

***difference between CP and schizophrenia, Mann Whitney U, p≤0.01*

Biochemical parameters:

As compared to controls, serum BDNF levels were lowered in patients with schizophrenia, and plasma glutamate levels appeared to be increased in both patient groups. Concerning plasma levels of glycine, significant higher values were found in CP patients at both time points as compared to patients with schizophrenia as well as control subjects. Also, at both time points, plasma tryptophan levels were significantly lower in patients with CP as compared to controls, but differed only at baseline from the schizophrenia group. Trp/LNAA ratio was lowered in both patient groups as compared to controls. Plasma levels of HVA did not differ between the groups. All data are presented in Table 3.

Table 3. Blood levels of biochemical parameters in cycloid psychosis (CP, n=10), schizophrenia (SCH, n=33) and controls (n=75)

	CP	Schizophrenia	Controls
BDNF baseline[1]	20.4 ± 7.1	19.6 ± 5.8***	24.4 ± 6.7
BDNF 6 weeks[1]	19.9 ± 8.1	19.1 ± 6.0***	
HVA baseline[2]	60.4 ± 21.3	58.5 ± 19.7	53.4 ± 13.7
HVA 6 weeks[2]	51.8 ± 20.4	52.1 ± 15.8	
Glutamate baseline[3]	56.3 ± 24.8**	69.5 ± 30.5***	34.4 ± 16.1
Glutamate 6 weeks[3]	64.9 ± 44.6**	66.2 ± 30.9***	
Glycine baseline[3]	292.2 ± 96.9*	215.1 ± 62.3#	224.2 ± 47.8
Glycine 6 weeks[3]	280.9 ± 86.2*	223.7 ± 62.3#	
Tryptophan baseline[3]	37.4 ± 14.0**	48.3 ± 11.5#	47.5 ± 7.7
Tryptophan 6 weeks[3]	38.1 ± 10.8**	43.5 ± 11.7	
Trp/LNAA ratio baseline	7.1 ± 1.4**	7.7 ± 1.5*	8.6 ± 1.5
Trp/LNAA ratio 6 weeks	7.4 ± 1.6*	7.8 ± 1.7*	
Phenylalanine baseline[3]	52.4 ± 10.2	63.4 ± 15.1*#	56.3 ± 8.9
Phenylalanine 6 weeks[3]	51.7 ± 10.1	55.3 ± 11.2	
Isoleucine baseline[3]	69.1 ± 22.1	82.7 ± 32.8	71.0 ± 22.2
Isoleucine 6 weeks[3]	63.6 ± 19.6	71.8 ± 22.1	
Leucine baseline[3]	121.7 ± 36.0	158.5 ± 60.0*	130.3 ± 32.4
Leucine 6 weeks[3]	123.3 ± 39.5	136.9 ± 39.2	
Valine baseline[3]	218.7 ± 65.2	267.6 ± 76.1	245.3 ± 56.6
Valine 6 weeks[3]	218.7 ± 49.8	239.6 ± 58.0	
Tyrosine baseline[3]	61.5 ± 14.9	72.2 ± 25.6	63.9 ± 17.0
Tyrosine 6 weeks[3]	61.5 ± 18.7	62.1 ± 15.4	

1 = µg/l; 2 = nmol/l; 3 = µmol/l

Abbreviations: BDNF = brain derived neurotrophic factor; HVA = homovanillic acid; Trp/LNAA ratio = tryptophan/large neutral amino acids ratio

Difference versus controls (Mann-Whitney U)
** p<0.05; ** p≤0.01; *** p≤0.001*
 # difference between SCH and CP, p<0.05

In both the subgroup of patients with schizophrenia who were treated with clozapine (n=9) and the subgroup of eight medication naïve patients (CP: n=3; schizophrenia: n=5), lowered serum levels of BDNF and elevated levels of glutamate were found at both time points. However, in the clozapine subgroup, glycine levels were significantly lowered as compared to controls at baseline (177.6 ± 45.1 versus 224.2 ± 47.8 µmol/l), whereas in the medication-naïve subgroup glycine levels did not differ from controls at both time points.

The fifteen patients with diagnoses other than CP or schizophrenia (schizoaffective disorder: n=1; bipolar disorder: n=5; delusional disorder: n=1; brief psychotic disorder: n=2; schizotypal personality disorder: n=1, psychotic disorder not otherwise specified: n=5) were analyzed separately. Glutamate levels were significantly elevated as compared to controls at both time points. Data on biochemical parameters in this group are depicted in Table 4.

Table 4. Blood levels of biochemical parameters in patients with other psychotic disorders (n=15) and controls (n=75)

	Baseline	6 weeks	Controls
BDNF[1]	21.9 ± 8.1	20.4 ± 7.6	24.4 ± 6.7
HVA[2]	75.5 ± 36.6	63.5 ± 23.3	53.4 ± 13.7
Glutamate[3]	51.1 ± 13.9 ***	50.9 ± 16.6 ***	34.4 ± 16.1
Glycine[3]	268.5 ± 137.5	263.7 ± 124.9	224.2 ± 47.8
Tryptophan[3]	47.4 ± 9.6	46.0 ± 7.8	47.5 ± 7.7
Trp/LNAA ratio	7.9 ± 2.2	8.0 ± 1.6	8.6 ± 1.5
Phenylalanine[3]	59.8 ± 12.0	58.3 ± 10.4	56.3 ± 8.9
Isoleucine[3]	81.1 ± 23.1	72.7 ± 22.3	71.0 ± 22.2
Leucine[3]	149.4 ± 43.2	141.6 ± 38.7	130.3 ± 32.4
Valine[3]	264.4 ± 52.4	252.1 ± 65.1	245.3 ± 56.6
Tyrosine[3]	73.7 ± 21.1	70.5 ± 20.7	63.9 ± 17.0

1 = µg/l; 2 = nmol/l; 3 = µmol/l

Abbreviations: BDNF = brain derived neurotrophic factor; HVA = homovanillic acid; Trp/LNAA ratio = tryptophan/large neutral amino acids ratio

Difference versus controls (Mann-Whitney U)
** p<0.05; ** p≤0.01; *** p≤0.001*

As to intercorrelations of biochemical and clinical parameters, both in the total patient sample and in the schizophrenia subgroup, baseline glutamate levels were positively correlated with changes in PANSS cognitive scores (total sample: T 0.280, p=0.012; schizophrenia: T 0.360, p=0.005). Glutamate levels after six weeks were positively correlated with PANSS cognitive scores at both time points in the total patient group (baseline T 0.221, p=0.043; six weeks T 0.279, p=0.011) and with PANSS cognitive scores after six weeks in schizophrenia patients (T 0.289, p=0.023).

Baseline glycine levels did not correlate with any of the clinical (sub)scales. Glycine levels after six weeks correlated significantly with changes in PANSS cognitive scores (T 0.523, p=0.038) in CP patients. No other correlations were found in CP between glutamate or glycine levels and other PANSS or CGI scores at both time points.

No significant correlations were found for (changes in) any of the biochemical parameters from Table 3 and (changes in) other clinical parameters (PANSS or CGI) in the two subgroups at both time points.

Discussion

In this study, patients with CP and schizophrenia were assessed on both clinical and biochemical profiles. Essentially, the CP group showed better clinical outcome than the schizophrenia group and differed significantly in terms of biochemical parameters, particularly plasma levels

of glycine and tryptophan. Serum levels of BDNF were significantly lower in the schizophrenia group as compared to controls.

With respect to glycine, in CP, plasma levels were elevated as compared to both schizophrenia and healthy controls. Although in 2004, Sumiyoshi and coworkers found lowered levels of glycine for schizophrenia in comparison with controls and patients with major depression, current findings are in line with those reported in 2006 by Hoekstra et al. in patients with bipolar mania.[38,39]

Since glycine is an essential co-agonist for glutamate at the NMDA receptor, increased levels could be regarded as a reflection of disturbances in glutamatergic neurotransmission. With respect to the latter, since plasma glutamate levels did not differ significantly between the two groups, it could be speculated that in CP, glycine levels are elevated as a compensatory reaction to NMDA receptor hypofunction, whereas patients with schizophrenia would have insufficient neuroplasticity to produce such a response. This hypothesis is corroborated by the present lowered serum BDNF levels in the schizophrenia group and by other studies showing that PCP-induced psychotic symptoms can be ameliorated by administration of glycine.[40,41] Further support is found in earlier studies that show beneficial effects of adjuvant high-dose glycine augmentation to other antipsychotic agents.[42-44]

In patients with other psychotic disorders, both BDNF and glycine levels did not differ from controls. It could be speculated that, even in the presence of sufficient neuroplasticity, the ability to adaptively increase glycine levels might be characteristic for CP.

The observation that plasma levels of glutamate are increased in all patient groups as compared to controls, is in accordance with reports that relate elevated glutamate levels with psychosis and psychotic relapse, albeit that decreased levels in schizophrenia and bipolar disorders have also been reported.[29,45,46] Elevated glutamate levels are hypothesized to be the result of NMDA receptor hypofunction, leading to diminished glutamatergic neurotransmission and to the evolvement of schizophrenic symptoms, including negative and cognitive symptoms.[15,16]

The Trp/LNAA ratio was significantly lower in CP and schizophrenia as compared to controls. This finding is suggestive of a decreased central serotonergic activity in both patient groups. The lower tryptophan levels in CP might point to an increased breakdown of tryptophan via the kynurenine pathway. One of the products in this pathway is kynurenic acid, which is not only an antagonist of the NMDA receptor, but also a neuroprotectant.[47,48] It could be speculated that in CP, other than in schizophrenia, this neuroprotective mechanism is still activated which would correspond with better neuroplastic properties and a more favourable course of disease in CP.

Apart from small sample size and the use of peripheral measurements only, a limitation can be identified in that a substantial number of patients were treated earlier with a wide range

of FGA and SGA agents. The latter, however, most probably did not interfere with the results since no influences were found regarding medication status in the two patient groups.

In conclusion, in both CP and schizophrenia, systemic glutamate metabolism and the Trp/LNAA ratio were altered, which could be related to changes in glutamate signaling. Moreover, differences in especially glycine, between CP and schizophrenia were found, which may point at a better neuroplasticity in CP than in schizophrenia. This may be in line with better clinical outcome in CP. Therefore, it is crucial to identify CP as a separate group of disorders within the psychosis spectrum.

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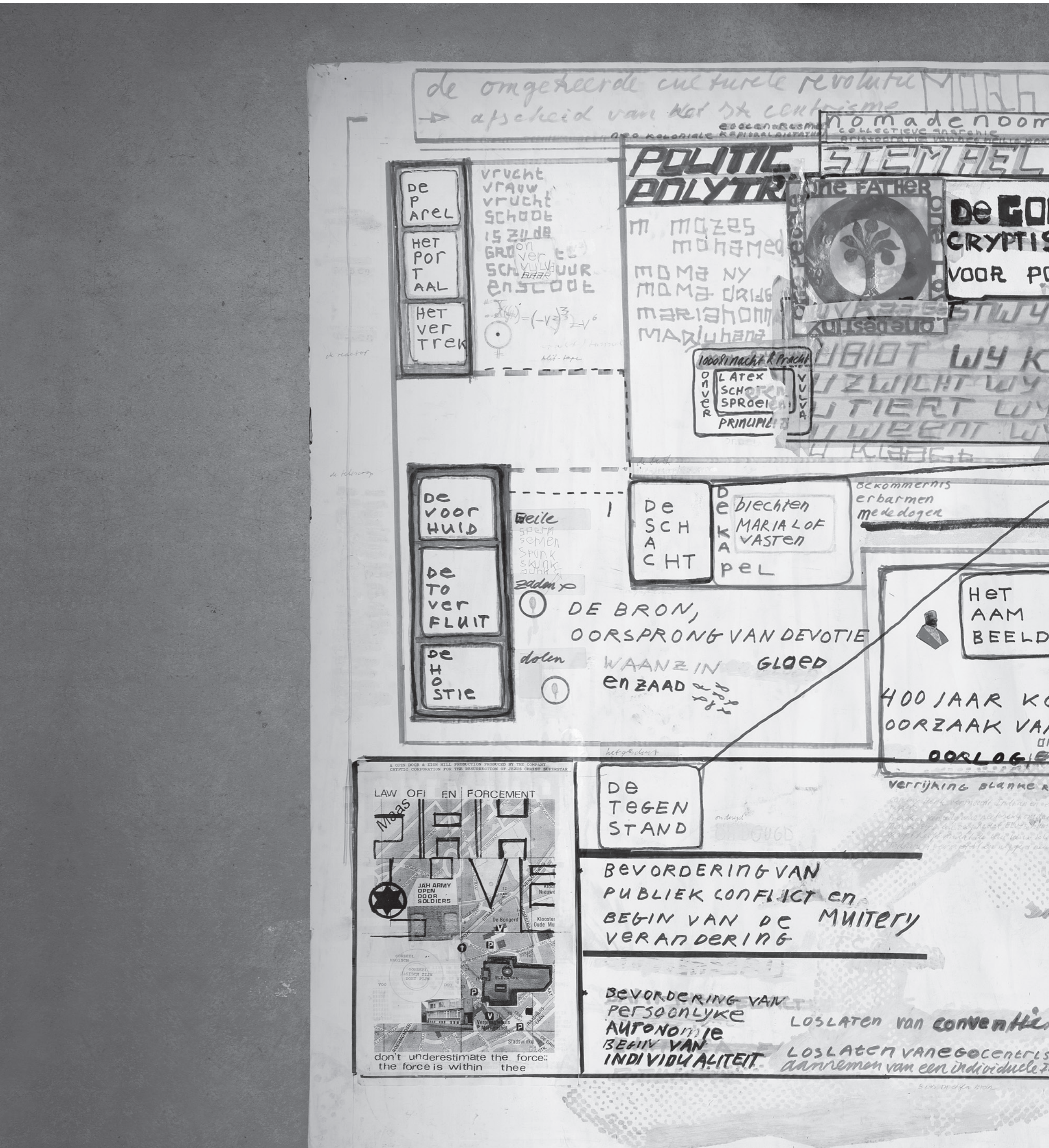
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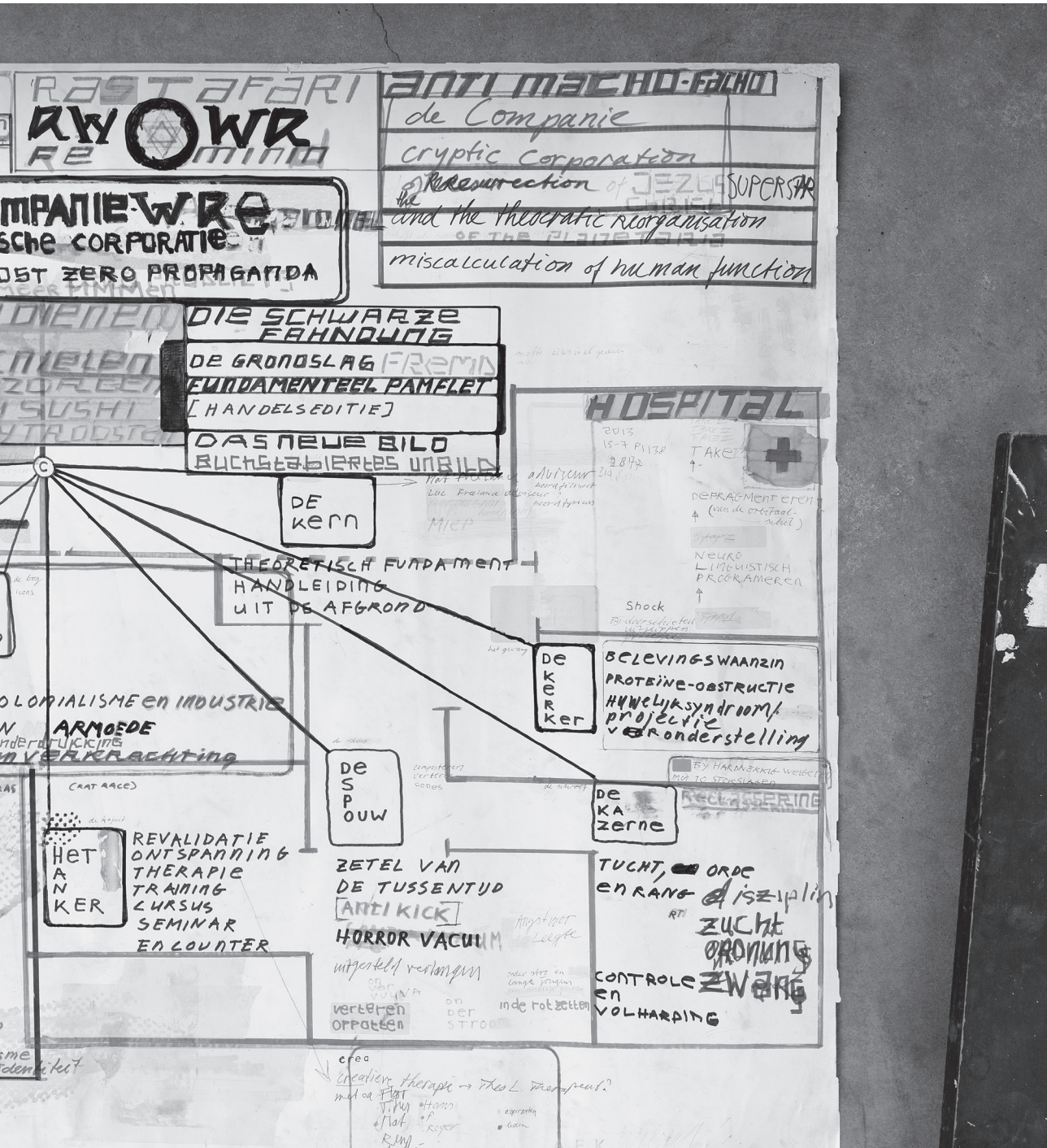
Chapter 7

General discussion



The aim of this thesis was to investigate ways to evaluate psychotic disorders in individual patients across diagnostic boundaries, in a way that is applicable in everyday practice. In order to build upon available research, evaluation and classification by means of DSM-IV[1] was also performed. Main findings are discussed below followed by a section with theoretical and clinical considerations. Finally, some limitations are mentioned to identify future research directions.

Main findings

Copy Number Variations (CNVs)

Routine screening for CNVs by means of micro-array was performed in 80 patients presenting with psychosis. Although in 3 out of 80 patients a CNV was found, i.e. 2 microduplications (1p13.3 and 7q11.21q11.22, respectively) and 1 microdeletion (1q21.1), these could not be related to the psychotic symptoms. From a clinical point of view, routine screening for CNVs in psychotic disorders seems to be of limited additional value.

It should be noted that targeted screening for CNVs can contribute to extension of knowledge about the genetic architecture predisposing for psychiatric and non-psychiatric disorders. Recent studies that appeared after publication of our results, showed that genetic polymorphisms at the 1p13.3 locus are associated with coronary artery disease.[2] Since 2008 deletions and duplications on 1q21.1 have been reported to be associated with a broad variety of neuropsychiatric and developmental disorders.[3,4] Aberrations (though not duplications, as found in our patient) in the 7q11.21q11.23 region were reported to give rise to infantile spasms and pontocerebellar hypoplasia.[5,6] Furthermore, studies into CNVs in both patients and controls show similar subtle cognitive defects related to microdeletions in 15q11.2.[7] These defects could possibly be generalized to the overall genetic basis of connectivity and information processing in the brain.[8]

For current clinical practice, these promising results stress the importance of careful evaluation of symptomatology, dysmorphic features, cognition, (childhood) development and family history, in order to search for chromosomal aberrations in a purposeful way. In specific cases, such as Prader-Willi syndrome or 22q11.2 deletion syndrome, identification of the genetic disorder is of great importance for adequate counselling and treatment of psychotic symptoms associated with the syndrome.

Cycloid psychoses according to Leonhard (LCP)

The term cycloid psychosis comprises acute and relapsing psychoses with a pleiomorphic symptom profile. Depending on the subtype, an intraphasic bipolarity can be observed consisting of severe anxiety or ecstasy, confusional states and psychomotor disturbances.[9] Outcome is usually favourable, with little to no residual symptomatology nor cognitive decline.[10,11]

The concept of cycloid psychoses according to Leonhard (LCP) was investigated in a cohort of 80 patients admitted for treatment of psychoses by means of a checklist according to Leonhard's original descriptions. A prevalence of ~15% was found, which is in line with previously reported prevalence rates of 8-24%.[12,13] Symptomatic reduction was found to be greater in the LCP group as compared to the non-CP group.

In spite of the small patient sample, the three subtypes of LCP could be discriminated from other psychotic disorders by their specific symptomatology and intraphasic bipolarity. Key features of the core syndromes included pananxiety, perplexity, psychomotor disturbances, mood swings and hallucinatory experiences.

Patients diagnosed with LCP were mostly classified as DSM Brief Psychotic Disorder (DSM-BPD) or ICD Acute Polymorphic Psychotic Disorder (ICD-APP).[14] The highest concordance rates were found for LCP and ICD-APP. A concordance rate of 0.63 ($p<0.001$) for LCP and the operational criteria as formulated by Perris and Brockington[15] further illustrates that cycloid psychoses according to Leonhard are not sufficiently covered by current classification systems.

Cycloid psychoses differ from schizophrenia and related disorders with respect to symptomatology, course and prognosis and it was advocated to acknowledge the cycloid psychoses as different from existing classification categories. Merely adding a diagnostic category should nonetheless never be the main objective of clinical research and in the acute phase, cycloid psychoses can indeed be treated effectively with antipsychotic agents. However, there is no evidence for long-term use of antipsychotic medication to prevent relapses, and most (though little) evidence points in the direction of mood stabilizers as the agents of choice in case of maintenance therapy.[16] The possible influence on important treatment choices made in clinical practice illustrates the instrumental value of the cycloid psychoses.

With respect to research into psychosis spectrum disorders, the cycloid psychoses might be a valuable counterpart for schizophrenia and related psychoses. The observed differences in clinical picture and treatment point in the direction of different neurobiological underpinnings, with cycloid psychoses as disorders in which neuroplasticity and connectivity might be better developed or preserved versus profound 'disconnectivity' in schizophrenia. This disconnectivity model probably exceeds the boundaries of current classification systems.

Biochemical parameters

The neurotrophic proteins Brain Derived Neurotrophic Factor (BDNF) and S100B were measured in the serum of 58 patients with psychotic disorders. It was found that BDNF was lowered in patients with an acute psychotic episode, irrespective of diagnostic category. It was concluded that BDNF can be regarded as a general marker for neuroplasticity in both psychotic and non-psychotic disorders. In the case of S100B, it was found that higher baseline levels corresponded with more negative symptoms after 6 weeks of treatment, which was in line

with other studies.[17,18] Interestingly, it also appeared that lower baseline levels of S100B were associated with more positive symptoms after 6 weeks of treatment as compared to the other subgroups. Since S100B has both neurotoxic and neuroprotective effects, it was speculated that the elevated levels of S100B in this group might represent deficiencies in neuroprotective mechanisms in these patients. The findings should be regarded cautiously, since a study from Van der Leeuw et al. (GROUP) found no associations between serum S100B levels and illness parameters in patients with psychotic disorders.[19] In contrast, a recent meta-analysis did establish relationships between S100B, illness duration and clinical symptoms in patients with schizophrenia.[20]

It was hypothesized that subnormal levels of S100B might initially induce positive symptoms while during the course of disease S100B levels might rise, resulting in the development of negative symptoms due to a neurotoxic effect of the higher S100B levels in the brain. BDNF and S100B might be related to neuroplasticity and (dis)connectivity, maybe not individually, but as members from a network with other neurotrophic proteins interacting with each other.

Plasma levels of the main dopamine metabolite homovanillic acid (HVA) were measured in 58 psychotic patients.[21] Overall baseline plasma HVA (pHVA) concentrations did not differ from a matched control sample and were not associated with treatment responsiveness of symptomatology, which was in line with other studies.[22] However, after 6 weeks of treatment a larger decrease in pHVA concentrations was observed in patients with first episode psychosis (FEP) as compared to patients with relapsing or chronic psychoses. This larger decrease was significantly associated with better symptomatic improvement. Better treatment outcome in patients with FEP was previously reported by other investigators.[23,24]

The observed differences between patients with FEP and those with relapsing or chronic psychoses could be related to the individual's state of neuroplasticity, reflected by the ability to alter pHVA levels. Lack of plasticity is suggested to be related to loss of antipsychotic efficacy, poor prognosis and chronic course of disease.[25,26] The same holds for the association between changes in plasma HVA levels and antipsychotic responsivity in other psychosis spectrum disorders such as bipolar disorder, schizoaffective disorder, and delusional disorder.[27-30] These findings illustrate the importance of investigating psychoses across the boundaries of current classification systems. The model of neuroplasticity and (dis)connectivity might provide a more suitable framework for connecting clinical and biochemical aspects of psychotic disorders.

Biochemistry in cycloid psychoses

Since LCP was considered a valuable counterpart for schizophrenia, the two disorders were investigated in order to establish whether the clinical differences, especially the absence of cognitive decline in LCP, were possibly associated with different biochemical underpinnings.

Next to dopamine, the glutamate system has been extensively investigated and it has become clear that disturbed glutamatergic neurotransmission is associated with negative symptoms and cognitive dysfunction via the NMDA receptor.[31-33] Furthermore, earlier studies have shown beneficial effects of high dose (0.8mg/kg/day) glycine augmentation to antipsychotic treatment.[34-36] Glycine is an essential co-agonist for the N-methyl-D-aspartate (NMDA) receptor.[37]

With respect to the dopamine metabolite HVA, no differences were found. Glutamate levels were elevated in both disorders. Levels of BDNF were lowered in patients with schizophrenia, but not with LCP, as compared to controls. In patients with LCP, elevated levels of glycine were found as compared to controls, patients with schizophrenia, and patients with other psychosis spectrum disorders. Since biochemical profiles in patients with LCP were, to date, not previously investigated, these findings could be of help in further understanding of the pathophysiology and treatment of LCP and other psychotic disorders.

The elevated levels of glycine in LCP might be explained as a compensatory reaction to the disturbed glutamatergic neurotransmission. This would suggest better neuroplasticity and connectivity in LCP as compared to schizophrenia, which is consistent with the finding of lowered levels of BDNF in schizophrenia and a more favourable prognosis for LCP. Differences in the extent of (dis)connectivity between LCP and other (schizophrenia-like) disorders could possibly contribute to understanding the common base of psychosis spectrum disorders.

Theoretical and clinical considerations

Chromosome aberrations, neurotrophic proteins and neurotransmitter metabolites could each be regarded as representatives of neuroconnectivity and -plasticity in psychosis spectrum disorders. The concept of LCP appears to differ from other psychotic disorders with respect to symptomatology and disease course, but also with respect to biochemical characteristics. They could therefore be of great heuristic value for understanding psychosis in general. Psychotic symptoms are highly prevalent and emerge in a broad variety of psychiatric disorders. In the spectrum of psychotic disorders, most research to date has focused on schizophrenia, but over the years it has become evident that there is a considerable overlap between schizophrenia and the other disorders in the spectrum, such as schizoaffective disorder, atypical psychoses, delusional disorder and bipolar manic psychosis.[30,38-40]

Connectivity

The concept of (dis)connectivity has gained attention in the past years as being a possible common denominator in the etiology and pathophysiology of psychotic symptoms in a neurodevelopmental rather than in a neurodegenerative sense.[41-44] Connectivity and synaptic

plasticity are related and appear to be key factors in brain development, maintenance and protection.

The theory of physiological connectivity is as old as the 19th century.[45] Subsequently, Karl Wernicke hypothesized that disturbed connection between the two language areas in the brain could result in aphasia (called conduction aphasia). He broadened this concept to psychiatric disorders and postulated that they emerged from disruptions of "psychischen Reflexbogen" which he called "sejunctions".[46] It should be noted that, at that time, schizophrenia had not been described as yet. When Kraepelin wrote about "dementia praecox"[47], the young physician Otto Gross, who worked under direction of Eugen Bleuler, proposed that this concept was related to sejunction problems and coined the term "dementia sejunctiva".[48] Bleuler himself was an associationist thinker and tried to identify the fundamental psychological disorder in terms of problems in the relationship between ideas or concepts: "der Spaltung", or in English "dissociation".[49] In summary, from a historical point of view, sejunction (connectivity) and dissociation (schizophrenia) have always been closely related.

Disconnectivity and psychosis

In the disconnection hypothesis, connection is referred to as functional rather than anatomical. It is proposed that psychiatric disorders are a result of disturbed functional connectivity in the adult developing brain. Several observations point especially in the direction of psychotic disorders such as schizophrenia.[50,51] It was also suggested that psychosis is more likely to occur in the presence of both disconnection (white-matter lesions) and high DA levels, suggesting that psychosis is the result of faulty interplay between DA and reduced connectivity.[52,53]

Taken together, the core pathology of psychoses can be considered as an impaired control of synaptic plasticity, manifesting as abnormal integration of neural systems, i.e. disconnectivity. This can be considered in line with the finding that in schizophrenia, reduced spine densities and smaller dendritic arbors are found postmortem.[54,55] Pharmacological studies in healthy volunteers show that impairments of synaptic plasticity are consistent with schizophrenic symptoms, as was shown for NMDA-antagonists, D2-agonists, amphetamines and serotonin agonists.[21,56,57]

In patients with psychosis spectrum disorders, (psychopharmacological) treatment could be regarded as a way to "detach" from psychosis and to start re-establishing the cognitive and emotional interaction with the real world.[58] In turn, this could lead to enhanced synaptic plasticity associated with reality.[59] Investigating models for synaptic plasticity that can be evaluated in individual patients might be a useful and promising approach in the search for alternatives for diagnostic classification. Furthermore, it could facilitate genetic studies or have predictive value for pharmacological treatment.[57]

Limitations and future directions

Limitations

Apart from a modest sample size which is inherent to this type of clinical investigation, several limitations can be discerned of which at least two should be mentioned here.

First of all, patients were assessed with rating scales that were originally designed for schizophrenia, thus collecting data about dimensions that could possibly not (all) be applied to non-schizophrenic psychoses or affective disorders with psychotic features. Affective symptoms therefore may have been underrepresented since the focus of most questionnaires (such as PANSS) is on overt positive symptomatology and negative symptoms. This stresses the importance of using both targeted and global/ extensive rating scales to tap detailed changes in the clinical picture of a patient as well as his subjective experience. Since treatment should essentially be directed towards functional recovery instead of symptomatic improvement only, such assessment strategies could be of value in future research.

Second, the heterogeneity of the sample with respect to diagnostic classifications, substance abuse, medication history and antipsychotic treatment could have influenced the results. Therefore, possible confounding effects were carefully evaluated in all analyses. Given the complex nature of psychosis spectrum disorders, certain to date unknown factors may have been overlooked. In order to certify clinical utility of our findings, it was decided to study psychoses across categorical diagnostic boundaries and to address this point in each relevant chapter.

Conclusion and future directions

The connectivity hypothesis provides a valuable framework to better understand psychosis spectrum disorders and exceeds the boundaries of current classification systems. In order to provide patients and clinicians with information applicable in everyday practice, research should not only focus on established diagnostic categories from existing classification systems, but should also broaden the scope to psychotic symptomatology across the boundaries of described syndromes. Efforts should be made to carefully describe symptomatology, illness severity and response to treatment. Subsequently, connectivity-related, measurable parameters (e.g. biochemical or genetic) could be used to identify new or establish existing subgroups of patients with specific characteristics or prognosis.[60-62] The development of the Research Domain Criteria (RDoC) may facilitate this kind of research, by providing a framework for the integration of clinical and neurobiological parameters.[63] This strategy may yield clinical syndromes ("exophenotypes") or endophenotypes, which can be the focus of further investigation. But maybe even more importantly, patients might eventually be provided with better, personalized information on the nature and prognosis of their illness.

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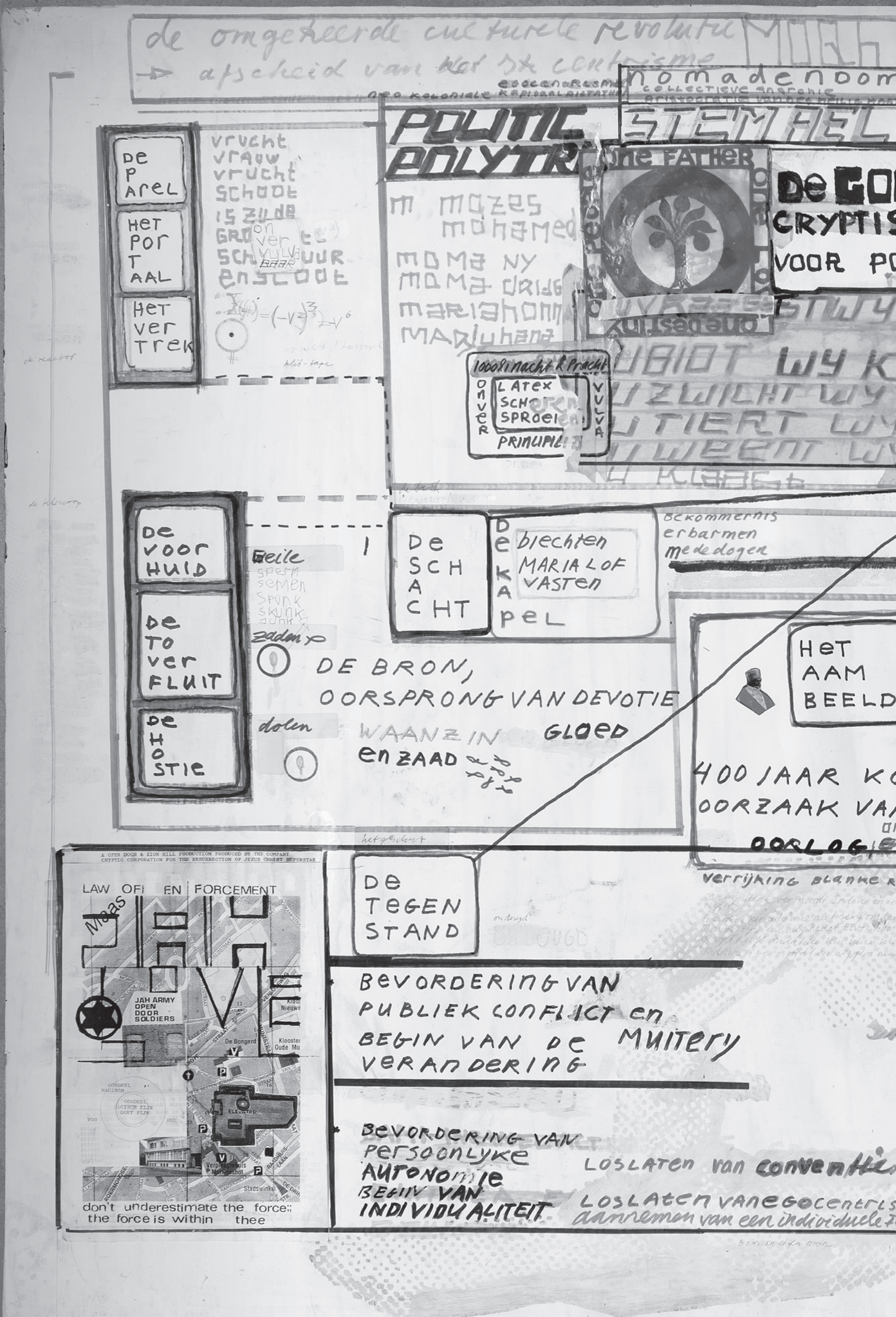
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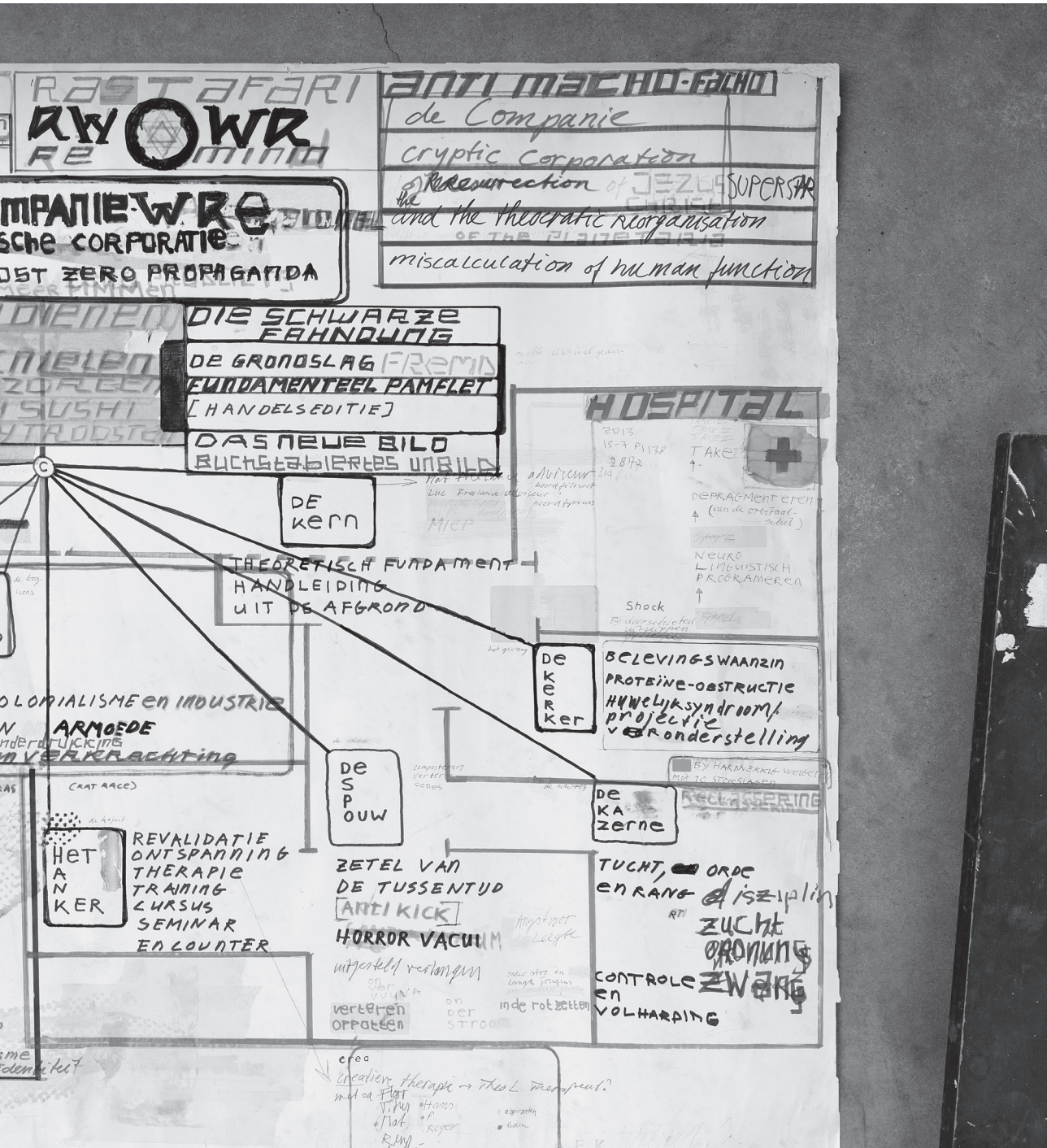
Chapter 8

Summary



The development of classification systems, of which the Diagnostic and Statistical Manual (DSM) is the most widely used and has worldwide been of great importance for psychiatry. The use of operational criteria to establish diagnoses has improved communication between psychiatrists and other (mental) health workers. Furthermore, by providing a nosological framework, it has promoted research into illness concepts. For patients, the establishment of certain diagnostic classes (e.g., post-traumatic stress disorder) has legitimated the burden of their mental problems by delineating these as a psychiatric disorder, herewith promoting proper use of mental health care facilities and/or social services. Also, evidence based treatment guidelines have been developed to improve efficacy of treatment and outcome of disease. Finally, in a domain as complex as psychiatry, a classification system may function as an easy accessible tool for those who deal with known, possible or probable mental disorders in other than health care settings, such as policemen, lawyers, politicians and welfare workers.

Most of the categorical labels from psychiatric classification systems such as DSM are delineated by means of consensus instead of a known etiology. This makes them mostly informative about clusters of symptoms at the time of establishing a "diagnosis". However, diagnoses may alter during the course of the disease either because of their limited stability over time or change of definition of the diagnostic criteria in subsequent versions of the applied classification system. Albeit that many general risk factors for developing psychiatric disorders have been identified, longitudinal predictions for an individual patient are hard to establish. Psychiatrists generally accept that classification, though helpful in many ways, is not the same as diagnosing. Still, categorical diagnoses in psychiatry have become increasingly important not only for choosing the most appropriate treatment, but also for other purposes such as eligibility for social services avoiding imprisonment or for regulation (mental) health care costs.

The present thesis examined the utility of individualized diagnoses across diagnostic boundaries in patients with psychotic disorders, that are both informative and easily applicable in everyday practice. In all studies patients were therefore typically assessed by different diagnostic methods including also DSM or ICD in order to extend upon previous research.

Chapter 1 summarizes the way in which psychosis spectrum disorders are classified in DSM-5 and addresses the pros and cons of classification.

In **chapter 2**, it was investigated whether it would be valuable to perform routine screening for copy number variations (CNVs) in patients with psychosis spectrum disorders. Micro-array analysis was performed in 80 patients presenting with psychosis.

In 3 out of 80 patients a CNV was found (2 microduplications (1p13.3 and 7q11.21q11.22) and 1 microdeletion (1q21.1)). In none of the patients, these CNVs could be related to the psychotic symptoms.

From a clinical point of view, routine screening for CNVs in psychosis spectrum disorders seems to be of limited additional value. However, the results stress the importance of careful evaluation of symptomatology, dysmorphic features, cognition, (childhood) development and family history, in order to search for chromosomal aberrations in a purposeful way. In specific cases, identification of the genetic disorder can be of great importance for counselling and treatment of psychotic symptoms associated with the syndrome.

Cycloid psychoses were described in the 1950s by Karl Leonhard, but are not included as such in the current classification systems. The term "cycloid psychosis" comprises acute and relapsing psychoses with a pleomorphic symptom profile that shows an intraphasic bipolarity (subtypes anxiety-happiness psychosis, confusion psychosis and motility psychosis). Prognosis is usually favourable and without cognitive decline and there is no evidence for long-term use of antipsychotic medication to prevent relapses.

In **chapter 3**, the concept of cycloid psychoses according to Leonhard (LCP) was investigated in a cohort of 80 patients admitted for treatment of psychoses by means of a checklist according to Leonhard's original descriptions. Objectives were to estimate the prevalence of LCP, to identify the discriminating symptoms and to calculate concordance with established diagnostic categories from DSM and ICD.

A prevalence of ~15% was found, which is in line with previously reported prevalence rates of 8-24%. Symptomatic reduction was found to be greater in the LCP group as compared to the non-CP group. Key features of the core syndromes (subtypes) included pananxiety, perplexity, psychomotor disturbances, mood swings and hallucinatory experiences. Patients diagnosed with LCP were mostly classified as DSM Brief Psychotic Disorder (DSM-BPD) or ICD Acute Polymorphic Psychotic Disorder (ICD-APP), with low concordance rates (K 0.35 and 0.58, respectively ($p \leq 0.001$)). A concordance rate of 0.63 ($p < 0.001$) was calculated for LCP and the operational criteria as formulated by Perris and Brockington.

It was concluded that cycloid psychoses according to Leonhard are not sufficiently covered by current classification systems. The possible, but relevant influence on treatment choices made in clinical practice illustrates the instrumental value of the cycloid psychoses. With respect to research into psychosis spectrum disorders, the cycloid psychoses might be a valuable counterpart for schizophrenia and related psychoses.

The next part of the thesis comprises studies into peripheral biochemical parameters in patients with psychosis spectrum disorders.

Neurotrophic proteins are involved in the development, maintenance and survival of the central nervous system (CNS) and can be measured in peripheral blood. It is known that disturbances in the CNS can lead to the development of psychosis and vice versa.

In **chapter 4**, the neurotrophic proteins Brain Derived Neurotrophic Factor (BDNF) and S100B were measured in the serum of 58 patients with psychosis spectrum disorders at baseline and after 6 weeks of treatment. Symptomatology and disease severity were assessed by means of CASH, PANSS and CGI.

It was found that BDNF was lowered in patients with an acute psychotic episode irrespective of diagnostic category, as compared to controls (20.3 ± 6.6 versus 24.4 ± 6.7 μg/l, $p \leq 0.001$). It was concluded that BDNF can be regarded as a general marker for neuroplasticity in both psychotic and other psychiatric disorders.

In the case of S100B, it was found that higher baseline levels (0.107 ± 0.030 μg/l) corresponded with more negative symptoms after 6 weeks of treatment, which was in line with other studies. Interestingly, it also appeared that lower baseline levels of S100B (0.034 ± 0.005 μg/l) were associated with more positive symptoms after 6 weeks of treatment as compared to the other subgroups. Since S100B has both neurotoxic and neuroprotective effects, it was speculated that the lowered levels of S100B in this group might represent deficiencies in neuroprotective mechanisms in these patients.

The hypothesis was formulated that subnormal levels of S100B might initially induce positive symptoms while during the course of disease S100B levels might rise. This could in turn result in the development of negative symptoms due to a neurotoxic effect of the higher S100B levels in the brain.

BDNF and S100B might be related to neuroplasticity and (dis)connectivity, maybe not individually, but as members from a network with other neurotrophic proteins interacting with each other.

The neurotransmitter dopamine plays an important role in the pathophysiology of psychoses. Homovanillic acid (HVA) is the main metabolite of dopamine. In **chapter 5**, plasma levels of HVA (pHVA) were measured in 58 patients admitted for treatment of psychosis spectrum disorders. Biochemical and clinical assessments (by means of CASH, PANSS and CGI) were done at baseline and after 6 weeks of treatment.

Mean baseline plasma HVA (pHVA) concentrations did not differ from a matched control sample (53.4 ± 13.7 nmol/l) and were not associated with treatment responsiveness of symptomatology, which was in line with other studies. However, after 6 weeks of treatment a larger decrease in pHVA concentrations was observed in patients with first episode psychosis (FEP) as compared to patients with relapsing or chronic psychoses (-20.7 ± 22.9 versus -4.9 ± 23.1 nmol/l, respectively ($p<0.05$)). This larger decrease was significantly associated with better

symptomatic improvement. Better treatment outcome in patients with FEP was previously reported by other investigators.

The observed differences between patients with FEP and those with relapsing or chronic psychoses could be related to the individual's state of neuroplasticity, reflected by the extent to which pHVA levels change during treatment.

Since LCP (from chapter 3) was considered a valuable counterpart for schizophrenia, in **chapter 6**, the two disorders were investigated in order to establish whether the clinical differences, especially the absence of cognitive decline in LCP, were possibly associated with different biochemical underpinnings.

Besides dopamine, the glutamate system has gained special attention, since it has become clear that disturbances in glutamatergic neurotransmission are associated with negative symptoms and cognitive dysfunction via the N-methyl-D-aspartate (NMDA) receptor. Glycine is an essential co-agonist for the NMDA receptor.

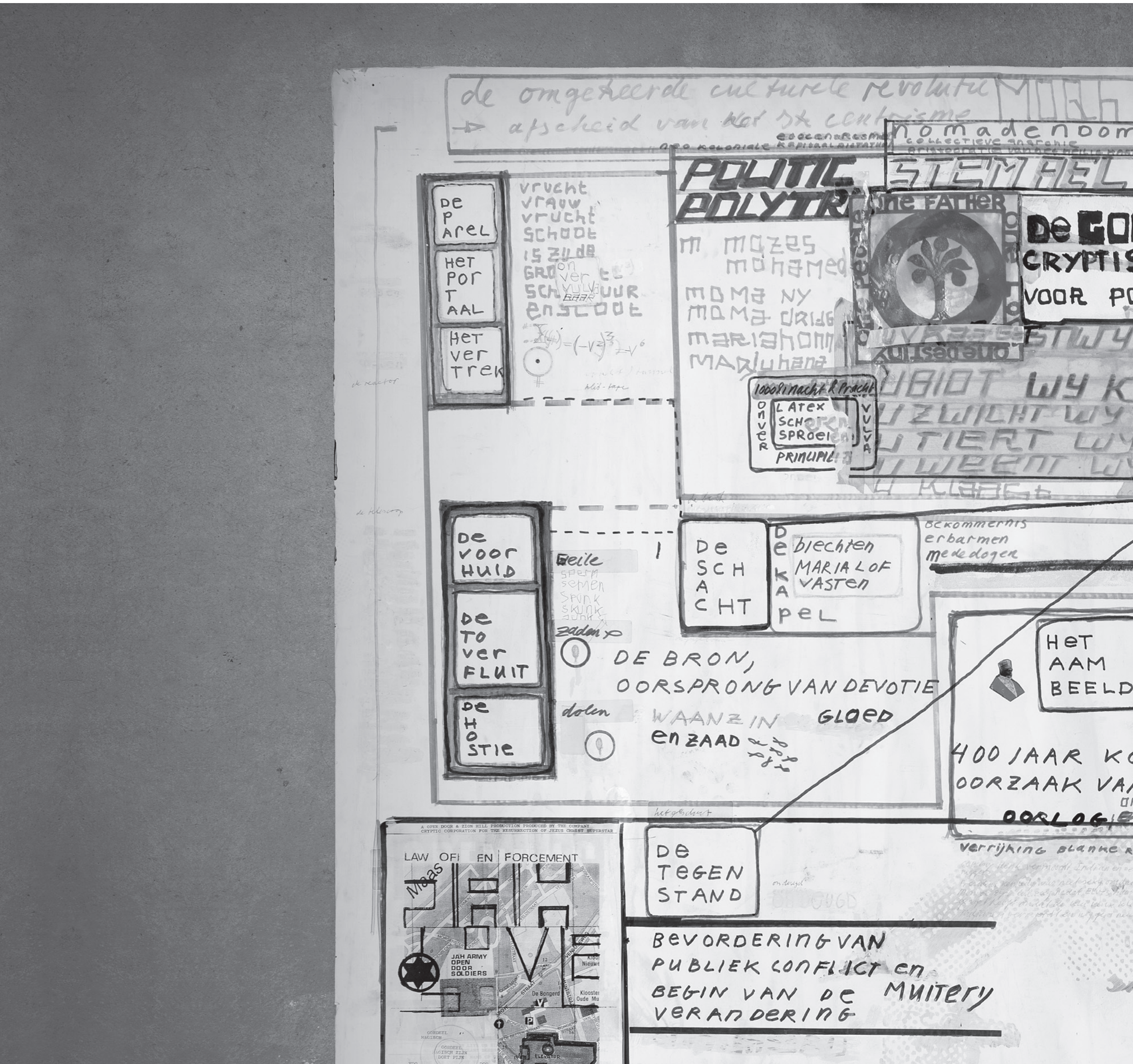
The study group consisted of 33 patients with schizophrenia and 10 patients with LCP, who were assessed by venipuncture and rating scales according to the same methods as in chapter 4 and 5. For diagnoses of LCP, the checklist from chapter 3 was used.

Symptomatic reduction was the largest in patients with LCP. With respect to HVA, no differences were found. Glutamate levels were elevated in both disorders as compared to controls. Serum levels of BDNF were lowered in patients with schizophrenia, but not with LCP, as compared to controls. In patients with LCP, elevated levels of glycine were found as compared to controls, patients with schizophrenia, and 15 patients with other psychosis spectrum disorders.

The elevated levels of glycine in LCP were explained as a compensatory reaction to the disturbed glutamatergic neurotransmission that patients with schizophrenia and other psychoses might not be able to. It could imply better neuroplasticity and connectivity in LCP as compared to schizophrenia. This would be consistent with the finding of lowered levels of BDNF in schizophrenia and the more favourable prognosis for LCP.

Since biochemical profiles in patients with LCP were, to date, not previously investigated, these findings could be of help in further understanding of the pathophysiology and treatment of psychosis spectrum disorders. Differences in the extent of (dis)connectivity between LCP and other (schizophrenia-like) disorders could possibly contribute to a better understanding of the common neurobiological base of psychosis spectrum disorders.

In **chapter 7**, results are summarized and discussed. Theoretical and clinical considerations are made with respect to the concept of neuroconnectivity as common denominator in psychosis spectrum disorders.



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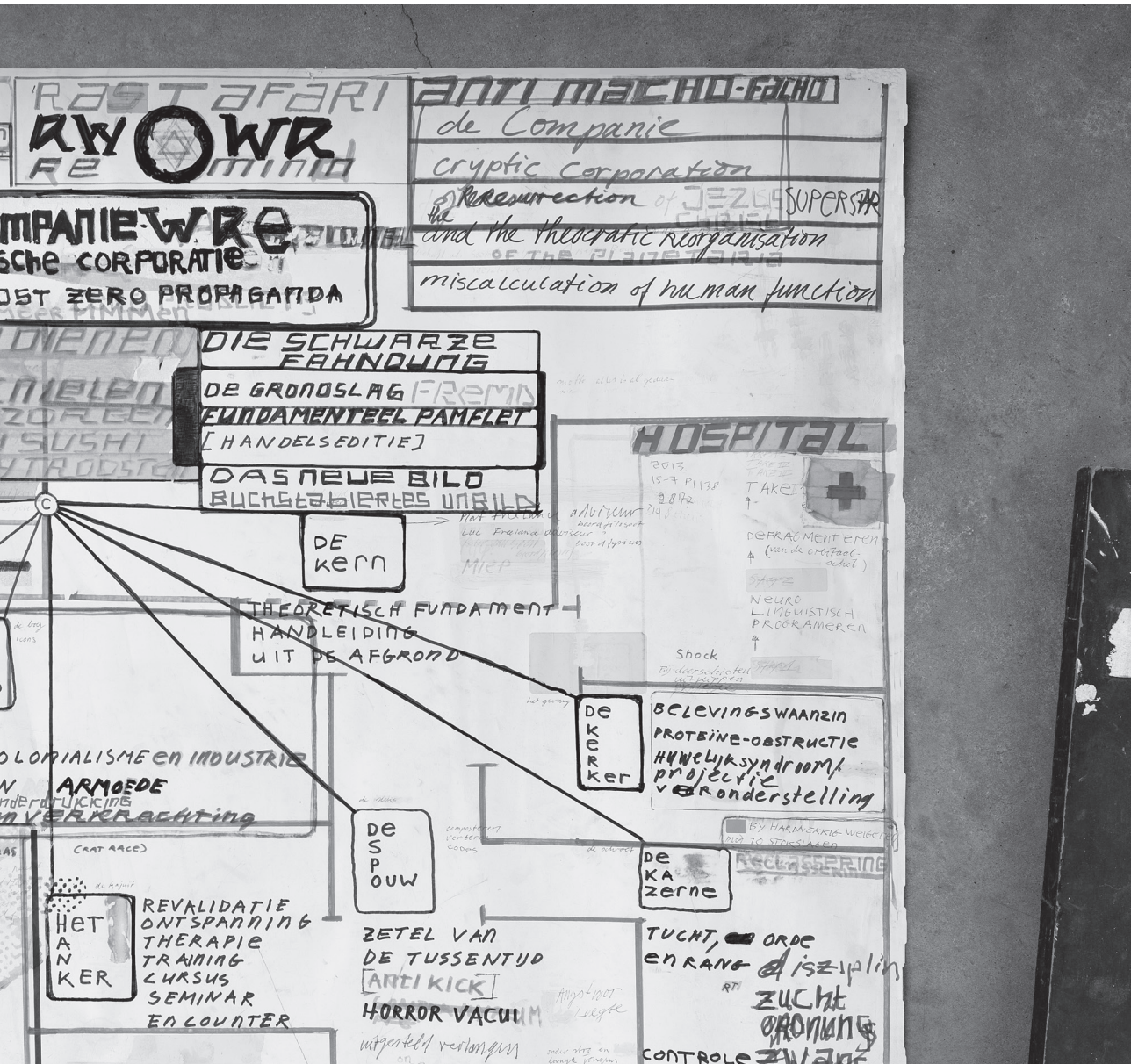
Chapter 9

Samenvatting / summary in Dutch
Dankwoord / acknowledgments
Publications
Curriculum Vitae



Samenvatting / summary in Dutch

De ontwikkeling van classificatiesystemen binnen de psychiatrie, waarvan de Diagnostic and Statistic Manual for Psychiatric Disorders ("de DSM") de bekendste en meest gebruikte is, heeft wereldwijd een belangrijke invloed gehad op veel aspecten van het vakgebied. Het gebruik van eenduidige operationele criteria om een classificerende diagnose te stellen heeft de communicatie tussen psychiaters onderling verbeterd, evenals die met andere professionals in de (geestelijke) gezondheidszorg. Daarnaast heeft het beschikbaar zijn van een gemeenschappelijk nosologisch raamwerk het wetenschappelijk onderzoek naar de beschreven ziekteconcepten bevorderd. Voorts betekende de invoering van bepaalde diagnostische classificaties (zoals de posttraumatische stress-stoornis) voor veel patiënten een rechtvaardiging van hun psychische problemen, doordat deze erkend werden als psychiatrische stoornis. Voor velen van hen werd het hierdoor mogelijk om gebruik te maken van (geestelijke) gezondheidszorg en/of sociale voorzieningen. Op basis van de uitkomsten van wetenschappelijk onderzoek konden algemene behandelrichtlijnen worden ontwikkeld, waarmee de uniformiteit, effectiviteit en uitkomsten van behandelingen verbeterd werden. Tot slot is een classificatiesysteem, zeker in een complex domein zoals de psychiatrie, een eenvoudig toegankelijk instrument voor hen die te maken krijgen met bekende, mogelijke of waarschijnlijke psychiatrische stoornissen op plaatsen buiten de gezondheidszorg, zoals politie, justitie, politiek en sociale diensten.

De meeste labels in een classificatiesysteem zoals de DSM zijn categorieën die middels consensus zijn vastgesteld. Ze zijn veelal niet gebaseerd op een bekende oorzaak en geven hoofdzakelijk informatie over symptoomclusters ten tijde van het stellen van de "diagnose". Diagnoses kunnen veranderen gedurende het ziektebeloop vanwege de beperkte diagnostische stabiliteit, maar ook doordat de diagnostische criteria veranderen in een volgende versie van het classificatiesysteem. Daarnaast blijft het, ondanks het feit dat veel algemene en specifieke aspecten van psychiatrische stoornissen bekend zijn, bijzonder moeilijk om een individuele patiënt duidelijkheid te geven over wat hij of zij kan verwachten op de korte of langere termijn. Psychiaters zijn zich er in het algemeen van bewust dat classificatie behulpzaam is, maar niet hetzelfde is als het stellen van een diagnose met bekende oorzaak/ontstaanswijze. In de loop der jaren is echter in toenemende mate nadruk komen te liggen op die "diagnostische" classificaties, niet alleen om een behandeling te kiezen, maar ook om bijvoorbeeld te bepalen of iemand aanspraak kan maken op sociale voorzieningen, of iemand veroordeeld wordt tot een gevangenisstraf en ook om (geestelijke) gezondheidszorgkosten te reguleren.

Dit proefschrift gaat over psychotische stoornissen. De studies in dit proefschrift hadden als doel om de bruikbaarheid te onderzoeken van geïndividualiseerde diagnoses bij patiënten met een psychotische stoornis, dóór de categorale diagnostische grenzen heen en op een manier die

zowel informatief is als ook eenvoudig toepasbaar in de dagelijkse praktijk. In elke studie werden patiënten op één zo'n manier onderzocht. Om aan te sluiten bij het bestaande onderzoek, werden patiënten ook ingedeeld conform een bekend classificatiesysteem (DSM of ICD).

In **hoofdstuk 1** wordt een overzicht gegeven van de wijze waarop psychotische stoornissen in de DSM worden ingedeeld en wordt ingegaan op de voors en tegens van classificatie.

In **hoofdstuk 2** werd onderzocht of het zinvol kan zijn om patiënten met een psychose routinematige te screenen op zogenoemde copy number variations (CNVs; bepaalde zéér kleine chromosomale afwijkingen). Hiertoe werd een micro-array verricht bij 80 patiënten die in ons psychiatrische ziekenhuis werden behandeld vanwege een psychose. Bij 3 van de 80 patiënten werd een CNV gevonden (2 microduplicaties (1p13.3 en 7q11.21q11.22) en 1 microdeletie (1q21.1)). Deze konden evenwel bij geen van de patiënten worden gerelateerd aan de psychotische symptomen.

Vanuit klinisch oogpunt lijkt het *routinematig* screenen op CNVs bij psychotische stoornissen van weinig toegevoegde waarde. Het is in de dagelijkse praktijk evenwel van groot belang om een zorgvuldige evaluatie te verrichten van symptomatologie, dysmorfe kenmerken, cognitieve stoornissen en (vroegkinderlijke) ontwikkelings- en familieanamnese. Op die manier kan op *gerichte* wijze worden gezocht naar aanwijzingen voor eventuele chromosomale afwijkingen. Het is van belang om genetische syndromen te identificeren, teneinde adequate voorlichting te kunnen geven en (psychotische) symptomen die gepaard gaan met het syndroom op de juiste manier te behandelen.

De cycloïde psychose werd in de jaren '50 van de vorige eeuw beschreven door Karl Leonhard, maar komt als zodanig in de huidige classificatiesystemen niet voor. De term "cycloïde psychose" slaat op acute en recidiverende psychoses met een veelzijdig symptoomprofiel, dat binnen de psychotische fase snel kan wisselen tussen 2 extreme polen (zoals angst en gelukzaligheid). De prognose is doorgaans gunstig, zonder cognitief verval en er is geen bewijs voor een langdurige onderhoudsbehandeling met antipsychotica om recidieven te voorkomen.

In **hoofdstuk 3** werd onderzocht of het van waarde zou kunnen zijn om in de praktijk te werken met concept van de cycloïde psychose. Hierbij waren de vragen: 1. hoe vaak de cycloïde psychose voorkomt, 2. wat de symptomen zijn die de cycloïde psychose onderscheiden van andere psychotische stoornissen en 3. in welke bestaande diagnostische categorieën patiënten met een cycloïde psychose worden ingedeeld. Om de diagnose cycloïde psychose conform de beschrijvingen van Leonhard (LCP) te stellen werd gebruik gemaakt van een checklist gebaseerd op die originele beschrijvingen. De studiegroep bestond uit 80 patiënten die waren opgenomen voor de behandeling van een psychose.

Bij 12 van de 80 patiënten werd de diagnose LCP gesteld, wat neerkomt op een prevalentie van ~15%. Dit getal is in overeenstemming met eerder gerapporteerde prevalentiecijfers van 8-24%. De symptomatische verbetering was groter in de LCP-groep dan in de non-CP groep. De belangrijkste onderscheidende symptomen van LCP waren allesoverheersende angst, verbijstering, psychomotore stoornissen, stemmingswisselingen en hallucinatoire belevingen. Patiënten met LCP werden het vaakst geclassificeerd als Kortdurende Psychotische Stoornis conform DSM-IV (DSM-PBD) of Acute Polymorfe Psychotische Stoornis conform ICD-10 (ICD-APP), waarbij de concordantie laag was (K respectievelijk 0.35 en 0.58, $p \leq 0.01$). De concordantie van LCP met de set bestaande set operationele criteria zoals geformuleerd door Perris en Brockington was 0.63 ($p < 0.001$).

Er werd geconcludeerd dat de cycloïde psychosen (LCP) niet adequaat zijn geïncorporeerd in de huidige classificatiesystemen. Vanwege de directe invloed op de keuze van een (onderhouds)behandeling lijken de cycloïde psychosen echter wel relevant voor de praktijk en zou het wenselijk zijn om ze als zodanig op te nemen in volgende versies van de bestaande classificatiesystemen. In het wetenschappelijk onderzoek naar psychosespectrumstoornissen zouden de cycloïde psychosen een waardevolle aanvulling op het spectrum van schizofrenie en schizofrenie-achtige psychoses kunnen zijn.

Zijn er stoffen in het bloed die patiënt en behandelaar informatie kunnen geven over symptomatologie, behandelbaarheid of prognose? Deze vragen werden behandeld in de volgende hoofdstukken.

Neurotrofe eiwitten zijn stoffen die betrokken zijn bij de aanleg, onderhoud en herstel, ook wel genoemd "plasticiteit", van het centraal zenuwstelsel (CZS). Sommige van deze eiwitten kunnen betrouwbaar in het bloed worden bepaald. Het is bekend dat verstoringen in het CZS aanleiding kunnen geven tot psychoses en vice versa.

In **hoofdstuk 4** werden de neurotrofe eiwitten Brain Derived Neurotrophic Factor (BDNF) en S100B gemeten in het serum van 58 patiënten met een psychotische stoornis. De metingen werden verricht bij aanvang van behandeling en na 6 weken behandeling met antipsychotica. Tevens werden de symptomen en de ernst van de psychose gemeten met behulp van vragenlijsten.

Er werd gevonden dat de BDNF-concentraties verlaagd waren bij patiënten met een psychose ten opzichte van een controlegroep (20.3 ± 6.6 versus 24.4 ± 6.7 µg/l, $p \leq 0.001$), ongeacht de diagnostische categorie waar de patiënten waren ingedeeld. Er werd geconcludeerd dat BDNF beschouwd kan worden als een algemene marker voor neuroplasticiteit in zowel psychotische als niet-psychotische stoornissen.

Met betrekking tot S100B werd gevonden dat hogere concentraties bij aanvang van de behandeling (0.107 ± 0.030 µg/l) correspondeerden met meer zogeheten "negatieve symptomen" na 6 weken behandeling, hetgeen in andere onderzoeken eerder ook werd gevonden. Interessant genoeg bleek eveneens dat verlaagde S100B-concentraties bij aanvang (0.034 ± 0.005 µg/l), geassocieerd waren met meer zogenaamde "positieve symptomen" na 6 weken behandeling. Omdat S100B zowel een neurotoxische als een neuroprotectieve werking heeft, die afhangt van de concentratie, werd gespeculeerd dat de verlaagde concentraties in deze groep wellicht wijzen op tekorten in de neuroprotectieve mechanismen bij deze patiënten.

De hypothese werd geformuleerd dat verlaagde concentraties van S100B in het begin leiden tot positieve symptomen, waarna gedurende het ziektebeloop de S100B-concentraties juist stijgen. Dat zou op zijn beurt weer leiden tot het ontstaan van negatieve symptomen door ofwel het neurotoxisch effect van de hoge S100B-concentratie ofwel als reactie op door de psychose aangerichte schade in het brein. Dat zou echter verder onderzocht moeten worden.

BDNF en S100B zijn waarschijnlijk beide gerelateerd aan neuroplasticiteit en (dis) connectiviteit, wellicht niet individueel, maar als onderdelen van een netwerk van neurotrofe factoren die met elkaar interacteren.

De neurotransmitter dopamine speelt een voorname rol bij het ontstaan van psychoses. Homovanillinezuur (HVA) is de belangrijkste metaboliet van dopamine. In **hoofdstuk 5** werden de plasmaconcentraties van HVA (pHVA) gemeten bij 58 patiënten die waren opgenomen voor de behandeling van een psychotische stoornis. De metingen werden verricht bij aanvang en na 6 weken behandeling en op die momenten werd tevens de symptomatologie en ernst van de psychose gemeten met vragenlijsten.

De gemiddelde pHVA van de patiënten verschilde niet van een controlegroep (53.4 ± 13.7 nmol/l). Er kon geen verband worden gelegd tussen pHVA en bepaalde symptomen of respons op behandeling, hetgeen door andere onderzoekers eerder ook werd gevonden.

Na 6 weken behandeling werd echter een grotere afname van de pHVA gemeten bij patiënten met een eerste psychotische episode (first episode psychosis; FEP) in vergelijking met patiënten met een recidief of chronische psychose (respectievelijk -20.7 ± 22.9 versus -4.9 ± 23.1 nmol/l, $p<0.05$). Deze sterkere afname was significant geassocieerd met een grotere verbetering van de psychotische symptomen. Betere behandeluitkomsten bij patiënten met FEP werden al eerder beschreven in andere studies.

Het lijkt erop dat patiënten met een eerste psychose beter in staat zijn om de verstoringen in het CZS te herstellen dan patiënten met een chronische of recidiverende psychotische stoornis. Deze verschillen zouden verband kunnen houden met de mate van neuroplasticiteit in het individu, weergegeven als de mate waarin de pHVA verandert tijdens behandeling.

Omdat LCP in hoofdstuk 3 werd aangemerkt als mogelijk waardevolle aanvulling op het schizofrenie-spectrum, werden in **hoofdstuk 6** beide stoornissen rechtstreeks met elkaar vergeleken. De vraag was of de verschillen in klinisch beeld en prognose (in het bijzonder de afwezigheid van cognitief verval bij LCP) mogelijk verklaard kunnen worden vanuit verschillen in het onderliggend biochemisch profiel.

Naast dopamine en neurotrofe eiwitten werd in de biochemische analyse aandacht besteed aan het glutamaterge systeem, omdat uit onderzoek duidelijk is geworden dat een verstoring in de glutamaterge neurotransmissie verband houdt met het ontstaan van negatieve symptomen en cognitieve dysfunctie via de N-methyl-D-aspartaat (NMDA) receptor. De stof glycine is een essentiële co-agonist voor de NMDA-receptor. In dit onderzoek werden 10 patiënten met LCP en 33 patiënten met DSM-schizofrenie onderzocht middels bloedafname en vragenlijsten conform de werkwijze in hoofdstuk 4 en 5. Voor de diagnose LCP werd checklist uit hoofdstuk 3 gebruikt.

De symptomatische verbetering was het grootst in de LCP-groep. Er werden geen verschillen tussen de groepen gevonden met betrekking tot de concentraties van HVA. De glutamaatconcentraties waren verhoogd bij beide stoornissen ten opzichte van gezonde controles. De serumconcentraties van BDNF waren verlaagd bij patiënten met schizofrenie, maar niet met LCP, in vergelijking met controles. Bij patiënten met LCP werden verhoogde concentraties van glycine gevonden in vergelijking met zowel de controles, de patiënten met schizofrenie én 15 patiënten met andere psychosespectrumstoornissen.

Het verhoogde glycine bij LCP werd uitgelegd als een compensatoire reactie op de verstoorde glutamaterge neurotransmissie, waartoe de patiënten met schizofrenie of andere psychotische stoornissen niet in staat zouden zijn. Dit zou betekenen dat de neuroplasticiteit en connectiviteit bij LCP beter zijn dan bij schizofrenie. Hierbij past het gevonden verschil in BDNF-concentraties, die bij schizofrenie (maar niet bij LCP) lager zijn dan bij controles. Ook de betere prognose van LCP past bij deze bevindingen.

Omdat de biochemische profielen van patiënten met LCP tot op heden niet eerder werden onderzocht, kunnen deze uitkomsten behulpzaam zijn bij het verder begrijpen van de pathofysiologie en behandeling van psychotische stoornissen. Verschillen in de omvang van de (dys)connectiviteit tussen LCP en andere (schizofrenie-achtige) stoornissen kan mogelijk bijdragen aan het beter begrijpen van de gemeenschappelijke neurobiologische basis van psychosespectrumstoornissen.

In **hoofdstuk 7** worden de belangrijkste resultaten samengevat en bediscussieerd en worden theoretische en klinische overwegingen gemaakt met betrekking tot het concept van neuroconnectiviteit als grote gemene deler bij psychosespectrumstoornissen.

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Curriculum Vitae

Nora Wilhelmina Ardina (Noortje) van de Kerkhof was born on July 11th, 1981 in Geldrop. She graduated in 1999 at the Eckart College Eindhoven and started studying medicine at the Katholieke Universiteit (Radboud University) Nijmegen. During her study period, she was active in the student's rowing club NSRV Phocas as vice-president (2001-2002) and as coxswain of the Women's 8 (2003) and Women's 4 (2004). In 2003, she was co-founder and first president of sorority Dameschdispuut Hard Roeien en Meer. During the residencies, her interest in psychiatry and psychotic disorders was born. She received her medical degree in 2006.

After her medical degree in 2006, Noortje started working at the Vincent van Gogh Institute for Psychiatry (addiction clinic Paschalis). In 2007, she started her traineeship at this institute (head instructor: Prof. Dr. W.M.A. Verhoeven). During her traineeship, from 2008, she started the research projects as described in this thesis. She was Chief Resident for 2 years and participated in the local research advisory board (CWOP) for 5 years, from which 2 years as secretary. In 2012, she was registered as psychiatrist and started working at the Flexible ACT (FACT) of the Vincent van Gogh Institute for Psychiatry. To date, she combines this work with clinical research and the function of head instructor for the education of interns (co-assistenten).

Noortje lives in Nijmegen with Michel Spaan and 4 guinea pigs.