

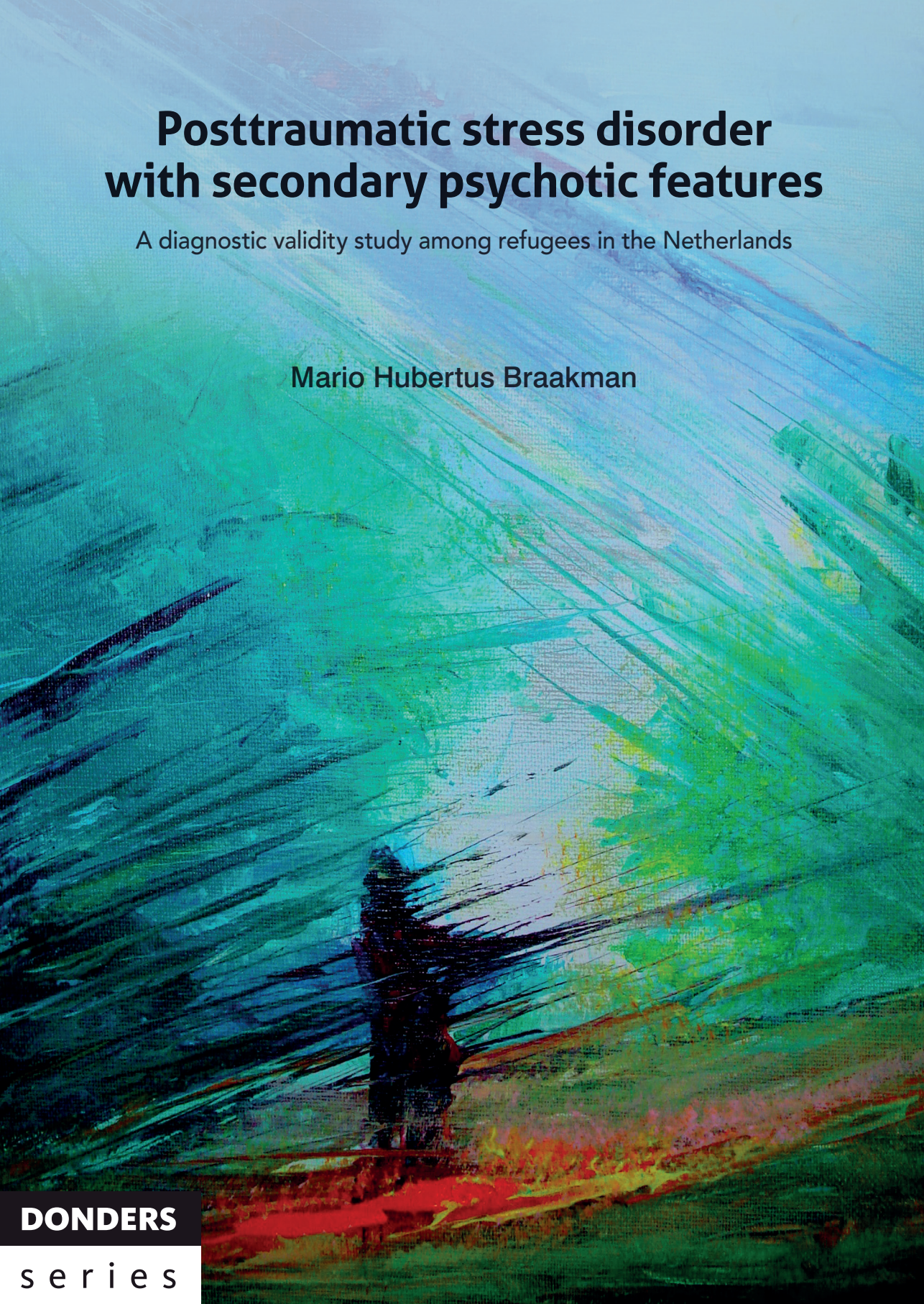
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An abstract painting with vibrant colors and expressive brushstrokes. The background is a mix of blue, green, and purple, with a dark, vertical, textured shape in the lower center. The overall style is dynamic and emotional.

# Posttraumatic stress disorder with secondary psychotic features

A diagnostic validity study among refugees in the Netherlands

Mario Hubertus Braakman

**DONDERS**

series

# Posttraumatic stress disorder with secondary psychotic features

A diagnostic validity study among refugees in the Netherlands

## Proefschrift

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aan de Radboud Universiteit Nijmegen  
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# Chapter 1

## **Introduction**

## Introduction

The study presented in this thesis originated from a clinical observation. During our clinical work in an inpatient treatment facility for refugees and asylum seekers in the Netherlands we encountered many patients suffering from symptoms of posttraumatic stress disorder (PTSD) in conjunction with symptoms of chronic psychosis, especially delusions and hallucinations. These traumatized patients, with a poor response to antipsychotic medication, had developed PTSD and subsequently, sooner or later, psychotic symptoms as well. These patients were referred to our clinic by colleagues who time and again wondered what the correct diagnosis was and what the best treatment policy should be. One of those referring psychiatrists wrote:

*Our impression is that the symptoms are strongly related to PTSD. However the paranoid delusions and acoustic and visual hallucinations could also fit the DSM-IV diagnosis of 'schizophrenia'. On the other hand many facts plea against this diagnosis:*

- *the non-bizarre content of the patients perceptions*
- *the normal way of making contact*
- *the age of the client (onset of first psychosis at 35 years of age)*
- *the course of the disorder*
- *the fact that the traumatic events and the disruption of this patients life may constitute a reasonable explanation of the experienced symptoms.*

The questions that were raised about the diagnosis of these patients among referring psychiatrists, as well as, the repeatedly encountered treatment resistance of the chronic psychotic symptoms, paved the way for the main questions of this thesis. The ultimate goal would be: to find adequate and effective treatment options. However before such an endeavor could be undertaken another important question emerged: what is the most appropriate diagnostic position of this manifestation of posttraumatic stress disorder and subsequent psychosis? Is it a form of (late onset) schizophrenia, a complex PTSD, a special kind of affective psychotic disorder, or is it a diagnostic entity on its own?

Thus the goal of this thesis is to either refute or find evidence for the validity of this complex clinical picture as a separate diagnostic entity. Or more specific: is PTSD with secondary psychotic features a diagnostic entity on its own or could this combination of symptoms be appropriately described by familiar and already existing diagnostic categories?

First, we had to define a clear focus of our research. Therefore, we studied the present state of knowledge in the realm of trauma and psychosis. This was done by an extensive survey of the existing literature (Chapters 2 & 3). This survey revealed the

presence of an increasing scientific interest in the complex interrelationships between trauma and psychosis. Available studies could be divided in three interrelated groups of subtopics. Most studies deal with patients suffering from schizophrenia and subsequently became traumatized and developed PTSD (1-4). A second group of studies focused on childhood trauma leading to psychosis and schizophrenia in adulthood (5-8). A third group of studies focused on adult patients who first developed posttraumatic stress disorder and after that started to suffer from secondary co-morbid psychotic features, especially chronic hallucinations and delusions. Given the goal of our own study we were mainly interested in this last group.

An increasing number of papers had been published on this group. However, none of these studies systematically assessed and tested the validity of the emerging concept of 'posttraumatic stress disorder with secondary psychotic features' (9-12).

In Chapter 2 we aimed at finding all available empirical studies and analyzed them according to the six criteria of Robins and Guze (13) in order to establish the diagnostic validity of PTSD-SP as a separate diagnostic entity. In Chapter 3 we expanded this search with a focus on neurobiological aspects. These two chapters not only summarized what was known about PTSD-SP but also showed us the main gaps in our knowledge and the issues that needed additional empirical research.

## Research questions

In our study we focused on five issues that needed further inquiry:

1. Previous studies were almost exclusively limited to male outpatient war veterans from the U.S. exposed to combat-related trauma. We therefore focused on a different and more diverse population: a multi-ethnic sample of refugees, both male and female, who had been exposed to a wide range of traumas, not exclusively combat-related.
2. Previous epidemiological studies focusing on psychosis and PTSD were often based on the lifetime presence of PTSD, psychosis and other comorbid conditions, and did not take into account the temporal relationships between these conditions. Thus, we explicitly aimed at recording the temporal relationship between PTSD and psychotic symptoms focusing our study on those patients with a PTSD diagnosis that was followed by the onset of psychosis.
3. Previous studies revealed that patients suffering from PTSD-SP had psychotic features similar but not necessarily identical to schizophrenia. Therefore, we wanted to compare the psychotic features in both groups in order to determine similarities and/or differences. This was the main objective of Chapter 4.

4. In earlier studies a discussion emerged regarding highly prevalent comorbid psychiatric conditions in patients suffering from PTSD, like major depressive disorder. Maybe, these secondary psychotic symptoms were part of a psychotic depression. Most studies found no evidence for this hypothesis, but some did. This issue needed attention since it was as yet unresolved. Therefore in Chapter 5 we explored the associations between psychotic features in PTSD-SP and other comorbid psychiatric conditions. In addition, we investigated two related issues that could account for the presence of psychotic features in PTSD-SP: 1. severity of the PTSD re-experiencing cluster, and 2. type and severity of the traumatic events.
5. In a previous study, Hamner and Gold (14) reported an increased level of blood plasma activity of dopamine  $\beta$ -hydroxylase (D $\beta$ H) in patients with PTSD and psychotic symptoms compared to healthy controls and PTSD patients without psychosis, suggesting that the psychotic features in patients suffering from PTSD are not attributed to major depressive disorder with psychotic features since in those patients blood plasma activity of D $\beta$ H has shown to be decreased. In Chapter 6, we replicated and expanded this study by using 1. a larger sample size of PTSD-SP patients, 2. adding a group of patients suffering from schizophrenia and 3. controlling for possible group differences in the *D $\beta$ H* -1021C/T gene polymorphism since this polymorphism accounts for up to 52% of the inter-individual variations in plasma D $\beta$ H activity.

In order to answer these questions (Table 1) we designed the following study.

## Study design

We designed a cross sectional study in which we recruited patients from two mental health hospitals in the Netherlands<sup>1</sup> that provide inpatient treatment for asylum seekers and refugees from different parts of the world. In the screening phase, recently admitted patients meeting the following criteria were asked to participate: being a refugee/asylum seeker, 16 years or older, and at least one DSM-IV PTSD symptom or at least one psychotic symptom. After oral and written description of the study to the participants, written informed consent was obtained, in some cases together with the patient's representative. All study procedures were approved by the Mental Health Institutions Ethical Review Board (METIGG).

<sup>1</sup> The Phoenix Centre, Pro Persona, Wolfheze and de Vonk, Centrum 45, Noordwijkerhout. These are the only two national inpatient treatment facilities for refugees and asylumseekers.



**Table 1** Overview

Chapter	Title	Research Question
2	Validity of 'posttraumatic stress disorder with secondary psychotic features': a review of the evidence	What is the current evidence supporting the validity of 'posttraumatic stress disorder with psychotic features'?
3	'Posttraumatic stress disorder with secondary psychotic features': neurobiological findings	What is the current neurobiological evidence supporting the validity of 'posttraumatic stress disorder with psychotic features'?
4	Clinical differences between psychosis in 'posttraumatic stress disorder with secondary psychotic features' and schizophrenia among refugees	Can chronic psychosis in PTSD-SP be distinguished from psychosis in schizophrenia by clinical features and trauma history?
5	Psychosis in PTSD	Can the presence of psychotic features in PTSD-SP be explained by psychiatric comorbidity, by more severe PTSD re-experiencing-symptoms, or by more severe or a specific type of traumatic events?
6	Plasma dopamine-beta-hydroxylase activity is not increased in posttraumatic stress disorder with secondary psychotic features	Is genotype controlled ( <i>DBH-1021 C&gt;T</i> ) plasma dopamine-beta-hydroxylase activity increased in posttraumatic stress disorder with secondary psychotic features?

### Diagnostic assessment and group allocation

After screening and informed consent, symptoms, main diagnoses and comorbid disorders were assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)(15). The SCAN was preferred over the Structured Clinical Interview for DSM (SCID) because in the SCAN no diagnosis-driven a priori grouping of symptoms is enforced. Moreover, the SCAN has been shown to be cross-culturally valid and applicable(16). In addition, the Clinical History Schedule (CHS) of the SCAN provides detailed information on the onset of symptoms and disorders.

We recruited three groups of patients (PTSD-SP, PTSD, schizophrenia) and one group of healthy controls:

1. The group of patients with posttraumatic stress disorder and secondary psychotic features, the '**PTSD-SP-group**', was defined as patients with a DSM-IV diagnosis of PTSD and psychotic symptoms, in whom the onset of PTSD preceded the onset of psychosis. Patients with sub-threshold or no PTSD were excluded from this group as well as patients who suffered from PTSD without psychotic symptoms. We carefully distinguished psychotic symptoms from (dissociative) flashback episodes with illusions and hallucinations while reliving the experience. These latter symptoms were interpreted as part of the conventional DSM-IV diagnostic criteria for PTSD.
2. The group of PTSD patients without current or life time psychotic features constituted the '**PTSD group**'. Patients of this group met the PTSD criteria of the DSM IV and had no positive psychotic features outside re-experiencing episodes.
3. The '**schizophrenia group**' was defined as those patients meeting DSM-IV criteria of schizophrenia but without a DSM-IV diagnosis of PTSD prior to the onset of the first psychotic episode. Patients in this group were allowed to meet criteria for DSM-IV PTSD only if this disorder had an onset clearly after the onset of the schizophrenia diagnosis.
4. Healthy controls were recruited from non-genetically related family members, friends or acquaintances as well as subjects from regional refugee asylums. They were screened for the presence of psychiatric disorders with the Composite International Diagnostic Interview (CIDI), developed by the WHO(17, 18). The CIDI is a cross-culturally valid diagnostic screening instrument and is well-fitted for the general population. Subjects meeting CIDI diagnostic criteria for any psychiatric diagnosis were excluded.

In all groups, patients with bipolar disorder, organic mental disorders or malingering were excluded.

### Symptom Measures

In both patient groups with psychotic symptoms (PTSD-SP and schizophrenia), psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS)(19). In addition, the psychotic symptom rating scale (PSYRATS) was administered to assess delusions and hallucinations in more detail (20). Since the PSYRATS covers only delusions and acoustic hallucinations, we added analogous items to assess visual hallucinations as well.

The Clinician Administered PTSD Scale (CAPS) was used for a detailed assessment of the frequency and intensity of PTSD symptoms in the PTSD and the



PTSD-SP group (21). The CAPS was performed by an experienced psychiatrist blinded for diagnostic group status. The CAPS also contains a trauma-list in order to assess more general traumatic events, not specific for refugees.

The experienced traumatic events were measured in all groups with the trauma scale of the Harvard Trauma Questionnaire (HTQ) which contains a traumatic events scale specifically designed for trauma's experienced by adult refugees (22). The HTQ has proven cross-cultural reliability and validity for the groups under study (23).

The Hopkins Symptoms Checklist (HSCL-25) was used to assess the presence and severity of anxiety and depressive symptoms in all four groups (24). The HSCL-25 has proven cross-cultural reliability and validity for the groups under study (23).

All symptom measures were administered by interviewers that were blind for diagnostic group status. Professional interpreters assisted in 80% of all interviews.

### Dopamine $\beta$ hydroxylase activity and DBH genotyping

Blood samples were taken from all participants. All blood samples were collected between 9 and 11 a.m. to avoid potential diurnal variation of D $\beta$ H plasma activity in individuals. Blood samples were prepared and stored awaiting batch wise analysis. All laboratory staff was blinded for group status.

Assessment of D $\beta$ H activity was carried out at the Radboud University Nijmegen Medical Center, Department of Laboratory Medicine. Enzyme activity was expressed in units per liter; 1 U/L was defined as the amount of enzyme needed to convert 1M dopamine into 1M noradrenalin per minute.

Genotyping of the D $\beta$ H 1021 C>T (rs1611115) polymorphism was carried out at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre, in a laboratory, which has a quality certification according to CCKL criteria. The genotyping assay had been validated before use.

### Outline of the thesis

The results of our literature reviews are reported in Chapters 2 and 3, whereas the findings of the current study are reported in Chapters 4, 5 and 6. In the general discussion (Chapter 7) we reassess the question whether PTSD-SP is a valid diagnostic entity by combining the existing literature and our own findings together with findings from new studies published in the last five years.

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## Chapter 2

### **Validity of 'posttraumatic stress disorder with secondary psychotic features': a review of the evidence**

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## Abstract

**Objective:** To review the evidence from empirical studies regarding the validity of “posttraumatic stress disorder with secondary psychotic features” (PTSD-SP) as a separate diagnostic entity.

**Method:** The authors performed a review tracing publications published between 1980 and January 2008.

**Results:** Twenty-four comparative studies were included. From these studies, PTSD-SP is emerging as a syndrome that consists of posttraumatic stress disorder followed in time by the additional appearance of psychotic features. The psychotic features are not confined to episodes of re-experiencing, but remain present continuously. PTSD-SP seems to have some biological features differentiating it from schizophrenia and PTSD, e.g. there are differences in smooth pursuit eye movement patterns, concentrations of corticotrophin-releasing factor and dopamine beta-hydroxylase activity.

**Conclusion:** There is currently not yet full support for PTSD-SP as a nosological entity. However, the delineation of PTSD-SP from other psychiatric syndromes is notable and biological studies seem to support the validity as a separate diagnostic entity.

## Introduction

There is an increasing interest in the complex interrelationships between trauma and psychosis. Studies on this topic vary from traumatic psychotic experiences leading to posttraumatic stress disorder to childhood trauma leading to psychosis and schizophrenia in adulthood (1-4). This study focuses on adult patients suffering from posttraumatic stress disorder with secondary co-morbid psychotic features, especially chronic hallucinations and delusions. These patients have no history of schizophrenia prior to the traumatic event and psychotic symptoms emerged after the onset of PTSD. Although an increasing number of papers have been published on the presence of secondary psychotic features in patients suffering from posttraumatic stress disorder, none of these studies systematically assessed and tested the validity of the emerging concept of “posttraumatic stress disorder with secondary psychotic features” (5-13). The present study originated from the need of many psychiatrists who experience diagnostic uncertainty and lack of therapeutic success with this complex clinical condition that, according to them, does not correspond with schizophrenia (14, 15). An adequate diagnostic interpretation is needed before reasonable treatment-choices can be made or new and specific treatment methods can be developed and tested. The lack of some salient features of schizophrenia, the normal pre-trauma functioning, and the lack of success of routine treatments leads to the question whether the diagnostic concept “posttraumatic stress disorder with (secondary) psychotic features” (PTSD-SP) represents a valid separate diagnostic entity.

In this context, validity refers to the degree to which a diagnostic concept represents a discrete disease entity. Psychiatry generally lacks a gold standard that can be used to directly establish the validity of a psychiatric disorder. It, therefore, has to rely on indirect validation strategies. These strategies were delineated for the first time in the seminal paper of Robins and Guze (5) and further refined by others (6-9). The following criteria for a valid diagnostic entity can be distinguished:

1. Clinical description: identification and description of a syndrome;
2. Delineation: clear boundaries with other, related, syndromes;
3. Course: typical course and outcome of a syndrome;
4. Treatment response: typical treatment effect of a syndrome;
5. Family studies: particular syndrome runs in families;
6. Biological correlates/laboratory studies: distinctive biological characteristics related to a syndrome.



## Aims of the study

This study aimed to evaluate the empirical studies regarding the validity of PTSD-SP as a separate diagnostic entity against these six criteria.

### Material and methods

Publications in English, French, German, Dutch, and Spanish, issued between 1980 and January 2008 were traced, using the databases MEDLINE, PsycINFO, EMBASE Psychiatry, and Published International Literature On Traumatic Stress (PILOTS). The following full-text terms were used: 'PTSD', 'posttraumatic stress disorder', 'stress disorders, posttraumatic', 'psychological trauma', each combined with 'psychosis', 'psychotic', 'schizophrenia', 'hallucination', 'hallucinations', 'delusion', 'delusions', and 'reality testing'. Publications were screened, using the title and the abstract for relevance to the topic, i.e. PTSD and psychotic features. The reference lists of the publications were used to find additional studies.

A total of 184 publications on posttraumatic stress disorder, trauma and psychosis, or psychotic features were identified. From these 184 papers, 126 were excluded because of a primary focus on (a) psychosis following traumatic brain injury without PTSD (n=11), (b) schizophrenia or other psychotic disorders preceding the onset of PTSD (PTSD following (first onset) psychosis, traumatic reactions to psychotic illness, post-psychotic PTSD) (n=74), (c) (childhood) trauma leading to psychosis without a diagnosis of PTSD (n=30), and (d) psychosis and trauma in childhood or adolescence (age < 18 years; n=11). This selection process resulted in 58 publications on adult patients suffering from primary PTSD with secondary psychotic features (PTSD-SP). Of these 58 publications 16 were excluded because they did not contain original empirical data. In addition we excluded all studies (n=18) below level three of the Oxford Centre for Evidence-based Medicine levels of evidence (10). This means that we included systematic reviews, randomized controlled trials, (prospective, retrospective as well as non-consecutive) cohort studies, and ecological studies. We excluded case-series and papers based on expert opinions

Following this selection process, 24 studies remained (Table 1). This review is based on these 24 comparative studies with empirical data and minimum requirements regarding the level of evidence. Fourteen studies were performed in U.S. male war veterans, suffering from combat-related PTSD, and for the most part treated in outpatient facilities. Seven studies included females or civilians.

## Results

The results are presented according to the six validity criteria of Robins and Guze (16, 20). (See table 2 for the number of studies addressing validity criteria).

### Clinical description

To what extent has the clinical condition of PTSD-SP been described?

*Symptoms.* In several comparative population studies patients present a full-blown PTSD after traumatic events first, and subsequently report hallucinations and delusions (11, 13, 14, 20). The nature of these hallucinations is generally (71-100%) related to traumatic events, e.g. voices of dead buddies calling for help. The content of delusions is mainly paranoid/persecutory (16, 17, 29). These psychotic features are pervasive and chronic and do not occur exclusively in the context of a re-experiencing episode (14, 16). Several studies mention the presence of bizarre behavior. Formal thought disorders (e.g. flight of ideas, loose associations) are almost never reported.

*Severity.* Patients with PTSD-SP suffer from a higher burden of disease than patients with PTSD without psychotic features and the illness severity of PTSD-SP is similar to schizophrenia (14, 16, 17, 19). However, the presence or absence of psychotic features is not associated with the severity of PTSD as measured by the Clinician Administered PTSD Scale (CAPS) (14). The intensity of paranoid thinking and agitation is much higher in PTSD-SP patients than in patients with PTSD without psychosis or patients with psychotic disorder without PTSD (18).

*Trauma.* The nature and severity of the traumatic events are not associated with the presence or absence of psychotic features following PTSD (25, 27). In only one study, a positive correlation was found between the severity of the traumatic events and the presence of psychotic features (11). In this study, however, ethnicity could be a confounder: Hispanic American veterans with PTSD were more likely to develop positive psychotic features, but they also had more severe traumatic exposures.

*Ethnicity.* Hispanic Americans as well as African Americans displayed an increased incidence of PTSD-SP compared to Caucasians, even after controlling for differences in the nature and severity of the traumatic experiences, sociodemographic characteristics and family history of psychiatric illness (9, 22, 23).

*Personality disorders.* In one study personality disorders were investigated as a possible risk factor for PTSD-SP. In a group of Croatian war veterans and soldiers still in military service suffering from PTSD, psychotic symptoms were more often found among patients without co-morbid personality disorders (29).

*Age of onset.* The age of onset of PTSD-SP has not been studied systematically. From all studies included in this review PTSD-SP emerges in early adulthood or later in life (e.g. in war veterans). However, reports of childhood trauma, PTSD and

**Table 1** Characteristics of all published empirical studies on PTSD-SP (in chronological order) meeting evidence-level three or higher (no less than case-control studies)

Year	Author(s)	Subjects	Instruments	Tentative validity implications
1987	Mueser & Butler (11)	n = 36 (5 PTSD-SP; 31 PTSD) US male veterans; inpatients	Structured interview; MMPI; CES	PTSD-SP associated with Hispanic-American ethnicity and combat exposure; PTSD-SP is refractory to treatment
1991	Wilcox et al. (12)	n = 59 (PTSD-SP fraction not specified) US male veterans; outpatients	Clinical interview; Chart review	Hispanic-American ethnicity associated with PTSD-SP Age of combat, length of exposure to combat, age of onset of PTSD not significantly related to the occurrence of auditory hallucinations
1996	Butler et al. (13)	n = 38 (20 PTSD; 18 no PTSD) US male veterans & non-patient cohort. All: non treatment-seeking population	Clinical interview; M-PTSD; VCER; SADS-C; SANS; SAPS	Incidence of psychotic features in PTSD is higher than incidence in population without PTSD
1997	Hamner (14)	n = 25 (9 PTSD-SP; 16 PTSD) US male veterans; outpatients	SCID-III-R-P; CAPS; IES	Psychotic features do not reflect severity of PTSD-symptoms PTSD-SP not associated with impact of events Psychotic features: visual/auditive hallucinations and/or delusions, no formal thought disorder
1998	Hamner & Gold (15)	n = 41 (6 PTSD-SP; 13 PTSD; 22 healthy controls) US male veterans; in- and outpatients	SCID-P; CAPS; HRDS; IES	PTSD-SP is biologically different from PTSD and normal controls Dopamine $\beta$ -hydroxylase is a biological 'marker' for PTSD-SP
1999	David et al. (16)	n = 53 (21 PTSD-SP; 32 PTSD) US male veterans; Inpatients	SCID-III-R; clinical interviews; M-PTSD; DES	PTSD-SP associated with major depression and minority status. no association with alcohol/drug abuse no association with severity of PTSD; no association with dissociation
1999	Hamner et al. (17)	n = 45 (22 PTSD-SP; 23 PTSD) US male veterans; Outpatients	SCID-P; CAPS; HDRS; PANSS	Psychotic features in PTSD also present in patients without major depressive disorder. However strong association between PTSD-SP and major depressive disorder. PTSD-SP not associated with alcohol or drug abuse.
1999	Sautter et al. (18)	n = 62 (24 PTSD-SP; 22 PTSD; 16 psychotic no PTSD) US male veterans; PTSD and PTSD-SP: outpatients Psychotic group without PTSD: inpatients	SCID-IV; CES; M-PTSD; PANSS; PFAV; QLS	PTSD-SP: higher levels of psychopathology than PTSD or psychosis. Psychotic features in PTSD-SP not related to combat exposure African-American increased risk for PTSD-SP. Alcohol/drug dependence doesn't explain psychotic features in PTSD-SP
2000	Hamner et al. (19)	n = 80 (40 PTSD-SP; 40 schizophrenia) PTSD-SP: US male veterans; outpatients	SCID-P; CAPS; PANSS	PTSD-SP: less severe delusions and less conceptual disorganization and higher rating for 'hostility'
2000	Ivezic et al. (20)	n = 41 (8 PTSD-SP ; 33 PTSD) Croatian war veterans (1 female); inpatients	SCID-IV; SADS-L	PTSD-SP is highly associated with major depressive disorder. No association with personality disorder

Table 1 Continued

Year	Author(s)	Subjects	Instruments	Tentative validity implications
2002	Frueh et al. (21)	n = 53 (23 Afro-Americans; 30 Caucasians) US veterans (sex not mentioned; outpatients)	CAPS; SCID-P, MMPI-2; BDI; M-PTSD; DES	Afro-American ethnicity risk factor for PTSD-SP
2002	Monnier et al. (22)	n = 111 (12 PTSD-SP) US male veterans Outpatients	Clin. interview CAPS; MMPI-2; BDI; DES; M-PTSD	Ethnicity possible risk factor for development of PTSD-SP
2002	Sautter et al. (23)	n = 54 (23 PTSD-SP; 16 PTSD; 15 healthy matched controls) PTSD-SP & PTSD group: US veterans, sex not stated In- / outpatients: not stated	SCID-IV; FIGS;	PTSD-SP is associated with family history of major depression but not with higher rates of psychosis among relatives. No increased prevalence of psychotic disorders in first-degree relatives of patients with PTSD-SP.
2003	Hamner et al. (24)	n = 37 (All PTSD-SP: 19 risperidone, 18 placebo) US male veterans In- / outpatients: not stated	SCID-P; PANSS; CAPS; HAM-D	Positive and negative psychotic symptoms in PTSD seem to be much more 'refractory' on risperidone treatment compared to improvement of these symptoms in patients with schizophrenia
2003	Cerbone et al. (25)	n = 43 (14 PTSD-SP; 14 schizophrenia; 15 controls) PTSD-SP: US patients with combat related PTSD, males In- / outpatients: not stated	SCID-IV	Suggests that neurobiological abnormalities in PTSD-SP patients differ from schizophrenic patients
2003	Sautter et al. (26)	n = 29 (13 PTSD-SP; 8 PTSD; 8 controls) US male veterans Outpatients	SCID-IV	Suggests that PTSD-SP is a severe subtype of PTSD
2004	Pivac et al. (27)	n = 55 (All PTSD-SP: 28 olanzapine, 27 fluphenazine) male war veterans inpatients	SCID-IV ; WPQ ; PANSS ; CGI-S; CGI-I ; PGI-I ; DIEPSS	Fluphenazine and olanzapine reduced psychotic and PTSD symptoms in PTSD-SP
2004	Kaye (28)	n = 300 (56 PTSD-SP; 244 PTSD) US civilian outpatients, males and females	SCID-IV ; CGI ; GAF	No significant differences in risk factors. PTSD-SP: poorer outcome compared to PTSD
2005	Kozaric-Kovacic & Borovecki (29)	n = 969 (PTSD-SP 49; PTSD 371) Croatian male soldiers/veterans	Clin. Interview ; WPQ	Psychotic symptoms more often found in patients without personality disorders
2005	Kozaric-Kovacic et al. (30)	n = 26 (All PTSD-SP) All male Croatian war veterans Inpatients	SCID ; CAPS ; PTSD-I ; HAM-D ; PANSS	Risperidone reduced psychotic and PTSD symptoms in PTSD-SP
2006	Pivac et al. (31)	n = 274 (35 PTSD-SP; 67 PTSD; 36 exposed vets without PTSD; 136 healthy controls) Male war veterans Inpatients	SCID; CAPS; PANSS; HAM-D	Platelet serotonin concentration is increased in PTSD-SP compared to veterans with or without PTSD or to control subjects.



Table 1 Continued

Year	Author(s)	Subjects	Instruments	Tentative validity implications
2007	Kastelan (32)	n = 91 (All PTSD) Male war veterans	SCID; CAPS; HTQ	Severity of hyperarousal symptoms was positively correlated with occurrence of psychotic symptoms
2007	Kozaric-Kovacic & Pivac (33)	n = 53 Male war veterans	CAPS, CGI-I, CGI-S, PANSS, DIEPSS	Quetiapine reduced psychotic and PTSD symptoms in PTSD-SP
2007	Pivac et al. (34)	n = 386 (28 PTSD-SP; 78 PTSD; 41 exposed vets without PTSD; 242 healthy controls) All Croatian males	SCID; CAPS; PANSS; HAM-D	Higher platelet MAO-B activity in PTSD-SP compared to non-psychotic PTSD, Vets without PTSD and healthy controls

**BDI:** Beck Depression Inventory; **CAPS:** Clinician Administered PTSD Scale; **CES:** Combat Exposure Scale; **CGI:** Clinical Global Impression Scale; **CGI-S:** Clinical Global Impression Severity Scale; **CGI-I:** Clinical Global Impression Improvement Scale; **DES:** Dissociative Experience Scale; **DIEPSS:** Drug Induced Extra-Pyramidal Symptoms Scale; **FIGS:** Family Interview for Genetic Studies; **GAF:** Global Assessment of Functioning; **HAM-D:** Hamilton Depression rating scale; **IES:** Impact of Events Scale; **MMPI-2:** Minnesota Multiphasic Personality Inventory-2; **M-PTSD:** Mississippi scale for Combat-Related Posttraumatic stress disorder; **PTSD-I:** PTSD Interview; **PANSS:** Positive and Negative Syndrome

Scale; **PFAV:** Past Feelings and Acts of violence Scale; **PGI-I:** Patient Global Impression Improvement Scale; **QLS:** Quality of Life Scale; **SADS-C:** Schedule for Affective Disorders and Schizophrenia – Change Version; **SADS-L:** Schedule for Affective Disorder and Schizophrenia – Lifetime Version; **SANS:** Scale for the Assessment of Negative Symptoms; **SAPS:** Scale for the Assessment of Positive Symptoms; **SCID-III-R-P:** Structured Clinical interview for DSM-III-R with psychotic screen; **SCID-IV:** Structured Clinical Interview for DSM-IV ; **VCER:** Vietnam Combat Exposure Scale; **WPQ:** Watson's PTSD questionnaire.

psychosis do exist (excluded in this review). This and the preponderance of studies on war veterans could lead to a biased age of onset.

*Prevalence.* No epidemiological data are available. Frequency rates of psychotic symptoms in patients diagnosed with PTSD vary between 15% and 64% in patients with PTSD (20) primarily depending on sampling strategies.

### Delineation

To what extent can PTSD-SP be differentiated from other psychiatric syndromes?

*Schizophrenia.* Within current nosological classification systems, patients presenting with PTSD-SP would be classified as suffering from schizophrenia and co-morbid PTSD. However, there are differences in symptomatology between patients with PTSD-SP and schizophrenia. The content of hallucinations in PTSD-SP patients is almost always trauma-related, but often accompanied by non-trauma-related content (17, 19). Delusions in PTSD-SP patients are mainly paranoid and persecutory in nature, whereas in schizophrenia the delusions are often more complex and bizarre. Formal thought disorders (e.g. loose associations, incoherence, neologisms) are quite common in schizophrenia, but exceptional in PTSD-SP (19). There are no disturbances of affect (e.g. inappropriate) in PTSD-SP patients. No differentiation can be made between PTSD-SP and schizophrenia in terms of negative

symptoms. However, this may be due to the difficulty to differentiate between negative symptoms in schizophrenia and avoidance symptoms in PTSD (19).

It is obvious that PTSD can develop after the onset of schizophrenia. This psychopathological status is known as 'post-psychotic PTSD' (PP-PTSD). It is due to psychotic phenomena, experienced as traumatic by patients, or due to other traumatic events like rape, assault, or witnessing violence or traumatic events during forced admissions and treatment (35-39). Patients suffering from PP-PTSD can be distinguished from PTSD-SP by the fact that in PP-PTSD the psychotic features clearly precede the occurrence of PTSD.

*Affective disorders.* Co-morbidity of major depressive disorder and PTSD ranges from 44 to 84%, and co-morbidity between major depressive disorder and PTSD-SP is probably even higher (20, 40, 41). Therefore, the question arises whether the psychotic features in patients suffering from both depressive disorder and PTSD should be attributed to the depressive disorder (depressive disorder with psychotic features and co-morbid PTSD) or to the PTSD (depressive disorder and co-morbid PTSD-SP). A strong correlation was found between the severity of PTSD symptoms and the severity of depressive symptoms in PTSD-SP patients, as well as significantly higher PANSS-ratings of psychosis in PTSD-SP patients with major depressive disorder compared to PTSD-SP patients without a co-occurring major depressive

disorder (17). This finding suggests that PTSD, depressive disorder and psychotic features are somehow interconnected in patients suffering from PTSD-SP. It remains unclear, however, to what extent psychotic features in PTSD-SP can be explained by the co-morbid depressive disorder since a considerable portion of PTSD-SP patients do not have major depressive disorder. In one study 68% of all patients with PTSD-SP had a co-morbid depressive disorder, indicating that in at least 32% of the patients in this study the presence of psychotic features cannot be explained by the co-morbid depressive disorder (17). In an inpatient population of PTSD-SP patients, a significant association ( $p < 0.02$ ) was found between the presence of psychotic features and the presence of major depressive disorder, while none of these patients met the diagnostic criteria of depressive disorder with psychotic features (16, 42). A large scale study shows that patients suffering from a depressive disorder with psychotic features were almost four times more likely to suffer from co-morbid PTSD, compared to patients with a non-psychotic depression: 58% versus 16% (43). In another study, however, all depressive disorders with psychotic features were preceded by PTSD (44).

*Dissociative disorders.* The only study looking at comorbid dissociative disorders did not find a relationship between psychotic symptoms and dissociative features in patients with PTSD, as measured by the Dissociative Experience Scale (DES) (16).

*Alcohol/drugs dependency/abuse.* No relationships were found between psychotic features in PTSD and alcohol or drug dependence, nor were the psychotic features related to intoxication or withdrawal (11, 12, 16, 17).

### Course

Has PTSD-SP a typical course, i.e. a course that differs from that of PTSD, schizophrenia or psychotic depression?

No study that meets the necessary basic requirements of this review has been conducted on this specific topic.

### Treatment response

Are there treatment-effects that are typical for PTSD-SP?

*Pharmacotherapy.* Differences in drug effects can indicate the presence of distinct pathophysiological processes and hence add support to the validity of a nosological entity (45). Recently, the results of four trials have been published. The first is a randomised controlled trial in which risperidone ( $n=19$ ) or placebo ( $n=18$ ) were added to the already prescribed medications (mainly antidepressants) in combat veterans with PTSD-SP (24). This study showed that after six weeks of treatment the composite score on the Positive and Negative Syndrome Scale (PANSS) decreased significantly more from baseline in the risperidone group, compared to placebo group ( $p < 0.05$ ). This effect was due to a decrease in the

'general psychopathology' subscale of the PANSS. The scores on the positive and negative syndrome subscales in the risperidone group did not decrease significantly more than the scores in the placebo group. Two studies (uncontrolled pre-post comparisons:  $n=26$  and  $n=53$ ) reported a significant improvement on risperidone as well as quetiapine mono-therapy (30, 33). The fourth study compared olanzapine ( $n=28$ ) and fluphenazine ( $n=27$ ) as a mono-therapy in PTSD-SP patients in a six-week open trial (27). Compared to fluphenazine, olanzapine showed significantly ( $p < 0.05$ ) more improvement in negative symptoms and general psychopathology of the PANSS and in PTSD symptoms. These findings are consistent with a subtype of schizophrenia, or postpsychotic PTSD, or with a specific kind of affective disorder with psychotic symptoms as well as with PTSD-SP as a separate diagnostic entity.

*Psychotherapy.* No systematic empirical research on this topic was found.

### Family studies

Does PTSD-SP run in families?

No studies have been performed to detect the prevalence or incidence of PTSD-SP in relatives of patients suffering from PTSD-SP. One study focused on familial vulnerability to schizophrenia and other psychoses in first degree relatives of PTSD-SP patients. The study showed an increased prevalence of major depression, but no increased prevalence of psychotic disorders in first degree relatives (23). First degree relatives of PTSD-SP probands (as well as of PTSD probands) are at higher risk for depressive disorder, compared to healthy controls: Thirteen relatives (15.9%) of PTSD-SP patients and 18 relatives of PTSD-SP patients (15.9%) were diagnosed with major depression, compared to three relatives (4.8%) of the healthy comparison probands ( $p=0.01$ ) (23).

### Biological correlates/laboratory studies

Are there biological correlates/laboratory measures that can be used as external validators for PTSD-SP?

Significantly ( $p < 0.01$ ) elevated plasma dopamine beta-hydroxylase ( $D\beta H$ ) activity has been observed in patients suffering from PTSD-SP ( $n=6$ ) compared to patients with PTSD without psychotic features ( $n=13$ ) as well as compared to normal controls ( $n=22$ ) (15). In addition, cerebrospinal fluid concentrations of corticotropin-releasing factor (CRF) in PTSD-SP patients ( $n=13$ ) has been shown to be significantly higher ( $p < 0.01$ ) compared to patients with PTSD without psychotic features ( $n=8$ ) and healthy controls ( $n=8$ ) (26).

Furthermore, Pivac et al. (34) observed increased levels of blood platelet monoamine oxidase B activity (MAO-B) in PTSD-SP war veterans compared to non-psychotic veterans with or without PTSD and healthy control subjects. In another study increased blood platelet-levels of serotonin (5-HT) activity were identified as

well, in PTSD-SP war veterans compared to war veterans with or without PTSD and healthy control subjects (31).

Finally, PTSD-SP is associated with smooth pursuit eye movement (SPEM) deficits that are qualitatively different from SPEM-deficits of patients suffering from schizophrenia as well as healthy controls: PTSD-SP patients (n=14) are deficient in higher velocity SPEM as compared to patients suffering from schizophrenia (n=14), and schizophrenia is associated with lower velocity SPEM deficits than healthy controls (n=15) (25).

**Table 2** Number of studies with at least level three evidence (minimal requirement case-control studies) addressing specific validity criteria

Validity criteria	Number of studies
1 Clinical description	11
2 Delineation	9
3 Course	0
4 Treatment response	3
5 Family studies	1
6 Biological correlates/laboratory studies	5

## Discussion

It seems likely that PTSD-SP is distinct from schizophrenia, because there is no increased prevalence of psychotic disorders in first degree relatives, and because SPEM-deficits differ qualitatively from those seen in schizophrenia. Several (pre-post design) studies show a positive response of psychotic symptoms to neuroleptics in PTSD-SP. However in the only available RCT, delusions and hallucinations did not improve more with risperidone than with placebo, which would be expected in cases of schizophrenia. As to the phenomenology, there are clear differences between PTSD-SP and schizophrenia, although, the clinical description of PTSD-SP still shows some inconsistencies. In early studies, PTSD patients were described with merely auditory hallucinations as psychotic symptoms. In later studies delusions and negative psychotic features were depicted as well. Several studies show that co-morbid disorders like alcohol- or drug related disorders (which could give rise to positive psychotic symptoms) cannot account for the presence of the psychotic features in PTSD-SP.

Patients suffering from PTSD-SP often suffer from a depressive disorder as well. It is still unclear whether the psychotic features should be interpreted as part of a PTSD (i.e. PTSD-SP with a co-morbid depressive disorder) or as part of a depressive disorder (i.e. PTSD with a co-morbid depressive disorder with psychotic features). The increased dopamine beta-hydroxylase (DBH) activity in PTSD-SP patients favors the first explanation, since DBH activity is decreased in patients with a depressive disorder with psychotic features. However the study that found an increased DBH in PTSD-SP patients did not control for the presence of a co-morbid depressive disorder.

Studies clearly differentiating personality disorders, especially borderline personality disorder, from PTSD-SP are lacking.

No sound data are available on the clinical course of PTSD-SP. A few studies with a lower evidence level than three briefly touch upon the course of PTSD-SP. Two studies mention that PTSD-SP is a chronic condition without providing more specific empirical data (46-48). PTSD-SP differs from disorders like (brief) reactive psychosis or acute transient psychotic disorder due to a different course: in PTSD-SP posttraumatic stress disorder develops first and in a later stage psychotic features follow and become chronic.

Psychotic features in PTSD-SP, especially hallucinations, could be confused with dissociative features. Instruments like the MMPI-2 fail to differentiate adequately between dissociative and psychotic features in PTSD. One study did not find a dissociative disorder in patients with PTSD-SP and no association was found between PTSD-SP and DES-scores.

Sound data on psychotherapy and PTSD-SP are missing. One study describes a day hospital program for PTSD-SP patients, using trauma focus groups including graduated therapeutic exposure, cognitive restructuring, and relapse prevention (49). At the end of the program 70% of the patients reported greater control over PTSD symptoms, compared to the start of the treatment. However, this study did not use objective outcome measures and hence did not meet the minimal requirements for inclusion in this review.

Summarizing the reviewed studies, PTSD-SP is emerging as a syndrome that consists of posttraumatic stress disorder, joined by one or more psychotic features, especially hallucinations and delusions. The prevalence of PTSD-SP is unclear with varying rates in mental treatment seeking populations (15-64%). The psychotic features are not confined to episodes of re-experiencing, but remain present continuously. The content of these psychotic features is generally paranoid in nature, and no first rank Schneiderian psychotic features appear to be present. There is no history of psychotic episodes prior to the traumatic event(s). No relationship has been found between the nature or severity of the traumatic events and the presence of PTSD-SP. In first degree relatives there is an increased prevalence of major depression



(like in PTSD) but no increased prevalence of psychotic disorders (which would be expected in cases of schizophrenia). Positive correlations have been found in PTSD-SP patients with ethnicity (African-American and Hispanic), with co-morbid depressive disorder, with the enzyme-activity of DBH and with cerebrospinal fluid concentrations of CRF, blood platelet serotonin and MAO B activity. There are specific smooth pursuit eye movement deficits. General psychopathology improves on adjunctive risperidone treatment, positive and negative psychotic symptoms do respond in uncontrolled pre-post comparisons but not significantly compared to placebo in another study. Olanzapine treatment resulted in larger reductions in negative symptoms and PTSD symptoms than fluphenazine.

Most of the included studies have limitations. First, most studies focus on U.S. combat veterans, and very few data are available on female subjects. Second, a recurrent finding is the increased incidence of PTSD-SP among African-Americans and Hispanic Americans combat vets. This might be a research artifact since none of the applied research instruments have been cross-culturally validated. Therefore the question is still unresolved whether 'ethnicity' or racial group affiliation are risk factors for developing PTSD-SP, or whether certain ethnic groups have higher scores on items indicating psychosis due to measurement bias. Third, studies offering biological evidence for the validity of PTSD-SP have not been replicated. Finally, no research on co-existing personality disorders (especially borderline personality disorder) in PTSD-SP exists to elucidate the relationship between psychotic features occurring in PTSD and the presence of a severe personality disorder.

Based on the available studies we propose the following criteria for PTSD-SP, as a provisional diagnostic entity:

1. DSM-IV TR criteria of PTSD
2. positive psychotic symptoms such as delusions and/or hallucinations
3. Psychotic features are not confined exclusively to episodes of re-experiencing or flashbacks and should be distinguished from DSM IV-TR PTSD-criterion B3: "acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes)" (50, p. 468).
4. no formal thought disorder
5. no brief psychotic disorder
6. PTSD precedes the onset of psychotic features
7. no history of psychotic episodes prior to the traumatic event(s)

Although the abovementioned criteria for PTSD-SP are not yet fully validated, the reviewed studies offer ample indications for further inquiry. Additional research focusing on the validity of PTSD-SP is needed, not for the sake of adding another nosological subtype to DSM-IV or ICD-10, but to gain a clearer picture of this group of patients

leading to further research into specific interventions for this complex, severe and often chronic disorder. Special attention is warranted for research in other samples than male combat veterans, and research addressing the issue of differentiating PTSD-SP from depressive disorder with psychotic features. Additional studies are also needed that focus on co-morbid personality disorder (borderline, schizotypal, paranoid), the course of PTSD-SP, biological correlates and etiological factors.

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## Chapter 3

### **'Posttraumatic stress disorder with secondary psychotic features': neurobiological findings**

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## Abstract

The neurobiological knowledge on the potentially new diagnostic entity “posttraumatic stress disorder with secondary psychotic features” (PTSD-SP) is reviewed. Studies published between 1980 and 2006 were traced focussing on adult patients suffering from this “syndrome”. Studies on cortisol, corticotrophin releasing hormone, dopamine beta-hydroxylase, smooth pursuit eye movements and psychopharmacology are described and potential pathophysiological mechanisms briefly discussed. The results of this study corroborate preliminary phenomenological evidence that PTSD-SP can be delineated from other related disorders like schizophrenia, PTSD and, depressive disorder with psychotic features. More research is needed to validate the nosological status of PTSD-SP in order to promote neurobiological research and adequate therapeutic interventions.

## Introduction

A number of publications express the emergence of a new syndrome: posttraumatic stress disorder with secondary psychotic symptoms (PTSD-SP). This syndrome meets DSM-IV TR criteria of posttraumatic stress disorder, followed by psychotic features, especially hallucinations and delusions. These features are not confined to episodes of re-experiencing. The content of these psychotic features is often trauma-related, paranoid in nature, and not bizarre. There is no formal thought disorder. PTSD-SP appears to have a chronic course. Comorbid major depressive disorder occurs frequently. There is no history of psychotic episodes, prior to the traumatic event(s). No relationship has been found between the nature or the severity of the traumatic events and the subsequent manifestation of psychotic features in patients suffering from PTSD. In first degree relatives there is an increased prevalence of major depression, but not of psychotic disorders. Prevalence rates of PTSD-SP varies considerably between studies (from 15% to 64%), primarily depending on sampling strategies used. The prevalence rate in the general population is unknown (1).

In this paper all studies on this topic are reviewed to determine the state of neurobiological knowledge on this potential syndrome and its pathophysiological underpinnings. The main findings of these studies are reported as well as the varied spectrum of hypotheses put forward.

## Methodology

Studies published between 1980 and 2006 were traced using the databases MEDLINE, PsycINFO, EMBASE Psychiatry, and Published International Literature On Traumatic Stress (PILOTS), with the full-text terms: ‘PTSD’, ‘posttraumatic stress disorder’, ‘stress disorders, posttraumatic’, ‘psychological trauma’, each combined with ‘psychosis’, ‘psychotic’, ‘schizophrenia’, ‘hallucination’, ‘hallucinations’, ‘delusion’, ‘delusions’, and ‘reality testing’. Publications were screened, using the title and the abstract for relevance to the topic, i.e. PTSD and psychotic features. Reference lists were screened to find additional studies.

## Results

A total of 45 publications were detected dealing with adult patients suffering from PTSD-SP. Only nine out of these studies focused on neurobiological issues and surpassed the evidence level of case studies; five are mainly psychopharmacologically oriented. The main findings (summarized in table 1) concern corticotrophin



releasing hormone (CRH) plasma levels of cortisol, dopamine beta-hydroxylase (D $\beta$ H), smooth pursuit eye movement (SPEM) and pharmacotherapy.

### Corticotrophin releasing hormone

Based on the assumption that PTSD-SP could be a severe subtype of PTSD, enhanced hyperactivity of the CRH system can be expected. Therefore, Sautter et al. assessed the cerebrospinal fluid concentrations of CRH (2). Their results demonstrate that patients with primary PTSD and subsequent appearing psychotic symptoms have higher cerebrospinal fluid concentrations of CRH than patients suffering from PTSD without psychosis and healthy comparison subjects.

### Cortisol

Abnormal cortisol levels have been found in a wide array of psychiatric disorders, including psychosis, PTSD and depressive disorders. Manguno-Mire et al. (3) demonstrate that subjects with PTSD and secondary psychotic features show significantly higher baseline cortisol levels than subjects with PTSD without psychotic features and control subjects. In contrast to the non-suppression associated with major depressive disorder with psychotic features (4), PTSD-SP subjects show hypersuppression of cortisol following 1 mg of dexamethasone admission. This study indicates that PTSD-SP has a neuroendocrine profile different from PTSD and depressive disorder with psychotic features.

### Dopamine beta-hydroxylase

D $\beta$ H converts dopamine into norepinephrine. During synaptic transmitter release it enters the extracellular space and hence becomes present in the cerebrospinal fluid and in blood plasma. D $\beta$ H activity in plasma is a very stable heritable trait but varies extensively across unrelated individuals (5). Hamner and Gold (6) observed that plasma D $\beta$ H -activity was elevated in PTSD patients with psychotic features as compared to both PTSD patients without psychotic features and healthy control subjects.

### Smooth pursuit eye movement

SPEM refers to the movement of the eye that smoothly tracks slowly moving objects in the visual field. SPEM deficits are a well established phenomenon in schizophrenia (7). Cerbone et al. (8) studied SPEM in patients suffering from PTSD-SP and found marked differences compared to schizophrenia. The performance of patients with PTSD and secondary psychotic symptoms differed significantly from controls and from patients with schizophrenia in terms of the percentage of time in smooth pursuit. Patients with PTSD-SP showed impaired SPEM performance at higher velocity as compared to normal controls, while schizophrenia subjects were deficient in low

velocity SPEM. PTSD-SP subjects showed deficits in the continuation of smooth pursuit, while schizophrenia was associated with deficits in the initiation of smooth pursuit.

### Pharmacotherapy

Only one of the available pharmacological studies on PTSD-SP meets an adequate methodological quality, i.e. a randomized, double-blind, placebo-controlled trial. In this study risperidone or placebo were added to a standard regimen of antidepressant treatment (9). The risperidone group improved significantly more than the placebo group in terms of the total Positive and Negative Syndrome Scale (PANSS). A more detailed analysis revealed that the level of significance was reached due to the improvement of the 'general psychopathology subscale' of the PANSS. Neither the 'positive symptoms subscale' nor the 'negative symptoms subscale' of the PANSS improved significantly. Thus, while general psychopathological symptoms improved, positive symptoms like delusions and hallucinations improved to the same degree in both groups.

**Table 1** Summary of findings

	PTSD	PTSD-SP	Schizophrenia
Baseline cortisol (Manguno-Mire et al., in prep.)	= *)	↑ *)	
CRH in CSF (Sautter et al., 2003)	= *)	↑ *)	
Plasma D $\beta$ H (Hamner and Gold, 1998)	= *)	↑ *)	
SPEM performance (Cerbone et al., 2003)		High velocity impairment	Low velocity impairment
SPEM deficits (Cerbone et al., 2003)		Deficits in continuation	Deficits in initiation
Risperidone (Hamner et al., 2003)		Positive psychotic features do not improve **)	

\*) compared to healthy controls; \*\*) compared to placebo

## Pathophysiological hypotheses

A variety of pathophysiological hypotheses on PTSD-SP have been proposed in the abovementioned studies. Sautter et al (2) proposed several hypotheses based on increased activation of CRH-circuitry:

1. Increased activation of hypothalamic CRH would produce increased cortisol secretion from the adrenal gland, which in turn increases CNS dopamine-activity of the meso-cortical dopamine system.
2. Higher levels of CRH could lead to psychotic symptoms through the mechanism of CRH at the cyclic adenosine monophosphate (cAMP) level in the frontal cortex: High levels of CRH in PTSD-SP augment dopaminergic stimulation of cyclic AMP in the frontal cortex because both CRH receptor subtypes use G-protein stimulatory heterotrimeric receptors that increase cyclic AMP levels when activated by CRH.
3. Activation of CRH systems located outside the HPA-axis (e.g. locus coeruleus, amygdalae and the hippocampus) could, due to an increased frontal circuit dopamine activity, result in increased secretion of CRH in PTSD-SP subjects.
4. Another hypothesis, not based on dopaminergic activity, but on noradrenergic hyperactivity has been proposed by Hamner and Gold (6): Higher dopamine beta-hydroxylase activity could be expected to facilitate increased noradrenaline synthesis and might contribute to psychosis.

## Discussion

There is ample evidence that stress and cortisol are involved in dopaminergic alterations in the brain and that hypercortisolemia as in M. Cushing can lead to frank psychosis. Thus a dopamine-based pathophysiology is worthwhile exploring although the lack of antipsychotic activity of risperidone points towards a pathophysiological mechanism that is (at least partially) different from the one proposed in schizophrenia. The altered cortisol and CRH levels also indicate a (partially) different pathophysiological mechanism operating in PTSD-SP compared to PTSD and depressive disorder with psychotic features.

It should be noted that all published research findings await replication and the presented findings should, therefore, be met with caution and reliable pathophysiological hypotheses are still preliminary. Finally no direct comparison data exist comparing PTSD-SP with major depressive disorder with psychotic features.

Research focusing on the validation of PTSD-SP and the delineation of clear diagnostic criteria is of great importance for the promotion of neurobiological and pathophysiological research and the study of (pharmaco-) therapeutic interventions

of this complex disorder. Neurobiological studies focusing on PTSD-SP are limited. Nonetheless, the divergent topics, and the PTSD-SP specific findings of these studies, strengthen preliminary phenomenological evidence that PTSD-SP can be delineated from other related disorders like schizophrenia (differences in smooth pursuit and D $\beta$ H), PTSD (differences in D $\beta$ H and cerebrospinal fluid levels of CRH) as well as depressive disorder with psychotic features (differences in D $\beta$ H activity).

## Abbreviations

cAMP	cyclic adenosine monophosphate
CRH	Corticotrophin releasing hormone
D $\beta$ H	Dopamine beta-hydroxylase
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders, Text Revision
HPA-axis	hypothalamus-pituitary-adrenal axis
PANSS	Positive and Negative Syndrome Scale
PILOTS	Published International Literature On Traumatic Stress
PTSD	Posttraumatic stress disorder
PTSD-SP	Posttraumatic stress disorder with secondary psychotic features
SPEM	Smooth pursuit eye movement

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## Chapter 4

### **Clinical differences between psychosis in 'posttraumatic stress disorder with secondary psychotic features' and schizophrenia among refugees**

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## Abstract

The aim of this study was to evaluate whether chronic psychosis in 'posttraumatic stress disorder with secondary psychotic features' (PTSD-SP) can be distinguished from psychosis in schizophrenia by clinical features and trauma history. In a cross sectional study among refugees, inpatients with PTSD-SP were compared to inpatients suffering from schizophrenia. Main diagnosis and comorbid disorders were assessed as well as detailed clinical features and trauma history. Positive psychotic symptoms were equally present in both groups, except for conceptual disorganization which was less prevalent in the PTSD-SP group. Compared to the schizophrenia group, patients with PTSD-SP reported markedly fewer negative symptoms, less lack of judgment and insight, much higher levels of anxiety and depression, and more comorbid psychiatric disorders.

It is concluded that PTSD-SP can be distinguished from schizophrenia by clinical features. These findings suggest that PTSD-SP is clinically different from schizophrenia and support previous proposals to conceptualize PTSD-SP as a separate nosological entity in DSM-5.

## Introduction

Clinical and epidemiological studies have reported high rates of psychotic features in patients suffering from posttraumatic stress disorder (PTSD) (1-3). Psychotic features are present in up to 40% of patients with combat-related PTSD (4). In these patients, chronic hallucinations and delusions that are not limited to flashback episodes are most prominent (5). Frequently these patients meet DSM-IV criteria of schizophrenia (6-9). However, according to several authors, these patients do not suffer from schizophrenia (1, 10) and a separate diagnostic category has been suggested that is distinct from schizophrenia: psychotic posttraumatic stress disorder (2, 3, 10, 11). This suggestion led to the present study in which we compare the clinical features of patients with schizophrenia and patients with psychotic PTSD in order to answer the question whether or not these patients represent two distinct diagnostic entities. Previous studies on this topic were limited to male war veterans exposed to combat-related trauma (2). In this study we focus on a different and more diverse population: a multi-ethnic sample of refugees, both male and female, who have been exposed to a wide range of traumas, not exclusively combat-related. To our knowledge, this is the first study to address this question in a multi-ethnic refugee population. The main objective in this study is to search for similarities and differences in core clinical features of psychosis and trauma history in patients with schizophrenia and patients with posttraumatic stress disorder. Previous studies focusing on psychosis and PTSD were based on lifetime prevalence rates of PTSD, psychosis and other comorbid conditions and did not take into account the temporal relationships between these conditions (3, 12-14). The present study focuses on the temporal relationship between PTSD and psychotic symptoms. In contrast to previous studies we make a clear distinction between patients who developed a chronic psychotic disorder without preceding PTSD and patients who experienced traumatic events, developed PTSD and subsequently became chronically psychotic. This latter group of patients we will, from now on, identify as suffering from 'posttraumatic stress disorder with secondary psychotic features' (PTSD-SP).

In this study, we first compare the group of PTSD-SP patients (i.e. psychotic patients with a diagnosis of PTSD before the onset of the first psychotic episode) with a group of patients suffering from schizophrenia (i.e. psychotic patients without a diagnosis of PTSD or with an onset of PTSD after the onset of the first psychotic episode) regarding to the type and severity of psychotic features, the presence of comorbid disorders, clinical course, and experienced traumatic events. In addition, we explore whether PTSD-SP patients with a formal DSM-IV diagnosis of schizophrenia can be distinguished from PTSD-SP patients without a formal DSM-IV diagnosis of schizophrenia and whether these PTSD-SP subgroups can be distinguished from patients with schizophrenia (i.e. psychotic patients without a diagnosis of PTSD or

with an onset of PTSD after the onset of the first psychotic episode) based on clinical characteristics using MANOVA and discriminant analysis.

## Methods

### Participants and entry criteria

This cross sectional study recruited patients from two mental health hospitals in the Netherlands that provide inpatient treatment to refugees, who fled to the Netherlands from many parts of the world. Consecutive sampling was applied with recruitment of recently admitted patients meeting the following entry criteria: being a refugee, 16 years or older, and at least one DSM-IV PTSD symptom or at least one psychotic symptom according to the clinician. This was a pre-selection, performed in order not to miss any potentially eligible study-participants with PTSD and/or psychotic disorders. Subsequent accurate assessment of the diagnosis and final in- or exclusion was done with the Schedules for Clinical Assessment in Neuropsychiatry, as described in the next paragraph. After complete description of the study to the participants, written informed consent was obtained, some together with the patient's representative. All study procedures were approved by the Dutch Mental Health Ethical Review Board (METIGG).

### Diagnostic assessment and group allocation

Main diagnoses and the presence of comorbid disorders were assessed (both 'present state' and 'lifetime before') with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (15). The SCAN does not enforce diagnosis-driven a priori grouping of symptoms and has been shown to be cross-culturally valid and applicable (16). We recruited two groups of patients:

1. Similar to Sautter et al (17), we defined the 'PTSD-SP-group' as patients with DSM-IV PTSD and psychotic symptoms, in whom the onset of PTSD preceded the onset of psychosis. We carefully distinguished psychotic symptoms from (dissociative) flashback episodes with illusions and hallucinations while reliving the experience. These latter symptoms were interpreted as part of the conventional DSM-IV diagnostic criteria for PTSD.
2. The 'schizophrenia group' was defined as those patients meeting DSM-IV criteria of schizophrenia but without preceding DSM-IV PTSD.

In both groups, patients with bipolar disorder, organic mental disorders and malingering were excluded.

### Symptom Measures

In both groups (PTSD-SP and schizophrenia) we assessed current psychotic symptoms with the Positive and Negative Syndrome Scale (PANSS) (18) and the psychotic symptom rating scale (PSYRATS) (19). The Hopkins Symptoms Checklist (HSCCL-25) (20) was used to assess the presence and severity of current anxiety and depressive symptoms. The experienced traumatic events were measured with the trauma scale of the Harvard Trauma Questionnaire (HTQ) which contains a traumatic events scale specifically designed for trauma's experienced by adult refugees (21). All symptom measures were administered by interviewers that were blind for diagnostic group status. Professional interpreters assisted in 80% of all interviews. The HTQ and HSCCL-25 have proven cross-cultural reliability and validity for the groups under study (22). In that study, different translations of those scales were assessed and the Cronbach's internal consistency (alpha) was used as a measure of reliability. Cronbach's alpha was high, ranging between 0.8 and 0.9 across the different scales and language versions. Validity was assessed by item-total scale correlations. A few items with low item-total scale correlations were identified but their effect on the total scores were small.

### Statistical analysis

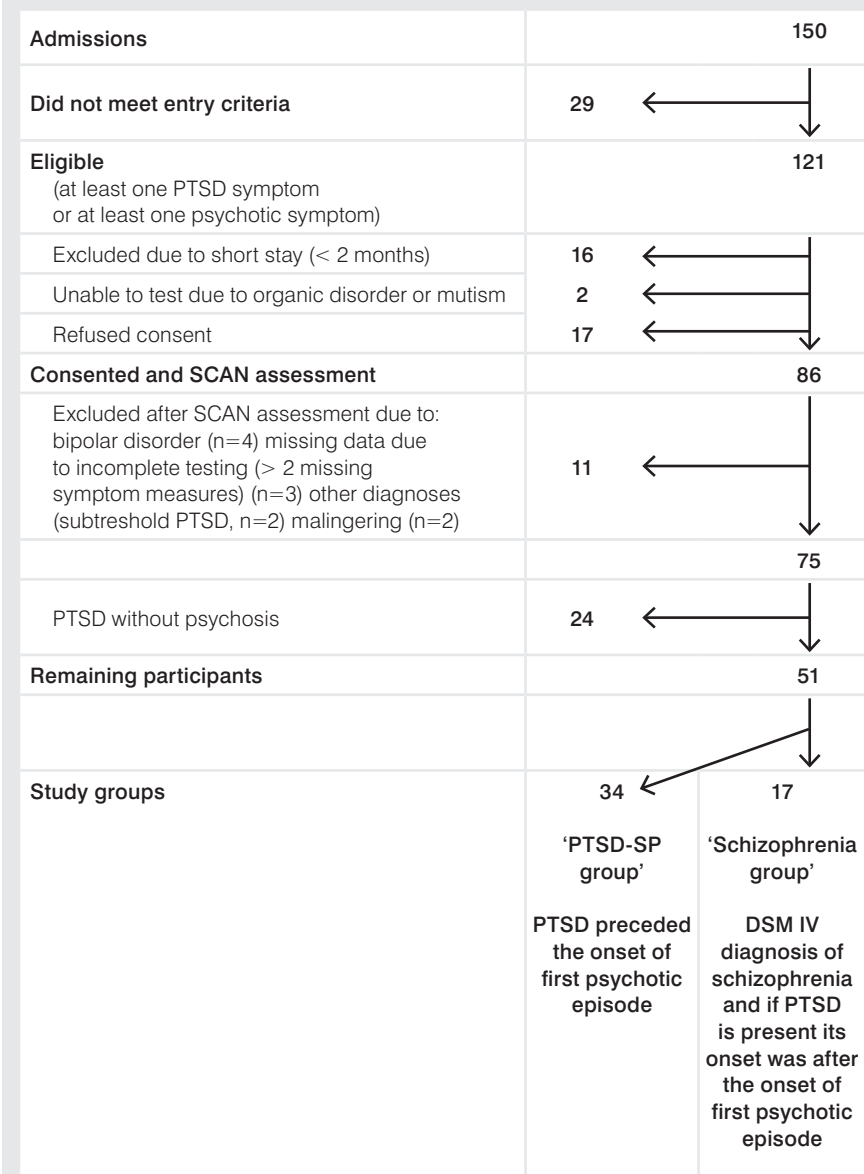
Variables were tested for normal distribution and homogeneity of variance. All tests were two-sided and p-values < 0.05 were considered significant. If appropriate, Bonferroni-corrections were applied and effect sizes were computed and added. Group differences were tested using t-tests for continuous variables and chi square tests or Fisher's exact tests for categorical variables. Logistic regression analysis was applied to identify significant and clinically useful independent predictors for diagnostic group status. Finally, multivariate analysis (MANOVA) followed by discriminant analysis was used to analyse the underlying symptom dimensionality of the diagnostic groups. All statistical analyses were performed using PASW Statistics 18.0 for Windows (SPSS/IBM Inc, Chicago, IL).

## Results

### Sample characteristics

A total of 150 consecutive inpatient refugees in the two sites were screened for eligibility resulting in 51 subjects, meeting all criteria for final assessments and including 34 patients with PTSD-SP and 17 patients with schizophrenia (Figure 1).

**Figure 1** Flow chart of study inclusion: subjects with PTSD and secondary psychotic features or subjects with schizophrenia without PTSD prior to first psychotic episode



**Table 1** Comparison of demographic sample characteristics of the 'PTSD-SP-group' and the 'schizophrenia-group'

	PTSD-SP N = 34		Schizophrenia N = 17		df	Test statistic	p-value (2-sided)
	Mean or N	SD or %	Mean or N	SD or %			
<b>Age</b>	38.6	9.9	37.6	10.3	49	0.33 <sup>1</sup>	0.74
<b>Sex</b>					1	- <sup>3</sup>	0.46
Male	26	76.5%	15	88.2%			
Female	8	23.5%	2	11.8%			
<b>Marital status</b>					1	2.56 <sup>2</sup>	0.11
Married	22	64.7%	7	41.2%			
Single	12	35.3%	10	58.8%			
<b>Years of education</b>	8.5	4.6	9.4	4.5	49	-0.68 <sup>1</sup>	0.50
<b>Religion</b>					2	0.15 <sup>3</sup>	1.00
Islamic	15	44.1%	8	47.1%			
Christian	13	38.2%	6	35.3%			
Other	6	17.6%	3	17.6%			
<b>Region of origin</b>					-	9.93 <sup>3</sup>	0.016
Southern & Eastern Europe	12	35.3%	1	5.9%			
Western Asia	9	26.5%	2	11.8%			
Southern & South-eastern Asia	5	14.7%	8	47.1%			
Africa	8	23.5%	6	35.3%			

<sup>1</sup>) t-test; <sup>2</sup>) Chi square test; <sup>3</sup>) Fisher's exact test

The two diagnostic groups did not differ significantly on demographic characteristics, except for the geographic region of origin ( $p=0.016$ , Fisher's exact test, Table 1): refugees with PTSD-SP came more often from West Asian and in particular from South and East European countries, whereas refugees from South and South-East Asian were overrepresented in the schizophrenia group.

### Clinical features

Table 2 shows a detailed comparison of the PANSS ratings between the PTSD-SP and the schizophrenia group.

**Table 2** PANSS: Comparison of positive, negative, and general psychopathology scores in the PTSD-SP group and the schizophrenia group

	PTSD-SP N=34		Schizophrenia N=17		t	df	p-value (2-tailed)	effect size <sup>b</sup>
	Mean	SD	Mean	SD				
Hallucinations	3.97	1.31	3.94	2.22	.050	21,76	.960	0.02
Hyperactivity	2.47	1.46	2.35	1.73	.255	49	.800	0.08
Hostility	1.71	1.17	1.82	1.47	-.311	49	.757	0.09
Delusions	3.53	1.83	4.00	1.73	-.881	49	.383	0.27
Suspiciousness/persecution	4.06	1.59	3.18	2.22	1.464	24,57	.156	0.49
Grandiosity	1.03	0.17	2.06	1.71	-2.472	16,16	<b>.025</b>	1.06
Conceptual disorganization	1.50	0.86	4.59	1.33	-8.728	22,98	<b>&lt;0.0001<sup>a</sup></b>	3.04
<b>Positive Scale</b>	18.26	5.40	21.94	6.09	-2.198	49	<b>.033</b>	0.67
Poor rapport	3.32	1.57	4.29	1.53	-2.097	49	<b>.041</b>	0.64
Passive/apathetic social withdrawal	3.56	1.67	4.71	1.49	-2.390	49	<b>.021</b>	0.72
Emotional withdrawal	3.06	1.58	4.41	1.77	-2.775	49	<b>.008</b>	0.84
Lack of spontaneity / conversation	3.06	1.54	4.47	1.51	-3.114	49	<b>.003</b>	0.94
Stereotyped thinking	2.56	1.33	4.00	1.77	-3.262	49	<b>.002</b>	0.99
Blunted affect	2.44	1.46	4.06	1.64	-3.581	49	<b>.0007<sup>a</sup></b>	1.09
Difficulty in abstract thinking	1.88	1.30	3.94	1.60	-4.940	49	<b>&lt;0.0001<sup>a</sup></b>	1.50
<b>Negative Scale</b>	19.88	7.29	29.88	9.15	-4.236	49	<b>0.0001<sup>a</sup></b>	1.28
Disturbance of volition	2.82	1.40	2.88	1.65	-.133	49	.895	0.04
Poor impulse control	2.44	1.64	2.53	1.77	-.177	49	.861	0.05
Preoccupation	1.88	1.25	1.76	1.64	.285	49	.777	0.09
Poor attention	2.26	1.16	2.12	1.36	.402	49	.690	0.12
Motor retardation	2.24	1.28	2.47	1.55	-.577	49	.567	0.17
Somatic concern	2.09	1.36	1.82	1.24	.676	49	.502	0.20
Disorientation	1.94	1.18	2.18	1.19	-.671	49	.506	0.20
Guilt feelings	2.18	1.87	1.41	1.46	1.602	39,90	.117	0.45
Active social avoidance	3.44	1.50	4.24	1.52	-1.773	49	.082	0.54
Unusual thought content	3.09	1.38	3.88	1.22	-2.012	49	.050	0.61
Uncooperativeness	1.59	0.93	2.65	1.97	-2.106	19,62	<b>.048</b>	0.80
Anxiety	4.18	1.34	2.18	1.67	4.635	49	<b>&lt;0.0001<sup>a</sup></b>	1.40
Tension	4.06	1.28	2.18	1.38	4.830	49	<b>&lt;0.0001<sup>a</sup></b>	1.46
Mannerisms and posturing	1.06	0.34	2.47	1.63	-3.543	16,72	<b>.003</b>	1.48
Depression	4.06	1.76	1.47	1.23	6.102	43,38	<b>&lt;0.0001<sup>a</sup></b>	1.65
Lack of judgment and insight	2.88	1.34	4.88	0.93	-5.505	49	<b>&lt;0.0001<sup>a</sup></b>	1.67
<b>General Psychopathology Scale</b>	42.21	11.14	41.12	14.69	.295	49	.769	0.09
<b>Total PANSS Score</b>	80.35	19.47	92.94	24.03	-2.011	49	.050	0.61

**Bold:** statistically significant without Bonferroni-corrections

<sup>a</sup> statistically significant after Bonferroni-corrections; <sup>b</sup> Cohen's d effect size: d<0.2: trivial; 0.2≤d≤0.5: medium effect; d>0.8: large effect



**Table 3** Additional clinical features on severity and course in PTSD-SP and schizophrenia

	PTSD-SP N=34		Schizophrenia N=17		t	df	p-value (2-tailed)	effect size R <sup>a</sup>
	Mean	SD	Mean	SD				
Severity depressive symptoms (HSCL)	3.21	0.54	2.14	0.80	5.01	23.54	<0.001	0.72
Severity anxiety symptoms (HSCL)	3.26	0.54	1.80	0.76	7.01	23.54	<0.001	0.82
Age of onset of the first psychotic episode	34.4	9.9	24.2	9.8	3.46	49	0.001	0.44
Duration of mental health care in months per year	7.61	4.1	7.63	5.9	-0.19	49	0.98	0.03
Number traumatic events (HTQ)	9.8	2.8	5.8	3.1	4.59	49	<0.001	0.55

<sup>a</sup>: Effect size R: <0.10 = trivial; 0.10-0.29 = small; 0.30-0.49 = medium; 0.50-0.69 = large; >0.70 = very large

Diagnostic groups did not differ on the PSYRATS ratings except for auditory hallucinations. These were significantly more severe in the PTSD-SP group (mean=29.1, SD=10.8) compared to the schizophrenia group (mean=19.1, SD=14.4) ( $t=2.52$ ,  $df=49$ ,  $p=0.018$ ). This was mainly attributable to the amount of negative content of the voices (mean=3.0, SD=1.5 versus mean=1.5, SD=1.5) ( $t=3.39$ ,  $df=49$ ,  $p=0.001$ ), the amount of experienced distress caused by voices (mean=3.2, SD=1.3 versus mean=1.6, SD=1.6) ( $t=3.36$ ,  $df=27.3$ ,  $p=0.002$ ), and the intensity of experienced distress induced by hearing voices (mean=3.1, SD=1.3 versus mean=1.6, SD=1.6) ( $t=3.28$ ,  $df=26.7$ ,  $p=0.003$ ). Additional features are presented in Table 3.

The mean duration between the onset of PTSD and the onset of the psychotic disorder in the PTSD-SP group was 4.5 years (SD=6.1). Of these patients 20.6% developed psychosis within 6 months after the onset of PTSD, 55.9% developed psychosis between 6 months and 5 years, and in 23.5% of the patients psychosis started more than 5 years after the onset of PTSD. The mean age of onset of PTSD in PTSD-SP patients was around 30 years (SD=12.7 years) of age (median=29 years).

**Table 4** DSM-IV comorbidity in the 'PTSD-SP' and the 'Schizophrenia' group

Comorbidity	PTSD-SP (N=34)		Schizophrenia (N=17)	
	N	%	N	%
Anxiety disorders				
Generalized anxiety disorder	12	35.3	-	-
Panic disorder	8	23.5	2	11.8
Phobic disorders				
Obsessive-compulsive disorder	3	8.8	-	-
PTSD <sup>a</sup>	-	-	4	23.5
Affective disorders				
Major depressive disorder	20	58.8	-	-
Dysthymic disorder	7	20.6	-	-
Other disorders				
Somatoform disorders	10	29.4	2	11.8
Dissociative disorders	6	17.6	1	5.9
Alcohol or drug dependence	4	11.8	3	17.7
Sleepwalking disorder	1	2.9	-	-
Any comorbid disorder <sup>b</sup>				
No diagnosis	6	17.6	11	64.7
One diagnosis	5	14.7	2	11.8
Two diagnoses	7	20.6	2	11.8
Three diagnoses	2	5.9	-	-
Four or more diagnoses	14	41.1	2	11.8

### Comorbidity

Patients in the PTSD-SP group had about three times as many comorbid disorders as patients in the schizophrenia-group (mean 2.74, SD=2.19 versus 0.94, SD=1.68;  $t=2.96$ ,  $df=49$ ,  $p=0.005$ ), see Table 4. Hierarchy-free diagnostic algorithms showed the same results, indicating that, the comparative paucity of co-morbid disorders in the schizophrenia-group was not attributable to this hierarchy. Four of the 17 patients in the 'schizophrenia group' (23.5%) suffered from PTSD that developed after the onset of schizophrenia.

**Table 5** Variables contributed significantly to the model of predicting diagnostic group status of PTSD-SP versus schizophrenia

Variable	B	SE	p	odds ratio	95% CI
age of onset of the first psychotic episode	- 0.14	0.06	0.020	0.86	0.77-0.97
total negative symptoms score	0.15	0.07	0.021	1.16	1.02-1.32
number of experienced traumatic events	- 0.39	0.20	0.045	0.68	0.46-0.99

### Predicting diagnostic group status

Binary logistic regression analysis was applied to investigate whether a practical set of clinical features could predict diagnostic group status of the patients. Besides age and gender a set of four potential predictors was selected based on clinical usefulness: age of onset of the first psychotic episode, number of comorbid disorders, total score of negative symptoms, and number of experienced traumatic events.

These three variables predicted 90.2% of the patients correctly as belonging to the PTSD-SP or schizophrenia group (Nagelkerke's adjusted R Square = 0.73, sensitivity = 91%, specificity = 88%, positive predictive value = 94%, negative predictive value = 83%). The number of comorbid disorders did not contribute significantly to this model nor did age or gender.

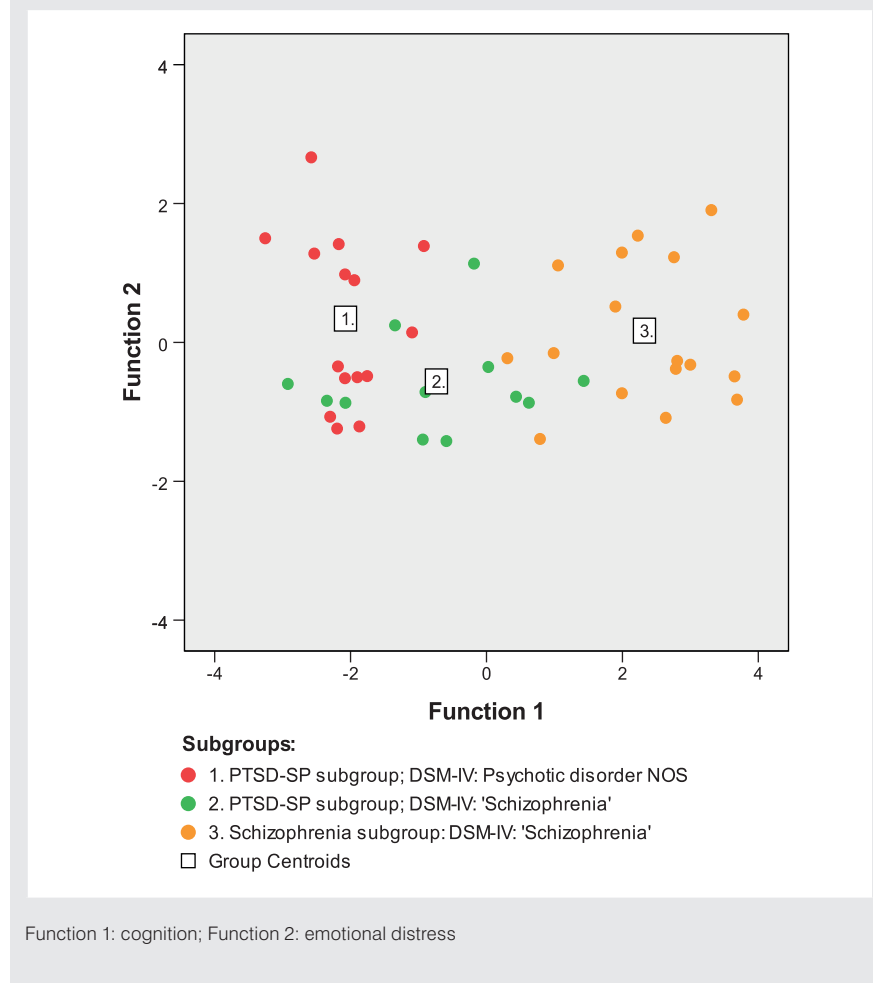
### PTSD-SP patients with and without a DSM-IV diagnosis of schizophrenia

In the schizophrenia group all patients met DSM-IV criteria for schizophrenia, but in the PTSD-SP group the DSM IV diagnostic algorithms produced four different types of DSM-labels: 'schizophrenia' (35.3%), 'schizoaffective disorder, depressive type' (11.8%), 'major depressive disorder, severe with psychotic features' (8.8%), and 'psychosis NOS' (44.1%).

First we were interested to know why part of the PTSD-SP sample did receive the diagnosis of schizophrenia, according to the current DSM classification system, while others did not. So we first compared PTSD-SP patients with DSM-IV schizophrenia (N=12) and PTSD-SP patients without DSM-IV schizophrenia ('psychosis NOS'; N=15) on all PANSS ratings using t-tests. There was only one significant difference between these two PTSD-SP subgroups: in the DSM-IV schizophrenia subgroup the mean score of delusions was 4.33 (SD=1.16), while the mean score in the DSM-IV psychosis NOS subgroup was 2.33 (SD=1.63) ( $t=-3.72$ ,  $df=24.9$ ,  $p=0.001$ ).

In order to test whether the PANSS symptom profile of patients in the PTSD-SP subgroup diagnosed as DSM-IV 'schizophrenia' was more similar to the patients in the schizophrenia group of the current study or more similar to the psychotic disorder NOS subgroup, we conducted a MANOVA followed by discriminant analysis on these three groups: (1) the schizophrenia group (N=17); (2) the PTSD-SP subgroup

**Figure 2** Canonical discriminant functions of three subgroups: 1. PTSD-SP subgroup classified by DSM IV as 'psychotic disorder NOS'(n=15); 2. PTSD-SP subgroup classified by DSM IV as 'schizophrenia' (n=12); 3. Schizophrenia group classified by DSM IV as 'schizophrenia' (n=17).



classified by DSM IV as 'schizophrenia' (N=12); and (3) the PTSD-SP subgroup classified by DSM IV as 'psychotic disorder NOS' (N=15). We excluded PTSD-SP subjects with the other two DSM-IV diagnoses '*schizoaffective disorder, depressive type*' (N=4), and '*major depressive disorder, severe with psychotic features*' (N=3), due to the small numbers. Due to restricted power we did not use all PANSS items for this analysis but only those seven items that were significantly different ( $p < 0.001$ ) between the PTSD-SP and the schizophrenia group (see Figure 2).

Patients from both PTSD-SP subgroups (i.e. DSM-IV 'psychotic disorder NOS' and DSM-IV 'schizophrenia') were both significantly different from patients in the schizophrenia group based on their PANSS ratings. Using Pillai's trace, there was a significant effect of group status on relevant PANSS symptoms ( $V = 0.93$ ,  $p < 0.001$ ). MANOVA was followed by discriminant analysis, which revealed two discriminant functions. The first function mainly consisted of cognitive symptoms ('conceptual disorganization', 'lack of judgement and insight', and 'difficulty in abstract thinking') and explained 96.5% of the variance (canonical  $R^2 = 0.80$ ;  $p < 0.001$ ). The second function mainly consisted of emotional distress and explained only 3.5% of the variance (canonical  $R^2 = 0.13$ ) and did not add significantly to the model ( $p = 0.53$ ). The correlations between diagnosis and discriminant function revealed that 'conceptual disorganization' ( $r = 0.77$ ) and 'lack of judgement and insight' ( $r = 0.53$ ) contributed most to the discriminant function. This analysis revealed that patients of the PTSD-SP subgroup meeting DSM-IV criteria of schizophrenia were most similar to the PTSD-SP subgroup meeting DSM-IV criteria of psychotic disorder NOS, whereas both PTSD-SP subgroups together were significantly different from patients of the schizophrenia group of which all patients met DSM IV criteria of schizophrenia.

## Discussion

PTSD with secondary psychotic features can be distinguished by clinical features from schizophrenia. A single prerequisite, whether PTSD preceded psychosis (PTSD-SP) or not (schizophrenia), defined two groups of chronic psychotic patients with considerable differences on many PANSS and some of the PSYRATS ratings. Patients of the PTSD-SP group had considerably less negative symptoms and less disorganisation than is commonly seen in schizophrenia and had more affective distress and more stress due to auditory hallucinations compared to patients in the schizophrenia group in this study. In addition, patients in the PTSD-SP group had many more comorbid disorders than patients in the schizophrenia group. PTSD-SP patients were also more depressed and anxious than patients suffering from schizophrenia and were more frequently traumatized. Another important feature that distinguished PTSD-SP from schizophrenia patients was that the first psychotic

symptoms in PTSD-SP patients started more than 10 years later than in schizophrenia, at least in males. These data, together with the MANOVA and discriminant analysis, suggest that PTSD-SP could be clinically different from schizophrenia and that PTSD-SP might be a valid new nosological entity.

Several other authors have published data that favour the classification of PTSD-SP as a separate diagnostic entity distinct from schizophrenia (2). For example, Sautter et al. (10) concluded that unlike schizophrenia, PTSD-SP was not associated with increased rates of familial psychosis. This suggests that PTSD-SP is a condition dissimilar to schizophrenia, since in the latter case family aggregation would be expected. This is supported by another study in which positive psychotic symptoms in patients with psychotic PTSD did not improve on risperidone treatment compared to placebo (23). Improvement would be expected if these symptoms were part of conventional psychotic disorders like schizophrenia or psychosis in bipolar disorder. The presence of unexpectedly low response rates in patients with PTSD-SP may indicate a different pathophysiology. Other studies report additional differences in biological features between schizophrenia and PTSD-SP, such as disparities in corticotrophin releasing hormone (CRH) and dopamine beta-hydroxylase ( $D\beta H$ ) levels, and differences in smooth pursuit eye movements (24).

It is difficult to directly compare our findings with those of Hamner et al (11), because of the differences in sample (mixed gender sample of multi-ethnic refugees vs. male U.S. combat veterans) and differences in diagnostic procedures. Despite these important differences, we also found hallucinations to be similar in schizophrenia and PTSD-SP and conceptual disorganization to be much more severe in the schizophrenia group. However we did not find delusions to be more severe in the schizophrenia group nor did we find negative symptoms to be equally severe in both groups.

In our sample there were no other additional comorbid conditions that could account for the presence of psychotic symptoms in the 'PTSD-SP group'. The most prevalent comorbid disorder in our sample that is known to have a psychotic subtype is major depressive disorder. Major depressive disorder with psychotic features might be responsible for the psychotic features in patients suffering from PTSD, suggesting that PTSD-SP, although different from schizophrenia, is not necessarily a valid separate nosological entity (12, 25). However, 41% of the PTSD-SP group in our study did not have a major depressive disorder, whereas in the remaining 59% only three patients (8.8%) were diagnosed as DSM-IV 'major depressive disorder with psychotic features'. These findings suggest that major depressive disorder is unlikely to account for the psychotic features in these patients; a finding similar to previous studies (1, 4) This conclusion is further supported by a study demonstrating that blood plasma levels of dopamine-beta-hydroxylase are increased in PTSD-SP patients while they are decreased in patients with major depressive disorder with psychotic features (26).

Our study has both strengths and limitations. The main strengths are the transparent way in which PTSD-SP and schizophrenia groups are separated, and the broad and in depth range of standardized symptom assessments. There are also limitations that should be considered. First, the sample sizes are fairly small. However, despite small sample sizes and notwithstanding adjustment of multiple comparisons, many significant differences between the groups were observed. Furthermore in order to support the correct interpretation by the readers, we added effect sizes if appropriate. Second, the differences in region of origin between the two groups may have influenced the results. However, there are no clear indications why and how that this should be the case. Third, there is growing evidence that (severe) childhood trauma contributes to the development of psychosis and schizophrenia in adult life (27, 28). Unfortunately, childhood trauma was not assessed in the current study and as a consequence we do not know whether (severe) childhood trauma is associated with (and thus a potential risk factor for the development of) PTSD-SP. Future research should clarify this issue. Another possible limitation of our study might be sampling-bias. The median age of onset of PTSD in our PTSD-SP patients was 29 years. Cross-national population studies point to a wide distribution in the median age of onset of PTSD (between 25 and 53 years of age) and a broad inter-quartile range (IQR) of the age of onset (15 to 75 years) (29, 30). The median age of onset of our refugee sample clearly fits in this wide distribution. In a Dutch study the median age of onset of PTSD was 28 years in a representative random sample of non-institutionalized inhabitants (31), while in the neighboring Belgium the median age of onset was 53 years in the adult general population (32). Sample selection may have had an influence on the median age of onset of PTSD also in our study among refugees. Finally, memory impairment or recall bias is known to exist in both patients with psychotic disorders and patients with PTSD. This poses some limitations regarding the accuracy of the retrospective assessments of the exact start of the chronic disorders in our sample and the amount and severity of life events. On the other hand, it is well known that trauma reports based on memories show at least fair to moderate test-retest reliability (33).

Culturally determined idioms of distress may play an important role in the pathoplasticity of psychotic symptoms (34-36). In a number of studies, African-American patients are reported to present with more symptoms and more severe psychotic symptoms than an otherwise similar group of Caucasian patients, independent of their diagnosis (37, 38). Similar findings were recently reported for Moroccan immigrant compared to native patients in the Netherlands (39, 40). The presence of these psychotic symptoms in patients with non-schizophrenic disorders may increase the risk of a misdiagnosis of schizophrenia (36, 37). In a study of 193 African- and Euro-American patients presenting for hospitalization with psychosis Arnold et al concluded that African-American patients had a higher number of first rank psychotic

symptoms, as well as more severe ones, compared to Euro-American patients (41). These African-American patients did not have increased rates of schizophrenia. Therefore, these differences may reflect ethnic and cultural differences in the symptomatic presentations of psychotic disorders and the authors warned against the risk of a misdiagnosis of schizophrenia. An alternative diagnosis of some of these patients might be PTSD-SP. Indeed, several studies have mentioned that non-Caucasian ethnicity might be a risk factor for PTSD-SP (42-44). To our knowledge, only one study was designed to test the hypothesis that ethnicity may influence the clinical presentation and symptom pattern in PTSD-SP (42). They concluded that African-Americans with PTSD endorsed more positive symptoms of psychosis, without higher rates of primary psychosis, depression, or anxiety than Caucasians. In our study PTSD-SP was seen in different groups of patients from a range of different cultures and with different trauma experiences. They were all refugees who left their country of origin and fled to the Netherlands. This fact increases the risk of developing PTSD (and possibly PTSD-SP) since, as reported by several studies on refugees mental health, protective factors are less likely to be present, such as the presence of an extended family, the opportunity to engage in meaningful cultural traditional practices or to recover from traumatic experiences in the local community with family of friends with informal support systems (45, 46). Symptoms were reported to be more severe in patients, like in our study, who were displaced and spend a long time in asylum-camps (46-49). Taking this all into account we assume that PTSD-SP is not just a cultural specific syndrome. The potential influence of psychosocial and cultural factors in the development of PTSD-SP is certainly an issue for future research.

## Conclusions

In conclusion, our study supports the validity of a new diagnostic entity called 'posttraumatic stress disorder with secondary psychotic features'. However, given the limited size and the specific nature of the sample and given the cross-sectional design, generalization of the main findings awaits replication in future research. Nevertheless our results are in line with result of several other studies mainly conducted among samples of war veterans.

Based on previous reviews (2, 24) and the current empirical study several criteria for PTSD-SP, as a provisional diagnostic entity, are beginning to take shape and should be exposed to future research:

- diagnostic DSM-IV TR criteria of PTSD should be met,
- positive psychotic symptoms such as delusions and/or hallucinations,
- no formal thought disorder,
- no conceptual disorganization,



- little lack of judgment or insight,
- generally later age of onset of psychosis compared to schizophrenia,
- psychotic features are not confined exclusively to episodes of re-experiencing or flashbacks, PTSD precedes the onset of psychotic features, and,
- no history of psychotic episodes prior to the traumatic event(s).

In addition to the importance of identifying PTSD in patients with psychotic disorders, we would like to add that clinicians should also notice whether the psychotic disorder preceded or followed the onset of PTSD. This distinction might prove to be important since in patients with PTSD-SP common treatment protocols used in schizophrenia often fail while treatment strategies used in the treatment of PTSD seem to have some beneficial effect (23, 24, 50). However intervention studies are still rare and further validation of PTSD-SP is necessary in order to pave the road for desired specific treatment intervention studies in the future.

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## Chapter 5

### **Psychosis in posttraumatic stress disorder**

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## Abstract

Posttraumatic stress disorder (PTSD) is associated with the occurrence of secondary psychotic features, complicating treatment and resulting in negative outcomes. Some authors have suggested that PTSD with secondary psychotic features (PTSD-SP) is a diagnostic subtype of PTSD or even a separate diagnostic entity. However, other studies suggest that these psychotic features are just a form of psychiatric comorbidity, or a more severe form of re-experiencing symptoms, possibly related to a more severe or to specific kinds of traumatic events. In this study we, therefore, explore the nature of the association between PTSD and secondary psychotic features. In a cross sectional study among refugees, inpatients with PTSD with secondary psychotic features (PTSD-SP) (N=34) were compared to patients with PTSD without psychotic features (N=24) in terms of the prevalence of mental disorders associated with psychotic features, the intensity and frequency of PTSD-symptoms, and, the severity and kind of experienced traumatic events.

The presence of secondary psychotic features in patients suffering from PTSD cannot be accounted for by psychiatric comorbid conditions, severity of re-experiencing or the severity of traumatic events. Together, these findings are less compatible with PTSD-SP as a subtype of PTSD than with PTSD-SP as a separate diagnostic entity.

## Introduction

Posttraumatic stress disorder (PTSD) is associated with an increased prevalence of psychotic symptoms both in the general population (odds ratio = 1,83) and in psychiatric out-patients (odds ratio 3.48) (1, 2). In part, this association has been explained by the fact that patients with schizophrenia are more likely to develop PTSD due to a higher risk of experiencing traumatic events related to their psychosis (3, 4). However, there is also a high co-occurrence of PTSD and psychosis in patients who do not suffer from schizophrenia. In this paper we focus on this latter condition, which has been labelled 'posttraumatic stress disorder with secondary psychosis' (PTSD-SP) (5-8). In this condition, patients who already developed PTSD, sooner or later started to suffer from delusions and hallucinations as well. These positive psychotic symptoms were not confined to episodes of re-experiencing or flashbacks, and, there was no history of schizophrenia prior to the onset of PTSD. In a previous paper, we have shown that PTSD-SP is not likely to belong to the schizophrenia spectrum (Braakman *et al.*, submitted).

Therefore, in this study, we investigate whether PTSD is more likely to be a subtype of PTSD or a separate diagnostic entity. First we explore the possibility that the psychotic symptoms in PTSD-SP can they be explained by other comorbid conditions common in PTSD, as Gaudiano and Zimmerman stated, such as major depressive disorder (affective psychosis) or substance-induced disorders (intoxication or withdrawal delirium) (1). Second, we investigate the possibility that the severity of the re-experiencing cluster in PTSD is associated with the presence of secondary psychotic symptoms in PTSD (9). Finally, we test whether more severe or specific traumatic events are associated with the presence of secondary psychotic symptoms in PTSD (10).

It is expected that improved diagnostic and etiological clarity might pave the road for future research into new treatment-approaches of this severe and chronic condition that does not respond adequately to the usual treatment options (6, 11).

## Methods

### Participants

We recruited two groups of refugee inpatients: refugees seeking treatment for PTSD patients without psychosis, and refugees seeking treatment for PTSD with secondary psychotic features. Patients were recruited in two mental health hospitals in The Netherlands that provide inpatient treatment for refugees. Participants were a consecutive sample of refugees who fled to the Netherlands from different parts of the world, were admitted to one of these two clinical facilities and met the following screening criteria: being a refugee, aged 16 years or older, at least one DSM IV PTSD



symptom or at least one psychotic symptom. All subjects meeting screening criteria were asked informed consent to participate in this study. Informed consent was obtained from all participants, and all study procedures were approved by the Dutch Mental Health Ethical Review Board (METIGG).

### Diagnostic assessment and group allocation

All psychiatric diagnoses were based on extensive assessments with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (12). The SCAN has been shown to be cross-culturally valid and applicable (13). All patients with a DSM-IV diagnosis PTSD were included. Patients with comorbid bipolar disorder, organic mental disorders or malingering were excluded. Similar to Sautter et al (8), we defined the group of patients with posttraumatic stress disorder and secondary psychotic features ('PTSD-SP-group') as those patients with DSM-IV PTSD and one or more psychotic symptoms, and with the onset of PTSD preceding the onset of the first psychotic symptom. Patients with psychotic symptoms prior to the onset of PTSD were excluded from this report. PTSD patients without current or life time psychotic features constituted the 'PTSD group'. Patients of this PTSD-group met the PTSD criteria of the DSM IV and had no positive psychotic features outside re-experiencing episodes. We carefully distinguished psychotic symptoms from flashback episodes in which reliving the experience, illusions, and dissociative flashback episodes can occur. These latter symptoms were interpreted as part of the PTSD diagnosis. The Clinical History Schedule (CHS) of the SCAN provided dates on the onset of symptoms and disorders.

### Symptom measures

The Clinician Administered PTSD Scale (CAPS) was used for a detailed assessment of the frequency and intensity of PTSD symptoms (14). The CAPS was performed by an experienced psychiatrist blinded for diagnostic group status. Severity of emotional distress (anxiety and depressive symptoms) was assessed with the Hopkins Symptoms Checklist (HSCL-25) (15). Finally, traumatic events were measured with the Harvard Trauma Questionnaire (HTQ). Cross-cultural psychometric properties of HTQ and HSCL-25 are adequate for the study population (16). The HTQ measures events that are most prevalent among refugees. The CAPS also contains a trauma-list in order to assess more general traumatic events, not specific for refugees (15, 17). All scales were completed in interviews by psychologists, blinded to diagnostic group status. In 80% of all interviews professional interpreters were required.

### Data analysis

Sample size was calculated with G-power 3.1.3 (18). We were mainly interested in clinically relevant differences between the two groups. Therefore power calculations were based on large effect sizes (Cohen's  $d = 0.8$ ). Given a two-sided alpha of 0.05 and a power of 0.80 we needed to include at least 52 patients to be divided into two groups. Variables were tested for normal distribution and homogeneity of variance. All tests were two-sided and  $p$ -values  $< 0.05$  were considered significant. Effect sizes were computed if appropriate. Group differences were tested using  $t$ -tests for continuous variables and Fisher's exact tests for categorical variables. If parametric assumptions were not met, independent samples Mann-Whitney tests were performed. All statistical data analyses were performed using PASW Statistics 18.0 for Windows (SPSS/IBM Inc, Chicago, IL).

## Results

### Sample characteristics

A total of 150 consecutive inpatients were screened for eligibility. Using the inclusion and exclusion criteria mentioned before, the final study population consisted of 58 subjects, 16 females and 42 males (Figure 1). Of these, 24 suffered from PTSD without psychotic features and 34 from PTSD with secondary psychotic features (PTSD-SP). Basic demographic variables were comparable for both groups (Table 1) except for region of origin. Patients originating from southern and eastern Europe were overrepresented in the PTSD-SP group, whereas patients from Africa and from southern and southeastern Asia were underrepresented in the PTSD-SP group. Patients in the total sample of 58 subjects belonged to 31 different ethnic groups.

In both groups the mean age of onset of PTSD was around 30 years of age. Patients suffering from PTSD-SP left their country of origin about 2.4 years after the onset of PTSD (95%CI = 1.3 to 3.5 years) while the PTSD group fled around the time of onset of PTSD (95%CI = -1.6 to 1.3 years;  $t=2.97$ ,  $df=54$ ,  $p=0.004$ ). (Two extreme outliers from the PTSD-SP group were excluded (deviated  $>5$  SD from the mean, remaining data were normally distributed).

Ten of the 34 patients with PTSD-SP (29,4%) developed their first psychosis before seeking refuge in the Netherlands, whereas nine patients (26,5%) became psychotic around their date of arrival in the Netherlands and 15 patients (44.1%) during the first years after arriving in the Netherlands. The mean length of residence in the Netherlands at the time of assessment was 7.3 years in the PTSD group (95%CI = 5.5 to 9.1 years) which was significantly longer than the length in the PTSD-SP group: 4,8 years (95%CI = 4.0 to 5.7 years;  $t=2.79$ ,  $df=56$ ,  $p=0,015$ ).

**Figure 1** Recruitment flow chart: subjects with 'PTSD and secondary psychotic features' and subjects with PTSD without psychosis

<b>Admissions</b>		150
<b>Did not meet entry criteria</b>	29	↓
<b>Eligible</b> (at least one PTSD symptom or at least one psychotic symptom)		121
Excluded due to short stay (< 2 months)	16	↓
Unable to test due to organic disorder or mutism	2	↓
Refused consent	17	↓
<b>Consented and SCAN assessment</b>		86
Excluded after SCAN assessment due to: bipolar disorder (n=4) missing data due to incomplete testing (> 2 missing symptom measures) (n=3) other diagnoses (subthreshold PTSD, n=2) malingering (n=2)	24	↓
<b>PTSD</b>		62
First psychotic episode prior to onset of PTSD	4	↓
<b>Remaining participants</b>		58
<b>Study groups</b>	24	34
	<b>'PTSD group'</b>	<b>'PTSD-SP group'</b>
	PTSD without psychosis	PTSD precedes the onset of first psychotic episode

**Table 1** Comparison of demographic sample characteristics of PTSD and PTSD-SP

	PTSD (N=24)	PTSD-SP (N=34)			
	Mean (SD) or N (%)	Mean (SD) or N (%)	df	Test- statistic	p-value (2-tailed)
<b>Age</b> in years	38.08 (11.82)	38.59 (9.99)	56	- 0.176 <sup>1)</sup>	0.860
<b>Sex</b> males N (%)	16 (66.7%)	27 (79.4%)	1	1.192 <sup>2)</sup>	0.275
<b>Marital status</b>				6.144 <sup>3)</sup>	0.072
Married	9 (37.5%)	20 (58.8%)			
Single	8 (33.3%)	12 (35.3%)			
Divorced	6 (25.0%)	2 (5.9%)			
Widowed	1 (4.2%)	-			
<b>Years of education</b>	10.0 (4.94)	8.5 (4.64)	52	1.156 <sup>1)</sup>	0.250
<b>Religion</b>				0.326 <sup>3)</sup>	0.878
Islamic	10 (41.7%)	13 (38.2%)			
Christian	11 (45.8%)	15 (44.1%)			
Other	3 (12.5%)	6 (17.6%)			
<b>Region of origin</b>				9.441 <sup>3)</sup>	0.022
Southern & Eastern Europe	1 (4.2%)	12 (35.3%)			
Western Asia	6 (25.0%)	9 (26.5%)			
Southern & Southeastern Asia	7 (29.2%)	5 (14.7%)			
Africa	10 (41.7%)	8 (23.5%)			

<sup>1)</sup> t-statistic; <sup>2)</sup> Chi-square <sup>3)</sup> Fisher's exact test

### PTSD-SP and comorbidity

Comorbidity of both groups is summarized in Table 2. The vast majority in both groups had one or more current comorbid psychiatric disorders (83.3% in the PTSD group and 85.3% in the PTSD-SP group).

Due to the higher percentage of patients in the PTSD-SP group with more than four comorbid disorders, patients in the PTSD-SP group had numerically more current comorbid disorders (mean 2.58; SD=1.97) than patients in the PTSD group (mean=1.83, SD=1.37), but this difference was not significant ( $t=1.72$ ,  $df=55.9$ ,  $p =$

**Table 2** DSM-IV comorbidity in the PTSD group and the PTSD-SP group

Comorbidity	PTSD (N=24)		PTSD-SP (N=34)		PTSD-SP versus PTSD Odds ratio	95% Confidence interval
	N	%	N	%		
<b>Anxiety disorders</b>						
Generalized anxiety disorder	7	29.2	12	35.3	1.32	0.43-4.09
Panic disorder	3	12.5	8	23.5	2.15	0.51-9.15
Phobic disorders	2	8.3	6	17.6	2.36	0.43-12.84
Obsessive-compulsive disorder	-	-	3	8.8	-	-
<i>Any anxiety disorder (in addition to PTSD)</i>	7	29.2	18	52.9	2.73	0.90-8.28
<b>Affective disorders</b>						
Major depressive disorder	10	41.7	23	67.6	2.93	0.99-8.65
Dysthymic disorder	5	20.8	7	20.6	0.99	0.27-3.58
<i>Any affective disorder</i>	14	58.4	26	76.5	2.32	0.75-7.22
<b>Other disorders</b>						
Somatoform disorders	4	16.7	10	29.4	2.08	0.57-7.66
Dissociative disorders	3	12.5	6	17.6	1.50	0.34-6.70
Alcohol or drug dependence	6	25.0	4	11.8	0.4	0.10-1.61
Sleepwalking disorder	1	4.2	1	2.9	0.7	0.04-11.72
<b>Any comorbid disorder</b>						
No diagnosis	4	16.7	5	14.7	0.86	0.21-3.61
One diagnosis	8	33.3	7	20.6	0.52	0.16-1.70
Two diagnoses	4	16.7	7	20.6	1.30	0.33-5.04
Three diagnoses	4	16.7	3	8.8	0.48	0.10-2.39
Four or more diagnoses	4	16.7	12	35.3	2.73	0.76-9.84

0.091). In both groups, the most frequent comorbid disorder group was major depressive disorder (41.7% vs. 67.6% in PTSD and PTSD-SP, respectively) followed by GAD (29.2% vs. 35.3%), but the differences between the groups were not significant. The prevalence of alcohol or drug dependence was numerically higher in the PTSD group compared to the PTSD-SP group (25.0% vs. 11.8 %, respectively), but again this difference was not significant.

In the PTSD-SP group, 23 patients (67.6%) met criteria for a comorbid major depressive disorder and in only three of these patients the SCAN algorithm resulted in a diagnosis of major depressive episode with psychotic features. In 19 out of 23 PTSD-SP patients suffering from a current comorbid major depressive disorder the temporal relationship between the start of the depressive episode and the start of the psychotic episode could be assessed. In 12 of these 19 patients the depressive episode started after the onset of the psychotic episode, whereas in three patients the depressive disorder started around the same time as the psychotic episode, and in four patients the depressive disorder started before the onset of the psychotic episode.

### PTSD symptomatology

Overall the CAPS revealed no significant differences in the prevalence or the intensity in PTSD symptoms. The only exception was 'avoidance and numbing' which was more intense in PTSD-SP group ( $p=0,002$ ) with a large effect size (Cohen's  $d = 0.92$ ).

### PTSD and emotional distress

The mean HSCL-25 depressive symptom and mean anxiety symptom scores were not significantly different between the two diagnostic groups. However, the mean HSCL-25 emotional distress score was significantly higher in the PTSD-SP group (mean = 3.24, SD = 0.49) than in the PTSD group (mean = 2.98, SD = 0.41;  $t = 2.074$ ,  $df = 56$ ,  $p = 0.043$ ;  $d = 0.58$ ).

### PTSD-SP and type and severity of traumatic events

The HTQ did not show significant differences in the type of experienced traumatic events between PTSD and PTSD-SP subjects (Table 3). In addition, no difference was found in the mean total number of experienced traumatic events: 10,3 (SD=4,1) in the PTSD-SP group versus 9,9 (SD=3,0) in the PTSD-group ( $t=0,31$ ;  $df = 56$   $p=0,755$ ). The most frequent reported trauma in both groups was 'being close to death'.

The trauma rates determined with the CAPS showed no differences in experienced events: mean 9,7 events (SD=2.4) in PTSD group vs. mean 8,4 events (SD=2.6) in the PTSD-SP group ( $t=1,7$ ;  $df = 56$   $p=0.085$ ) (data not shown).

**Table 3** Comparing types of experienced traumatic events between the PTSD group and the PTSD-SP group assessed by the Harvard Trauma Questionnaire (HTQ)

	PTSD (N=24)		PTSD-SP (N=34)	
	N	%	N	%
Being close to death	17	70,8%	24	70,6%
Combat situation	16	66,7%	18	52,9%
Unnatural death of family or friend	16	66,7%	16	50,0%
Torture	16	66,7%	28	82,4%
Lack of food or water	15	62,5%	23	67,6%
Serious injury	15	62,5%	24	70,6%
Forced isolation from others	15	62,5%	25	78,1%
Lost or kidnapped	15	62,5%	20	66,7%
Lack of shelter	14	58,3%	16	47,1%
Murder of family or friend	14	58,3%	18	56,3%
Forced separation from family members	13	56,5%	27	84,4%
Murder of stranger or strangers	13	56,5%	16	48,5%
Imprisonment	13	54,2%	23	67,6%
Ill health without access to medical care	12	50,0%	23	67,6%
Rape or sexual abuse	9	37,5%	12	38,7%
Brainwashing	8	34,8%	9	29,0%
Any other situation that was very frightening or you felt your life was in danger	20	83,3%	28	87,5%

## Discussion

Our main finding is that the emergence of psychotic symptoms after the onset of PTSD is not associated with and can thus not be explained by the presence of comorbid psychiatric disorders or the nature and severity of traumatic experiences..

### Psychosis in PTSD-SP due to comorbidity?

#### *Major depressive disorder*

Major depressive disorder is the most common comorbid condition in the PTSD-SP group. However, the current data indicate that the presence of psychotic symptoms is not attributable to comorbid major depressive disorder. First, 11 of the 34 patients with PTSD-SP (32.4%) did not have a current diagnosis of major depressive disorder. Second, our data regarding the temporal relationships make it unattainable that comorbid major depressive disorder could account for the presence of psychotic features in the majority of patients, because the psychotic symptoms emerged before the onset of major depressive disorder in more than half of the patients with a mean time lag of more than three years. These findings are supported by several earlier clinical studies among US male war veterans (6) and one biological study in which plasma dopamine-beta-hydroxylase (DbH), the enzyme catalysing the synthesis of norepinephrine from dopamine, has shown to be increased in patients with PTSD and psychotic features compared to patients with PTSD without psychotic features (19), whereas plasma DbH is decreased in patients with major depression with psychotic features (20-22).

#### *Substance-induced disorders*

PTSD and substance use disorders frequently co-occur. Moreover substance use disorders are associated with the occurrence of psychotic features during intoxication or withdrawal. However, in the study only 4 of the 34 patients with PTSD-SP (11.8%) met criteria for and alcohol or drug use disorder and substance use disorders did not occur more frequently in PTSD-SP patients (11.8%) than in PTSD patients (25.0%). Therefore, it seems unlikely that this type of comorbidity is responsible for long lasting psychotic symptoms in patients with PTSD.

In our study, none of the comorbid conditions known to be associated with psychosis were more frequent in the PTSD-SP group compared to the PTSD-group. These results are in contrast to a recent study by Gaudio and Zimmerman (1). In their study among 378 PTSD patients, the rate of patients with PTSD and psychosis (n=38) dropped from 17% to only 2.5% (one patient) after excluding patients with comorbid conditions also known to be associated with psychotic symptoms. The authors suggested that it is the cumulative effect of a number of comorbid disorders that accounts for the strong association of PTSD with psychotic symptoms. It should



be noted, however, that Gaudio and Zimmerman did not have data on the timing of the onset of psychotic symptoms and the temporal relationship with the psychotic symptoms and the comorbid disorders. In our study, temporal relationships revealed that comorbidity cannot explain the presence of psychosis in PTSD.

### **Psychosis in PTSD-SP linked to re-experiencing cluster of PTSD?**

The CAPS data show that none of the posttraumatic stress symptoms are more frequent in PTSD-SP patients than in PTSD without psychotic symptoms. The same is true for the intensity of PTSD symptoms with the exception of the avoidance cluster (more intense in the PTSD-SP group). The fact that frequency and intensity of the re-experiencing symptoms are similar in both groups suggests that the presence of psychotic symptoms cannot be explained by increased levels of re-experiencing, including intrusive memories and flashbacks. These findings are consistent with those of Sautter et al. in a population of US male war veterans (23).

### **Psychosis in PTSD-SP linked to trauma?**

Both patients suffering from PTSD and those suffering from PTSD-SP experienced a high but very similar amount of traumatic events according to the HTQ and the CAPS. Neither the type of traumas nor their severity can explain the occurrence of psychotic symptoms in patients with PTSD-SP. These findings are consistent with the results of other studies among US war veterans. Wilcox et al. (24) found no association between the length of exposure in combat and the presence of auditory hallucinations. Hamner (25) reported that PTSD with psychotic features was not associated with impact of events, and Sautter et al. (23) have demonstrated that psychotic features of PTSD-SP were not related to combat exposure.

### **Study limitations**

The major limitations of this study are its retrospective design and the limited sample size. Moreover, recall bias cannot be excluded, although there is no empirical evidence that recall difficulties differ between PTSD and PTSD-SP patients.

The main strength of the current study is that we were able to produce a more detailed description of the differences between PTSD patients with and without psychotic features than other studies. Prior studies had to rely on lifetime prevalence rates and were not able to take into account the temporal sequence of psychosis, PTSD and psychiatric comorbidity (1, 2, 7).

### **Conclusions**

None of the comorbid conditions known to be associated with psychosis were more frequent in the PTSD-SP group compared to the PTSD-group without psychotic features. This makes it unlikely that comorbidity is a plausible explanation for the

presence of psychotic features in PTSD-SP patients as was previously suggested by Gaudio and Zimmerman (1). In addition, neither frequency/intensity of PTSD symptoms nor frequency/type of traumatic events were related to the presence of psychosis in patients with PTSD. Together, these findings are less compatible with PTSD-SP as a subtype of PTSD than with PTSD-SP as a separate diagnostic entity. Elucidating its aetiology and acknowledging PTSD-SP as a diagnostic entity will promote indispensable research into effective treatment options for this complex and often treatment resistant condition.

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## Chapter 6

### **Plasma dopamine beta-hydroxylase activity is not increased in posttraumatic stress disorder with secondary psychotic features**

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## Abstract

**Aim:** The presence of secondary psychotic symptoms in patients with a posttraumatic stress disorder (PTSD-SP) complicates treatment compared to simple posttraumatic stress disorder (PTSD). A previous study among patients with PTSD and PTSD-SP suggested that the vulnerability towards developing psychotic symptoms in PTSD is associated with increased activity of dopamine beta-hydroxylase (D $\beta$ H), a critical enzyme in the synthesis of noradrenalin from dopamine. The present study aimed to validate these findings in a larger, mixed gender, multi-ethnic sample, also including patients with schizophrenia, in order to evaluate whether plasma D $\beta$ H activity is a biological marker for PTSD-SP. In addition, we also evaluated *DBH* -1021C>T (rs1611115) genotype because D $\beta$ H plasma levels are under strong genetic control.

**Methods:** In a cross-sectional study, D $\beta$ H plasma activity and *DBH* -1021C>T genotype were assessed in a consecutive series of patients with PTSD (n=17), PTSD-SP (n=27), schizophrenia (n=13) and in healthy controls (n=20).

**Results:** *DBH* -1021C>T genotype was strongly associated with plasma D $\beta$ H activity in the ethnically heterogeneous sample (51.3% variance explained). However mean plasma D $\beta$ H activity in patients with PTSD-SP was not different from that of patients with schizophrenia or PTSD or from that of health individuals, even after taking *DBH* -1021C>T genotype into account. The presence or absence of major depressive disorder in patients with PTSD-SP was not related to plasma D $\beta$ H activity either.

**Conclusions:** Plasma D $\beta$ H activity does not seem to be a suitable biological marker for discriminating patients with PTSD from patients with PTSD-SP or schizophrenia.

## Introduction

Posttraumatic stress disorder (PTSD) is frequently complicated by the co-occurrence of psychotic symptoms (1). There is increasing evidence that this condition called 'posttraumatic stress disorder with secondary psychotic features' (PTSD-SP) has biological characteristics that are distinct from those of schizophrenia as well as those of PTSD without psychotic features (2, 3). About 15 years ago, Hamner and Gold published the results of an, as yet not replicated, study in which they reported an increased level of blood plasma activity of the enzyme dopamine  $\beta$ -hydroxylase (D $\beta$ H) in patients with PTSD-SP compared to patients with PTSD without psychosis and to healthy controls (4). This finding is remarkable, since studies in several other psychiatric disorders with psychotic features have consistently found an association between lower plasma D $\beta$ H and psychotic features (5).

D $\beta$ H is a critical enzyme that catalyzes the synthesis of noradrenalin from dopamine in sympathetic noradrenergic neurons. D $\beta$ H enters the plasma after vesicular release from those neurons and the adrenal medulla (6). D $\beta$ H plasma activity is very stable within subjects after the age of 5 years (5, 7) and thus is more 'trait' than 'state' related. Longitudinal repeated measures vary no more than 5-10% within subjects (7). However, inter-individual variation is high, due to the *DBH* -1021C>T (rs1611115) genetic single-nucleotide polymorphism in the 5' flanking region of the *DBH* gene (8, 9). Therefore, Cubells and Zabetian recommended in their review on D $\beta$ H and psychiatric disorders to perform genotype-controlled studies (5). In three different ethnic groups (European Americans, African-Americans and ethnic Japanese), lowest mean levels of plasma D $\beta$ H activity were found in homozygous TT subjects, CT heterozygotes showed intermediate mean levels, and CC homozygous subjects showed the highest mean levels. This polymorphism accounts for 35–52% of the inter-individual variations in plasma D $\beta$ H activity (5, 10, 11) within and across different ethnic groups. The association of the *DBH* -1021C>T polymorphism to plasma D $\beta$ H activity was found to be far stronger than that of eleven other assessed SNPs evenly spaced across the *D $\beta$ H* gene (5, 10).

The purpose of the current study was to validate Hamner and Gold's findings (4) in a larger, more varied group of subjects. We aimed to test whether *DBH* -1021C>T genotype-controlled D $\beta$ H plasma activity levels can be used as a biological marker for the development of psychosis in PTSD as some authors have suggested (4, 12). Hamner and Gold's study had a very small sample size (6 patients with PTSD and psychosis and 13 patients with only PTSD), patients with PTSD and psychosis were not clearly defined, no patients with schizophrenia were included, and differences in *DBH* genotype or major depressive disorder were not taken into account as potential



confounders. Therefore, in the present study we included more patients with PTSD and psychosis, we clearly defined PTSD-SP as a condition in which PTSD preceded the onset of psychotic features, and we included a group of patients with a diagnosis of schizophrenia that was not preceded by PTSD. To be a useful biological marker for PTSD-SP, plasma D $\beta$ H activity should at least be different between patients with PTSD-SP and healthy controls and/or patients with adjoining conditions like PTSD without psychotic features or schizophrenia. Since the majority of patients with PTSD-SP suffer from comorbid major depressive disorder and several studies have reported correlations between D $\beta$ H plasma levels and major depressive disorder with psychotic features (7, 9, 13), we also evaluated possible confounding by major depressive disorder. Where Hamner and Gold's study was conducted among male US war veterans with combat-related PTSD we included male and female refugees suffering from different kinds of traumatic events in our study. Taking into consideration the *DBH* -1021C>T genotype enabled us to adjust for the differences in the ethnic of the diagnostic groups.

In addition to attempting to validate Hamner and Gold's findings, we also tested the hypothesis that plasma D $\beta$ H activity was decreased in the schizophrenia group compared to normal controls and PTSD-SP patients. Finally, we hypothesized that there would be no direct relation between plasma D $\beta$ H activity and major depressive disorder. If patients with PTSD-SP and major depressive disorder would be found to have lower levels of plasma D $\beta$ H activity this would strongly suggest that these patients suffered from major depressive disorder with psychotic features, a condition shown to be associated with low D $\beta$ H activity. In that case, PTSD-SP would less likely be a separate diagnostic entity.

## Materials and Methods

### Subject recruitment

This cross-sectional study recruited three groups of patients:

1. PTSD-SP: we defined this group of patients with posttraumatic stress disorder and secondary psychotic features similar to Sautter et al (14), as patients with DSM-IV PTSD and psychotic symptoms, in whom the onset of PTSD preceded the onset of psychosis. We carefully distinguished psychotic symptoms from (dissociative) flashback episodes with illusions and hallucinations while reliving the experience. These latter symptoms were interpreted as part of the conventional DSM-IV diagnostic criteria for PTSD.
2. PTSD: patients in the PTSD-group met the PTSD criteria of the DSM-IV and had no lifetime positive psychotic features outside re-experiencing episodes.

3. Schizophrenia: the schizophrenia group was defined as those patients meeting DSM-IV criteria of schizophrenia with no history of PTSD prior to the onset of the first psychotic episode.

In all groups, subjects with bipolar disorder, organic mental disorders or malingering were excluded. Patients were recruited from two mental health hospitals in The Netherlands that provide inpatient treatment to refugees originating from many parts of the world. Consecutive sampling was applied with recruitment of recently admitted patients meeting the following screening criteria: being a refugee, 16 years or older and showing at least one DSM-IV PTSD symptom or at least one psychotic symptom. After complete oral and written information about the study was given to the participants, written informed consent was obtained, together with the patient's representative if applicable. Subsequently, the main diagnoses and comorbid disorders of patients were assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (15). The SCAN has been shown to be cross-culturally valid and applicable (16).

Besides these three patient groups, healthy controls were recruited from non-genetically related family members, friends or acquaintances as well as subjects from regional refugee asylums. They were screened for the presence of psychiatric disorders with the Composite International Diagnostic Interview (CIDI), developed by the World Health Organization (17, 18). The CIDI is a cross-culturally validated diagnostic screening instrument and is well-fitted for use in the general population. Subjects meeting CIDI diagnostic criteria for any psychiatric diagnosis were excluded.

Professional interpreters assisted in 80% of all interviews. All study procedures were approved by the Mental Health Institutions Ethical Review Board (METIGG).

### Dopamine $\beta$ -hydroxylase activity and DBH genotyping

All blood samples were collected between 9 and 11 a.m. to avoid potential diurnal variation of D $\beta$ H plasma activity in individuals. Blood samples were prepared and stored at -70°C awaiting batch-wise analysis. All laboratory staff was blinded for group status. D $\beta$ H activity was measured as follows (19): serum samples (50  $\mu$ l) were mixed on ice with 100  $\mu$ l water, 70  $\mu$ l catalase (70 mg/ml in water; Sigma, St.Louis,USA) and 780  $\mu$ l substrate buffer (250 mM Na-acetate [pH 5.0], 37.5 mM N-ethylmaleimide, 31.25  $\mu$ M CuSO<sub>4</sub>, 0.5  $\mu$ M paragyline (Sigma), 125 mM Vitamin C, 125 mM Na-fumarate and 50 mM dopamine HCl). As a negative control 100  $\mu$ l of 1mM fusaric acid (an inhibitor of D $\beta$ H, Sigma) was used instead of water. Samples were then incubated at 37°C for 25 minutes and put on ice again. Reaction was stopped by the addition of 120  $\mu$ l perchloric acid (60%) and 30  $\mu$ l of 3,4-dihydroxybenzylamine hydrobromide

(DHBA, Sigma, 1 mM). Samples were vortexed and centrifuged at 13,000\*g for 5 minutes. 700  $\mu$ l of supernatant was loaded on a Sephadex G10 column, which was subsequently washed with 2 ml 0.03% formic acid and eluted with 2 ml 0.03% formic acid. To 1 ml of eluate 100  $\mu$ l of reagent 3 of a catecholamine assay (catecholamine kit 195-5841/N, Acidic Reagent 195-6093 Reagent 3; Bio-rad, Hercules, California, USA) was added. The samples were analysed on an Allsphere ODS(2) column (25 cm-4.6 mm-5  $\mu$ m) (Altech, Breda, The Netherlands). Mobile phase consisted of 25 mM citric acid, 25 mM Na<sub>2</sub>HPO<sub>4</sub>·2H<sub>2</sub>O, 0,7 mM sodium octanesulfonic acid (NaOcs), 6.5 mM NaCl and 0,27 mM NaEDTA, 4% methanol, pH 3.5. The detection was performed by using an electrochemical detector (ESA, 425 mV; Interscience) at a flow of 1.50 ml/min. Enzyme activity was expressed in units per liter; 1 U/l was defined as the amount of enzyme needed to convert 1 M dopamine into 1 M noradrenalin per minute.

Genotyping of *D $\beta$ H* was carried out at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre. High molecular weight DNA was isolated from full blood, stored at -70°C before analysis. The *D $\beta$ H* -1021C>T (rs1611115) polymorphism was genotyped using Taqman analysis (assay ID: C\_11592758\_10; Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). Genotyping was carried out in a volume of 10  $\mu$ l containing 10ng of genomic DNA, 5  $\mu$ l of Taqman 2x Mastermix (Applied Biosystems), 0.375  $\mu$ l of the Taqman assay and 3.625  $\mu$ l of water. Genotyping was performed on a 7500 Fast Real-Time PCR System and genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). The genotyping assay had been validated before use. Testing for Hardy–Weinberg equilibrium did not show deviations from the expected genotype distribution ( $P > 0.05$ ).

### Statistical methods

Variables were tested for normality with the Kolmogorov-Smirnov test. Homogeneity of variance was assessed with Levene's test. We used (factorial) ANOVA and ANCOVA to assess group differences in D $\beta$ H levels and chi square tests or Fisher's exact tests for differences in categorical demographic variables. We used Sidak's correction to correct for multiple comparisons. All tests were two-sided and p-values < 0.05 corrected for multiple testing were considered significant. All statistical analyses were performed using PASW Statistics 18.0 for Windows (SPSS/IBM Inc, Chicago, IL). Sample size need was calculated with G\*power (20). Based on Hamner and Gold's reported large effect size (4) we set eta-squared at 0.14 and, with alpha set at 0.05 and power at 0.80, a total sample size of 72 subjects appeared to be required.

## Results

### Sample characteristics

A total of 77 subjects participated in the study (Table 1), 17 with PTSD, 27 with PTSD-SP, 13 with schizophrenia and 20 healthy controls. Except for region of origin no significant differences were found between the groups. Religion was equally distributed between groups except for the healthy controls in whom Islamic subjects appeared to be overrepresented, although this effect was not statistically significant ( $p = 0.67$ ).

### Genotype and plasma D $\beta$ H activity

In the 77 subjects, the CC genotype was found in 62.3% ( $n = 48$ ), CT genotype in 33.8% ( $n = 26$ ), and 3.9% ( $n = 3$ ) carried the TT genotype. As expected, there was a highly significant effect of genotype on plasma D $\beta$ H activity ( $F(2,74) = 27.1$ ;  $p < 0.001$ ) with a mean plasma D $\beta$ H activity of 28.3 U/l (95% CI = 23.1 - 33.6) in the CC group, 15.6 U/l (95% CI = 11.5 - 19.7) in the CT group and, 1.1 U/l (95% CI = -0.2 - 2.4) in the TT group, respectively. Consistent with earlier findings, the distribution of plasma D $\beta$ H activity was significantly non-normal (K-S test:  $D(78) = 0.120$ ,  $p = 0.008$ ) (9, 11) and therefore further analyses were performed on square-root transformed values. Since Levene's test for homogeneity of variances was significant ( $p = 0.006$ ) the one-way ANOVA was repeated with the square-root plasma D $\beta$ H activity as dependent variable. This also resulted in a significant effect of genotype on square-root D $\beta$ H plasma levels ( $F = 13.2$ ,  $df = 2$ ,  $p < 0.001$ ,  $\eta^2 = 0.26$ ): 51.3% of the variance of square-root D $\beta$ H plasma levels in this multiethnic sample was explained by the *DBH* -1021C>T genotype.

### Diagnosis and D $\beta$ H plasma levels

To assess the effect of D $\beta$ H genotype on the relation between the square root of the D $\beta$ H plasma activity and diagnostic group, we first assessed in a 2-way ANOVA whether the effect of diagnostic group on mean D $\beta$ H plasma activity was modified by *DBH* genotype. This interaction effect was not significant ( $F(4,67) = 0.94$ ;  $p = 0.445$ , partial  $\eta^2 = 0.05$ ) and subsequently the interaction term 'diagnostic group \* *DBH*' was removed from the model. In this simplified model the square root of the the D $\beta$ H plasma activity was not significantly related to diagnostic group ( $F(3,73) = 2.20$ ;  $p = 0.09$ ,  $\eta^2 = 0.08$ ). Overall, plasma D $\beta$ H activity was lower in the schizophrenia group compared to healthy controls (3.73 versus 5.10), but this difference was not statistically significant (see Table 2).

In Figure 1 the mean square root plasma D $\beta$ H activity of the four groups is represented by CC and CT genotype. TT genotype is not shown in this figure since only two of the four groups contain TT genotype and the numbers ( $n = 3$ ) are too small.

**Table 1** Sociodemographic characteristics of the four study groups

	PTSD (N = 17)	PTSD-SP (N = 27)	Schizophrenia (N = 13)	Controls (N = 20)		
	Mean or N (SD or %)	Mean or N (SD or %)	Mean or N (SD or %)	Mean or N (SD or %)	Test statistic	p-value (2-sided)
<b>Age in years</b>	39.2(11.7)	39.0(9.9)	36.6(11.0)	35.0(10.5)	3	0.74 <sup>1</sup>
<b>Sex</b>					-	1.75 <sup>2</sup>
Male	13(76.5%)	21(77.8%)	11(84.6%)	13(65%)		
Female	4(23.5%)	6(22.2%)	2(15.4%)	7(35%)		
<b>Marital status</b>					3	1.83 <sup>3</sup>
Married	11(68.8%)	17(63%)	6(46.2%)	11(55.0%)		
Single	5(31.3%)	10(37%)	7(53.8%)	9(45.0%)		
<b>Religion</b>					-	4.05 <sup>2</sup>
Christian	7(41.2%)	9(33.3%)	4(30.8%)	3(15%)		
Islamic	8(47.1%)	13(48.1%)	6(46.2%)	13(65%)		
Other	2(11.8%)	5(18.5%)	3(23.1%)	4(20%)		
<b>Region of origin</b>					-	26.00 <sup>2</sup>
Southern & Eastern Europe	1 (5.9%)	11(40.7%)	1(7.7%)	0(0%)		
Western Asia	5(29.4%)	7(25.9%)	2(15.4%)	7(35%)		
Southern & South-east Asia	4(23.5%)	4(14.8%)	6(46.2%)	9(45%)		
Africa	7(41.2%)	5(18.5%)	4(30.8%)	2(10%)		
Other	0(0%)	0(0%)	0(0%)	2(10%)		

<sup>1</sup> = F-statistic ANOVA, <sup>2</sup> = Fisher's exact test, <sup>3</sup> = Chi square

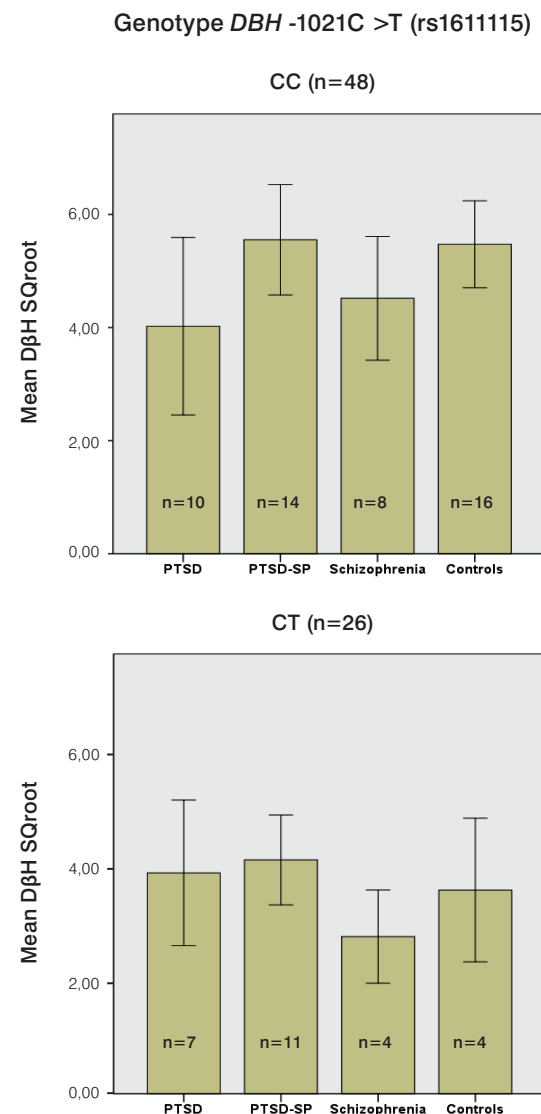
**Table 2** Plasma D $\beta$ H and DBH genotype findings in the four diagnostic groups

	PTSD (n=17)	PTSD-SP (n=27)	Schizophrenia (n=13)	Controls (n=20)		Effect size: Eta <sup>2</sup>
Plasma D $\beta$ H U/l Mean (SD)	19.04 (17.81)	24.91 (18.40)	16.03 (11.56)	28.21 (16.34)		
SQRoot Plasma D $\beta$ H Mean (SD) all genotype groups	3.98 (1.86)	4.63 (1.89)	3.73 (1.52)	5.10 (1.53)	F=2.20; p=0.09	0.08 <sup>1</sup>
SQRoot Plasma D $\beta$ H C/C genotype group Mean (SD)	4.02 (2.20)	5.56 (1.69)	4.52 (1.31)	5.47 (1.44)	F=2.28; p=0.093	0.13 <sup>1</sup>
SQRoot Plasma D $\beta$ H C/T genotype group Mean (SD)	3.91 (1.39)	4.13 (1.18)	2.78 (0.52)	3.60 (0.70)	F=1.46; p=0.25	0.17 <sup>1</sup>
SQRoot Plasma D $\beta$ H T/T genotype group Mean (SD)	-	0.92 (0.31)	1.23 -	-	-	-
D $\beta$ H 1021 C>T genotype N (%)	10 (58.8%)	14 (51.9%)	8 (61.5%)	16 (80%)	X <sup>2</sup> =5.76; p=0.39 <sup>3</sup>	
	C/T	7 (41.2%)	4 (30.8%)	4 (20%)		
	T/T	-	1 (7.7%)	-		

1. 2 way ANOVA

2. two-sided Fisher's exact test

**Figure 1** Mean square root plasma D $\beta$ H activity in four diagnostic groups by DBH -1021C>T genotype (CC,CT)



Error bars: 95% CI

### D $\beta$ H and major depressive disorder

Finally we evaluated a possible correlation between plasma D $\beta$ H activity and major depressive disorder in patients suffering from PTSD-SP. Within the PTSD-SP group we compared genotype-controlled D $\beta$ H plasma activity between patients with and without major depressive disorder. Since TT genotype frequency was very low in the PTSD-SP group (n=2) this genotype was excluded from this subanalysis. Major depressive disorder was not associated with DBH genotype ( $X^2(1) = 0.001$ ,  $p = 0.65$ ). The mean plasma D $\beta$ H activity in PTSD-SP patients with major depression (n=16) was higher (30.4 U/l; 95%CI= 22.2 - 38.7) than in PTSD-SP patients (n=9) without depression (20.5 U/l; 95%CI = 9.5-31.5), but this difference was not statistically significant ( $F(1,22) = 2.25$ ,  $p = 0.15$ , partial  $\eta^2=0.09$ ).

### Discussion

This study did not find increased plasma D $\beta$ H activity in PTSD-SP patients compared to PTSD patients or to healthy controls. Therefore, the current study did not validate the findings of Hamner and Gold (4). However, in line with earlier studies in subjects of European-American, African-American, Japanese, German and Croatian ancestry (11, 12, 21), this study confirmed, in a heterogeneous ethnic population, that plasma D $\beta$ H activity is strongly associated with DBH -1012C>T genotype, with TT, CT, and, CC genotype showing low, intermediate and high plasma levels of D $\beta$ H activity, respectively.

This inconsistency of our results and the increased levels of plasma D $\beta$ H activity in PTSD-SP patients found by Hamner and Gold is unlikely to be explained by the lack of genetic control in the Hamner and Gold study, since also genetically uncorrected plasma D $\beta$ H activity did not differ between the groups in our study. In addition, mean plasma D $\beta$ H activity did not differ significantly between the schizophrenia group and the healthy controls. The latter is not surprising given the fact that plasma D $\beta$ H activity was only found to be decreased in familial paranoid schizophrenia and not in other types of schizophrenia (5, 22). In our sample we did not differentiate between different schizophrenia subtypes, given sample size restrictions, and no information was available on the family history of schizophrenia patients. Finally, plasma D $\beta$ H activity did also not differ between the schizophrenia group and the PTSD-SP and PTSD groups. Thus, based on these findings (genotype-controlled) plasma D $\beta$ H activity is not a suitable biological marker to discriminate between PTSD, PTSD-SP and schizophrenia, nor is it suitable for differentiation of any of these disorders and healthy controls.

Interestingly, plasma D $\beta$ H activity was not decreased in PTSD-SP subjects with major depressive disorder compared to PTSD-SP without major depressive disorder:



there was even a non-significant trend for patients with PTSD-SP and major depressive disorder to have higher mean plasma D $\beta$ H activity compared to PTSD-SP patients without major depressive disorder. Patients with major depressive disorder with psychotic features have consistently shown to have lower levels of plasma D $\beta$ H activity compared to healthy controls (7, 9, 13, 23-25). Our findings therefore indicate that the presence of psychotic features in patients with PTSD-SP is unlikely to be explained by the presence of major depressive disorder with psychotic features since in that case plasma D $\beta$ H activity would have been decreased.

The role of plasma D $\beta$ H activity in PTSD-SP or in PTSD is still not fully understood. Mustaphic et al. found decreased levels of plasma D $\beta$ H activity in war veterans homozygous for the *DBH* -1012C>T CC genotype compared to healthy subjects (12). We nor Hamner and Gold found these decreased levels (4). The role of D $\beta$ H, dopamine as well as noradrenalin in PTSD and PTSD-SP is complex and remains unclear. Cubells and Zabetian (2004) suggested that lower plasma D $\beta$ H activity are associated with higher vulnerability for psychosis, both in schizophrenia, major depressive disorder with psychotic features and paranoia after cocaine self-administration (26). Indeed D $\beta$ H inhibitors like fusaric acid and disulfiram predispose humans to psychosis (5). Low levels of D $\beta$ H predicted disulfiram-induced psychosis in alcoholics (27), and inhibitors of D $\beta$ H elevated dopamine/noradrenalin ratios (28) leading to psychosis. Cubells and Zabetian postulated a metabolic 'bottleneck': low D $\beta$ H levels could lead to less efficient conversion of dopamine to noradrenalin and hence to an elevated dopamine/noradrenalin ratio potentially leading to psychotic symptoms (5). This is in line with recent research in which hyperresponsiveness of the hypothalamic pituitary adrenal axis (as observed in PTSD) leads to (subcortical) dopaminergic dysregulation and psychotic symptoms (29-32).

Even though our study included more subjects than that by Hamner and Gold, the main weakness is still a limited sample size and thus a limited power to detect existing differences between groups. In addition we were not able to control for medication exposure. Most included patients used antidepressants and/or antipsychotics, and there is at least one study indicating that antipsychotics could decrease plasma D $\beta$ H levels (33), although most authors agree that plasma D $\beta$ H is a stable trait and not highly variable within individuals. Finally, biological studies, especially those including genetic data, can lead to non-significant results when conducted in ethnically and genetically non-homogenous samples like ours.

The current study clearly shows that the presence or absence of major depressive disorder in patients with PTSD-SP is not related to plasma D $\beta$ H activity suggesting that psychotic features in patients suffering from PTSD-SP and major depressive disorder are unlikely to be explained by the co-occurring major depressive disorder. This last finding strengthens the position that PTSD-SP is a distinct subtype of PTSD

and not a variation of a major depressive disorder with psychotic features. Clinically this implies that patients with co-occurring PTSD, psychosis and major depressive disorder should not automatically be diagnosed or treated as patients with major depressive disorder with psychotic features. Instead, new treatment studies for patients suffering from PTSD with secondary psychosis (PTSD-SP) with or without concurrent depression are required.

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## Chapter 7

### **General discussion**

## General discussion

*“Psychiatry is in the position—that most of medicine was in 200 years ago—of still having to define most of its disorders by their syndromes. Because of the consequent need to distinguish one disorder from another by differences between syndromes, the validity of diagnostic concepts remains an important issue in psychiatry” (1)*

## Introduction

This thesis examined the validity of ‘posttraumatic stress disorder with secondary psychotic features’ (PTSD-SP) as a separate diagnostic entity. First, we systematically evaluated the existing literature (in Chapter 2 and 3) using the validation strategy delineated by Robins and Guze (2) and refined by others (1, 3-5). This strategy designated six criteria and all of them should be used simultaneously to assess the validity of a diagnostic concept:

1. Clinical description: identification and description of PTSD-SP
2. Delineation: clear boundaries of PTSD-SP with other, related, syndromes
3. Course: typical course and outcome of PTSD-SP
4. Treatment response: typical treatment effect in PTSD-SP
5. Family studies: PTSD-SP runs in families
6. Biological correlates related to PTSD-SP

With these criteria in mind, we assessed the validity of PTSD-SP as a separate diagnostic entity looking both at findings supporting and findings challenging the hypothesis that PTSD-SP is a separate diagnostic entity. In addition, we tried to identify domains in need for more scientific data to further elucidate the validity of the PTSD-SP-concept (Chapter 2 and Chapter 3). Subsequently, we designed and conducted a study to resolve some of the remaining questions. This study focused on three of the six previously mentioned validity-criteria: clinical description, delineation from other syndromes, and biological correlates. In this final chapter we summarize our findings and conclusions and discuss the clinical implications and some suggestions for future research.



## The evidence base of PTSD-SP as a separate syndrome

In this paragraph we discuss the available findings regarding the six criteria needed to accept PTSD-SP as a separate diagnostic entity. For each criterion, we start with a summary of the results from our reviews of the literature followed by the results of our own study and ending with an integration of these findings and a conclusion about each criterion.

### Clinical description: identification and description of PTSD-SP

#### *Results from our review (Chapter 2) and additional recent literature*

**Symptoms:** A number of comparative studies have reported on patients first presenting a full-blown PTSD and subsequently reporting hallucinations and delusions. The nature of their hallucinations was mainly related to traumatic events and the content of their delusions was mainly paranoid and/or persecutory. These psychotic features were chronic and did not occur exclusively in the context of a re-experiencing episode but were persistently present (see our review in Chapter 2). Patients with PTSD-SP seemed to suffer from a high burden of disease, similar to patients with schizophrenia and more than patients with PTSD without psychotic features (6). Since our review, several case-reports and case-series were published confirming this symptom pattern (7, 8). There was only one exception. In our review the presence of psychotic features was found not to be associated with the severity of PTSD as measured by the Clinician Administered PTSD Scale (CAPS) (Chapter 2), whereas in a recent study by Pivac et al. (9), patients with PTSD-SP reported much higher CAPS scores than PTSD patients (104.1 +/- 8.0 vs. 69.0 +/- 12.1).

**Traumatic events:** Several studies have reported a dose-response relationship between the number of traumatic events, especially in childhood, and the risk of psychosis later in life (10-12). In a large community-based survey Scott et al. (13) found a significant dose-response relationship between the number and types of traumatic events and the endorsement of delusional experiences. In addition, Saha et al. (14) found in a large community sample that delusional-like experiences were not only increased in subjects with first exposure to trauma in childhood, but also in subjects with first exposure to trauma in adolescence or adulthood. However, in clinical populations of patients suffering from PTSD (mainly male US military veterans) with mainly adulthood trauma's, the risk of subsequent manifestations of psychotic features was not related to the number, severity or the kind of traumatic events (see our review in Chapter 2).

**Age of onset:** In studies until 2008, age of onset of PTSD-SP has not been addressed systematically. Based on the studies included in our review (Chapter 2) we can only say that PTSD-SP seems to emerge in early adulthood or later in life (e.g. in war veterans).

### *Results from our study (Chapter 4 and Chapter 5)*

**Symptoms:** The symptom pattern of PTSD-SP in our population of refugees was very similar to the symptom pattern in PTSD-SP patients described in our review of, mostly, war veterans. Severity of visual hallucinations and delusions in our PTSD-SP patients was similar to our patients with schizophrenia. However, auditory hallucinations were more severe in the PTSD-SP group compared to the schizophrenia group. This was mainly attributable to a more pronounced negative content of the voices and the higher intensity of experienced distress induced by hearing voices. Table 1 shows that our patients with PTSD-SP were much less disorganized, showed considerably fewer negative symptoms and reported much higher levels of anxiety, depression and tension than our patients with schizophrenia. Moreover, as a group, our patients with PTSD-SP had a better insight in their problems than our patients with schizophrenia.

In our study, the Clinician Administered PTSD Scale (CAPS) revealed no significant differences between our patients with PTSD or PTSD-SP in the prevalence and the intensity in PTSD symptoms, with the exception of 'avoidance and numbing' which was much more intense in the PTSD-SP group.

Finally, in our PTSD-SP group, the mean duration between the onset of PTSD and the onset of the psychotic symptoms was 4.5 years (SD=6.1); 20.6% developed a psychosis within 6 months after the onset of PTSD, 55.9% developed psychosis between 6 months and 5 years after the onset of PTSD, and in 23.5% of the patients the psychosis started more than 5 years after the onset of PTSD.

**Age of onset:** In our study we found a large and significant difference in the mean age of onset of the first psychotic episode between patients with PTSD-SP (34.4 years) and patients with schizophrenia (24.2 years) (Chapter 4).

**Traumatic events:** In our study among refugees, like in clinical studies among war veterans, we found no differences in severity or the types of traumatic events between patients with PTSD-SP and patients with PTSD (Chapter 5). However, patients with PTSD-SP did experience more severe traumatic events than patients with schizophrenia. Ill health without access to medical care and rape or sexual abuse was reported much more often by the PTSD-SP group than by the schizophrenia group.

### *Clinical description and the validity of PTSD-SP as a separate diagnostic entity*

The fact that we found a symptom pattern in our patients with PTSD-SP that was distinct from our patients with schizophrenia and the fact that this symptom pattern in these patients with PTSD-SP in a multi-ethnic, mixed gender civilian population was very similar to the symptom pattern reported in studies among mainly male U.S. war veterans with PTSD-SP, strengthens the validity of PTSD-SP as a diagnostic concept.

The same applies for the fact that neither the type nor the severity of traumatic experiences seems to be related to the risk of developing psychotic features after the onset of PTSD. Like Hamner (1997), we found no differences in PTSD symptom severity between patients with PTSD and patients with PTSD-SP (15); Chapter 4). However, in a recent study, Pivac et al. (9) found much higher CAPS scores in PTSD-SP patients than in PTSD patients; an inconsistency that needs further explanation. Finally, the discrepancy between the age of onset of first psychosis in the schizophrenia group and the PTSD-SP group is an important and significant distinction and favors the validity of PTSD-SP and helps us to delineate PTSD-SP from schizophrenia. In the next pages we take a more detailed look at the issues of delineation.

### **Delineation: boundaries of PTSD-SP with other, related, syndromes**

#### ***Results from our review (Chapter 2) and additional recent literature***

**Psychotic symptoms:** Sareen et al. (16) examined the association of PTSD and positive psychotic symptoms in data from the U.S. National Comorbidity Survey Part II, a general population study with 5,877 participants. They found a strong association between PTSD and the presence of psychotic symptoms. Even after adjusting for a range of covariates, including psychiatric comorbidity, the relationship between PTSD and psychotic symptoms remained significant. This is in contrast with the findings of a more recent study among 1,800 U.S. psychiatric out-patients (17). In their report, the authors concluded that after excluding comorbid conditions, in which psychotic symptoms were prevalent, rates of psychotic PTSD dropped dramatically and only one patient with “pure” PTSD-SP was left. In a re-analysis of the previously mentioned data from the U.S. National Comorbidity Survey Part II, Shevlin et al. (18) excluded participants with a life time diagnosis of psychosis and applied latent class analysis to test whether a homogeneous group of PTSD patients could be identified with a psychotic subtype rather than simply a combination of PTSD and psychosis. Using this strategy, they found four groups of participants with PTSD, including two groups with a high probability of endorsing psychotic indicators. One of these two groups consisted of subjects with a high probability of PTSD symptoms in combination with a high probability of psychotic symptoms. The other group was characterized by a combination of a high probability of psychotic symptoms and a lower probability of PTSD symptoms. Unfortunately, none of the three studies made a clear and systematic distinction between subjects with PTSD preceding the onset of psychotic symptoms and patients with psychotic symptoms who later developed PTSD.

**Schizophrenia:** In the reviews in Chapter 2 and Chapter 3 we also looked for evidence showing that PTSD-SP could be differentiated from schizophrenia. Differences in symptom profiles were reported between patients with PTSD-SP and schizophrenia. The content of hallucinations in PTSD-SP patients was in most cases

trauma-related, but often these same patients also suffered from hallucinations with non-trauma-related content. Delusions in PTSD-SP patients were mainly paranoid and persecutory in nature, whereas in patients with schizophrenia the delusions were often more complex and bizarre. Formal thought disorders (e.g. loose associations, incoherence, neologisms) were quite common in schizophrenia but rare in PTSD-SP. No differences were detected between PTSD-SP and schizophrenia in the presence of negative symptoms.

**Major depressive disorder:** Comorbidity of major depressive disorder and PTSD varied between studies from 44 to 84%. Comorbidity between major depressive disorder and PTSD-SP was even higher. Moreover, there was a strong correlation between the severity of PTSD symptoms and the severity of depressive symptoms in PTSD-SP patients. Also PANSS-ratings of psychosis in PTSD-SP patients with major depressive disorder were higher compared to PTSD-SP patients without a co-occurring major depressive disorder. These findings suggested that PTSD, depressive disorder and psychotic features are somehow interconnected in patients suffering from PTSD-SP. Based on these findings from the literature, it remained unclear to what extent psychotic features in PTSD-SP could be explained by the presence of a co-morbid psychotic depression.

**Dissociative disorders:** At the time of our review, there was only one study examining the co-occurrence of dissociative disorders and PTSD. In this study no relationship was observed between psychotic symptoms and dissociative features in patients with PTSD, as measured by the Dissociative Experience Scale (DES) (Chapter 2). However, a recent study by Anketell et al. (19) found a positive correlation between dissociative symptoms and PTSD in a group of chronic PTSD patients in Northern Ireland: PTSD patients with auditory hallucinatory experiences had higher scores on the dissociative experience scale compared to PTSD patients without auditory hallucinations. Unfortunately this study did not collect information on other comorbid conditions, e.g. schizophrenia was not excluded, and their assessments could not distinguish between benign hypnopompic/hypnagogic experiences and hallucinations or pseudo-hallucinations. Finally it remains unclear in this study whether auditory hallucinations were present prior to the onset of PTSD or appeared after the onset of PTSD.

**Substance-induced disorders:** No relationships were found in studies before 2008 between psychotic features in PTSD and alcohol or drug dependence, nor were psychotic features related to intoxication or withdrawal. A recent study (18) reported a significantly increased likelihood of a diagnosis of alcohol dependence in a group of PTSD patients characterized by high levels of psychotic features and high levels of PTSD symptoms. In this study, however, it remains unclear to what extent this group of PTSD patients is similar to the group of PTSD-SP patients, i.e. patients with PTSD and psychotic symptoms occurring after the onset of PTSD.

### **Results from our study (Chapter 4 and Chapter 5)**

**Schizophrenia:** Although the presence of positive psychotic symptoms was similar in our patients with PTSD-SP and our patients with schizophrenia, conceptual disorganization was less frequent in the PTSD-SP group. Importantly, our patients with PTSD-SP also reported markedly fewer negative symptoms, less lack of judgment and insight, much higher levels of anxiety and depression, and more comorbid psychiatric disorders compared to our patients with schizophrenia. Patients in the PTSD-SP group had about three times as many comorbid disorders as patients in the schizophrenia-group.

**Major depressive disorder:** In contrast to previous studies, we carefully analyzed the time of onset of PTSD, of psychosis and of major depressive disorder. About one-third of our PTSD-SP sample did not have a comorbid major depressive disorder and in 63% of the patients with PTSD-SP and a comorbid major depressive disorder the onset of the first psychosis preceded the onset of the depressive disorder. Based on this analysis, we concluded that the emergence of psychotic symptoms in PTSD-SP can generally not be accounted for by the presence of a preceding comorbid major depressive disorder (Chapter 5).

**Dissociative disorders:** The finding of a lack of association between dissociative problems and PTSD was confirmed in our study (Chapter 5): comorbid dissociative disorders occurred in only 18% of our PTSD-SP patients, which was very similar to and not significantly different from the 13% in our PTSD group.

**Substance-induced disorders:** We found not difference in prevalence of alcohol and drug use disorders between patients with PTSD-SP and PTSD (Chapter 5), confirming previous findings from the literature (Chapter 2). However, the question remains unanswered why these findings are not congruent with the findings of Shevlin et al. (2010) showing an increased likelihood of alcohol dependence in their 'high psychosis-high PTSD'-group (18).

### ***Delineation and the validity of PTSD-SP as a separate diagnostic entity***

Our study added new findings to support of the hypothesis that PTSD-SP can be delineated from other psychiatric disorders with psychotic features, such as schizophrenia, major depression with psychotic features, dissociative disorder, and substance-induced psychotic disorder. PTSD-SP and schizophrenia could be successfully differentiated by a limited set of clinical features: PTSD-SP patients had a much later age of onset of their first psychosis, PTSD-SP had remarkably fewer negative symptoms and PTSD-SP patients experienced many more traumatic events than patients with schizophrenia. In addition, as mentioned earlier, we found a much higher comorbidity in PTSD-SP compared to schizophrenia, a finding in line with the study by Shevlin et al., which identified a homogeneous high-psychosis and high-PTSD class which suffered from high comorbidity as well (18).

Our study also provided strong clinical evidence that the psychotic features in PTSD-SP were not part of a (pre-existing) major depressive disorder or a dissociative disorder.

### **Biological correlates related to PTSD-SP**

#### ***Results from our review (Chapter 2 and Chapter 3) and additional recent literature***

Our literature review suggested that platelet monoamine oxidase B (MAO-B) activity might be a useful biological marker of psychotic symptoms in PTSD-SP. Pivac et al. (20) found significant higher MAO-B activity in a group of war veterans with PTSD and psychotic symptoms compared to war veterans with only PTSD and war veterans without PTSD. However, until now very little is known about the pathophysiology behind this finding. In another report by Pivac et al. (21) war veterans with PTSD-SP had increased blood platelet-levels of serotonin (5-HT) activity compared to war veterans with PTSD, war veterans without PTSD and healthy controls.

Sautter studied differences in cerebrospinal fluid concentrations of corticotrophin-releasing hormone (CRH) and somatotropin-release-inhibiting hormone (SRIF) between 13 PTSD-SP patients, 8 patients with PTSD without psychosis and 8 healthy controls in an attempt to differentiate PTSD-SP as a subtype of PTSD from a schizophrenia-related condition with comorbid PTSD (22). If PTSD-SP would be a complicated subtype of PTSD they expected to find more extreme perturbations in the neuroendocrine patterns that characterize PTSD. They choose CRH and SRIF, because these hormones are known to be increased in PTSD (23, 24) and because CRH covaries with SRIF (25). They found significantly increased CRH in patients with PTSD-SP compared to patients with PTSD and healthy controls. SRIF was not significantly increased (22). Unfortunately, the study did not include patients with schizophrenia without PTSD.

In another study, PTSD-SP was associated with smooth pursuit eye movement (SPEM) deficits that were qualitatively different from SPEM-deficits in patients suffering from schizophrenia as well as healthy controls: PTSD-SP patients were deficient in higher velocity SPEM compared to patients with schizophrenia (26). Significantly elevated plasma dopamine beta-hydroxylase (D $\beta$ H) levels were observed in patients suffering from PTSD-SP compared to patients with non psychotic PTSD as well as compared to normal controls (Hamner and Gold, 1998). It is important to note that D $\beta$ H is involved in the metabolism of dopamine into noradrenalin in noradrenalin nerve terminals.

Finally, a recent study genotyped brain-derived neurotrophic factor (BDNF) Val166Met variants in 576 male Caucasian Croatian war veterans (9). War veterans with PTSD-SP (n=76) were more frequent carriers of one or two Met alleles than veterans with PTSD without secondary psychotic features (n=294) and combat-

exposed veterans without PTSD (n=206). BDNF Met alleles are associated with psychotic symptoms in Alzheimer patients and in patients with schizophrenia and other psychotic disorders (9, 27, 28). The BDNF Met allele has also been found to be associated with impaired fear extinction (29).

### **Results for our study (Chapter 6)**

We aimed to validate the D $\beta$ H plasma findings of Hamner and Gold (30) in a study with larger samples and patients with schizophrenia as an additional comparison group. Since D $\beta$ H plasma levels are under high genetic control we also controlled for potential differences in the *DBH* -1021C/T gene polymorphisms. We did not confirm the elevated D $\beta$ H plasma levels in PTSD-SP patients compared to healthy controls, neither before nor after controlling for group differences in the *DBH* -1021C/T polymorphism. We also failed to find differences in D $\beta$ H plasma levels between patients with PTSD-SP and patients with schizophrenia or patients with PTSD without psychotic features. In the group of patients homozygous for the C-allele at *DBH*-1021 we even found a decreased level of plasma D $\beta$ H in PTSD compared to PTSD-SP, which was no longer significant after controlling for multiple comparisons. We also used major depressive disorder as a covariate in the relation between plasma D $\beta$ H and PTSD-SP, because Cubells et al. (31) found in patients with major depressive disorder with psychotic features that the level of plasma D $\beta$ H was lower than in healthy controls. However, plasma D $\beta$ H levels in PTSD-SP were not lower than in PTSD in our sample and were not correlated with major depressive disorder and therefore we concluded that plasma D $\beta$ H is not a suitable biomarker for PTSD-SP and that the psychotic symptoms in PTSD-SP are not very likely to represent the presence of a comorbid major depressive disorder with psychotic features.

### **Biological correlates and the validity of PTSD-SP as a separate diagnostic entity**

Currently available studies provide some support for PTSD-SP as a separate diagnostic entity. For example, the SPEM study clearly delineates PTSD-SP from schizophrenia, whereas the studies on CRH, MAO-B, 5HT and BDNF all found biological differences between PTSD-SP versus non-psychotic PTSD and healthy controls. The findings of Sautter et al. (22) support the hypothesis that PTSD-SP is a severe subtype of PTSD since the neuroendocrine perturbations were similar but more extreme compared to PTSD patients. Interestingly, in contrast to earlier studies that found increased levels of CRH in PTSD-patients (23, 24), Sautter et al. found no increased CRH in non-psychotic PTSD patients compared to healthy controls. A possible explanation for this might be that in those earlier studies PTSD-SP patients were not identified as such and therefore not excluded. Thus the increased CRH found in those studies might be due to PTSD-SP subjects and not due to the

non-psychotic PTSD patients. A recent study provided support for this assumption since in that study PTSD-patients with psychotic symptoms were explicitly excluded and the remaining patients with non-psychotic PTSD did not show increased levels of CRH (32). Thus it might be that increased CRH is a feature of PTSD-SP and not of non-psychotic PTSD.

It should be noted, however, that (with the exception of plasma D $\beta$ H levels, Chapter 6) none of these biological studies have been replicated or validated in different settings or populations. and that our attempt the replicate the D $\beta$ H findings of Hamner en Gold (30) failed.

However, our D $\beta$ H study did show that the psychotic symptoms of PTSD-SP are not very likely to be part of a comorbid major depression with psychotic features; a finding that corroborates the clinical evidence already reported in paragraph 2.2.2.

### **Course, treatment response and family studies related to PTSD-SP**

As far as the criteria 'course', 'treatment response' and 'family studies' are concerned, we summarize them shortly in this paragraph and refer to Chapter 2 and 3 because no new data are available since our reviews and these criteria were not addressed in our own empirical study.

#### **Results from our review (Chapter 2 and Chapter 3) and additional recent literature**

##### **Course**

No sound data are available in the literature on the clinical course of PTSD-SP except that PTSD-SP often is a chronic condition (33).

##### **Family studies**

With regard to family studies, we reported in Chapter 2 the finding of one single study focusing on familial vulnerability to schizophrenia and other psychoses in first degree relatives of PTSD-SP patients (34). That study showed an increased prevalence of major depression, but no increased prevalence of psychotic disorders in first degree relatives. Neither our own study nor any new study published since that of Sautter et al. presented new family data.

##### **Treatment response**

As far as treatment response is concerned we reported the findings of four studies in which risperidone addition to SSRI's and mono-therapy with quetiapine, olanzapine or fluphenazine were effective in the treatment of patients with PTSD-SP (Chapter 3). Compared to fluphenazine, olanzapine showed significantly ( $p < 0.05$ ) more improvement in negative symptoms and general psychopathology of the PANSS and in PTSD symptoms. Most studies were open-label, pre-post comparisons on the same subjects without comparison to placebo. Only one study included a placebo group and was double-blind (risperidone study by Hamner et al. (35) In that study



risperidone or placebo were added to an SSRI-regimen and a significant total improvement as measured with the PANSS was observed in the risperidone condition. However, closer examination revealed that neither the positive nor the negative psychotic symptoms improved but only the general psychopathology subscale of the PANSS. Our own empirical study did not contain any treatment data since this was not the objective of our study.

## The diagnostic validity of PTSD-SP

Clear distinctions are crucial for the recognition of clinical psychiatric syndromes as separate diagnostic entities (1, 3-5, 36). We therefore used Robins and Guze's criteria to assess the validity of 'posttraumatic stress disorder with secondary psychotic features'. Based on our reviews and our empirical study we conclude that substantial phenomenological and biological evidence is now available and that this evidence increases the likelihood that PTSD-SP can be delineated from other psychiatric disorders as a distinct psychiatric nosological entity. However to date there is no clear-cut and undisputed rule to affirm a nosological concept as sufficiently validated. As far as PTSD-SP is concerned, its validation is clearly strengthened yet several issues remain.

Recently, Stein et al. (37) proposed the following criteria for a mental/psychiatric disorder to be included in DSM-5:

1. a behavioral or psychological syndrome or pattern that occurs in an individual
2. the consequences of which are clinically significant distress or disability
3. must not be merely an expectable response to common stressors and losses
4. that reflects an underlying psychobiological dysfunction
5. that is not primarily a result of social deviance or conflicts with society
6. that has diagnostic validity on the basis of various diagnostic validators (eg prognostic significance, psychobiological disruption, response to treatment)
7. that has clinical utility (e.g. contributes to better conceptualization of diagnoses, or to better assessment and treatment)
8. diagnostic validators and clinical utility should help to differentiate a disorder from diagnostic 'nearest neighbors'
9. when considering whether to add a mental/psychiatric condition to the nomenclature potential benefits (better care, stimulate new research) should outweigh potential harms (e.g. be subject of misuse)

For PTSD-SP, many of these criteria are already met (1, 2, 3, 5, and 9). Criterion 4 is partially met: several studies point towards some specific psychobiological dysfunctions. However none of these has been replicated or validated and the exact psychobiological dysfunction of PTSD-SP is unknown. Criterion 6 is partially met:

diagnostic validators are investigated, however not replicated nor validated. However, the response of PTSD-SP to present day treatment methods is unclear: several open-label studies point towards effective treatment with antipsychotic medication, however the only available randomized controlled trial showed only partial effects. Criterion 7 seems to be fully met: PTSD-SP contributes to better conceptualization of diagnoses, e.g. being able to discriminate the disorder from schizophrenia and major depressive disorder with psychotic features. Criterion 8 is also met: PTSD-SP can be differentiated from its nearest neighbours (schizophrenia, non-psychotic PTSD, major depressive disorder with psychotic features). Finally, criterion 9 is also met since acknowledging PTSD-SP as a separate diagnostic entity will lead to additional research, especially to search for the underlying mechanism and new treatment options. Moreover, it seems that the diagnosis PTSD-SP has no potential harms since it separates this condition from a even more stigmatized disorder like schizophrenia and it helps people to find the most appropriate treatment.

## Strengths and weaknesses of the study

The main strength of our empirical study is that we were able to produce a more detailed description of the differences between PTSD patients with and without psychotic features than most other studies so far. An additional strength is that we studied a broader trauma cohort (male and female refugees) than in most other studies (only male war veterans). This increases the generalization of our findings regarding the PTSD-SP concept. Most importantly, other epidemiologic studies generally relied on lifetime prevalence rates and were not able to take into account the temporal sequence of psychosis, PTSD and psychiatric comorbidity (16-18). In contrast to that, we focused on the sequence of onset of PTSD, psychosis and depressive disorder. Therefore we were able to partially disentangle the complex interrelationships between these disorders.

Our study also has limitations. The first limitation is its cross-sectional design with retrospective data collection. This is especially important in a study with psychotic and PTSD patients; a clinical population known to suffer from memory impairment, recall bias or under-reporting traumatic events (38, 39). This raises questions regarding the accuracy of the retrospective assessments of the exact start of the chronic disorders in our sample and the amount and severity of life events. On the other hand, it is well known that trauma reports based on memories show at least fair to moderate test-retest reliability (40) and there is no evidence that recall difficulties differ between schizophrenia, PTSD and PTSD-SP patients. A second important limitation is the fact that our sample size was not very large and that some of the observed (and often substantial) differences did not reach statistical significance due

to a lack of statistical power. In order to recognize this limitation and to prevent type II errors in our conclusions, we also provided standardized effects sizes. A third limitation is that we failed to assess childhood traumas in our study population, whereas there is growing evidence that childhood trauma contributes to the development of psychosis and schizophrenia in adult life (41, 42). Hence, it is possible that subjects who experienced childhood trauma are overrepresented in our PTSD-SP sample. However, there is no unambiguous evidence that subjects with childhood trauma are more prone to expose themselves to new traumatic events leading to PTSD in adult life and subsequently to psychosis. Future research should clarify this issue. A final limitation is the multi-ethnic nature of our study population; a condition that hinders the study of especially biological parameters, including genetics. Countless genetic studies found positive associations in ethnic homogeneous samples but failed to be replicated in other, ethnically different samples. In our study we used *DBH*-genotyping to control for ethnic differences in our comparison of plasma  $D\beta H$  levels between the different diagnostic groups.

## Clinical implications

Clinicians should be sensitized by this study in two ways. First of all, in the clinical assessment of psychosis it is important to check for the presence of trauma and PTSD. PTSD in psychotic patients is often missed or underreported in charts (43-45). Closer examination could reveal that patients presenting psychotic features for a long time, and therefore being diagnosed as suffering from schizophrenia, might be incorrectly diagnosed and that PTSD-SP is a more appropriate diagnosis. Second, if PTSD-SP is different from schizophrenia, treatment options could be different as well. Accomplishing the most suitable diagnosis is not a goal in itself. It is in our opinion rather a means to achieve the best available treatment. Identifying PTSD-SP might prove to be important since common treatments used in schizophrenia have limited effect on positive and negative psychotic symptomatology, whereas interventions directed at the treatment of PTSD seem to have a beneficial effect (35, 46, 47). Based on the few available studies to date the following tentative clinical recommendations can be made:

### General recommendations

First, based on the description of three cases of refugees with PTSD-SP, Kurth et al. (48) mentioned several important treatment issues:

- a. Pharmacological treatment with antipsychotics is indicated and is helpful in stabilizing patients in such a way that additional psychotherapy is possible;

- b. Psychoeducation is helpful in order to enhance feelings of control in patients as is focussing on the 'here and now';
- c. Therapists should, depending on the patient's needs, be flexible and shift their treatment focus during the course of the disorder between emotional distancing ('there and then') of flashbacks i.a., and reintegration of dissociative symptoms ('here and now'), and cognitive distinction of psychotic symptoms (to improve reality testing).

These are quite general recommendations indeed, relevant to all psychotic disorders. What is different is that in explaining the origin of psychotic experiences patients with PTSD-SP get a new framework in which their symptom and suffering are explained meaningfully. In addition, many patients feel embarrassed about psychotic symptoms, and do not easily disclose these symptoms (49), and, feel less stigmatized and seek more help when they notice that their psychotic symptoms are not labeled as schizophrenia but as part of their past traumatization (50).

### Pharmacotherapy

The best evidence for pharmacotherapeutic efficacy in PTSD-SP came from the randomized controlled trial by Hamner et al. (35). In this study risperidone or placebo were added to a standard regimen of antidepressant treatment. In this study, general psychopathology improved, but there were no differences in positive or negative psychotic symptoms between risperidone and placebo. Also re-experiencing symptoms improved. For the treatment of patients this could be helpful. However, it is interesting to note that psychotic symptoms did not respond like conventional psychotic disorders would. All other studies are uncontrolled pre-post comparisons without placebo. Two of these reported significant improvements on risperidone and quetiapine mono-therapy in terms of a reduction of the majority of the psychotic and PTSD symptoms in these patients (51, 52). Another study compared olanzapine and fluphenazine as a mono-therapy in PTSD-SP patients in a six-week open label trial (53). Compared to fluphenazine, olanzapine showed significantly more improvements in terms of negative symptoms and general psychopathology on the PANSS and in PTSD symptoms. Based on my personal experience and two published case studies (54, 55), it seems that clozapine might be effective to remedy psychotic symptoms as well as PTSD and (other) anxiety symptoms in patients with PTSD-SP.

Given the present state of knowledge the best documented strategy is combining an SSRI with an atypical antipsychotic. Both agents are effective in treating PTSD symptomatology. In addition, although not yet conclusive, there is evidence that antipsychotics in PTSD-SP ameliorate general psychopathology. If this fails, based on clinical experience of several authors, clozapine could be the agent of last resort.

## Psychotherapy

Psychotherapy, especially focal exposure (47), cognitive behavioral therapy (CBT) and Eye Movement Desensitization Reprocessing (EMDR), appears to be the method of choice for the psychotherapeutic treatment of patients with PTSD-SP. The paper by Uddo et al (47) reported an improvement in PTSD-SP patients treated by focal exposure in group therapy. Unfortunately this study did not mention the instruments used to assess this improvement, nor the magnitude of the improvement. Therefore we could not include this study in our review (Chapter 2). However, recent studies suggest that CBT and EMDR could be effective in PTSD-SP based on the presumption that among the patients these studies included (schizophrenia with PTSD) some of them in fact could suffer from PTSD-SP since they did not screen for PTSD-SP nor did they map whether PTSD preceded or followed the onset of psychosis (56-58). The shortage of treatment studies is not only a consequence of insecure diagnostic status of PTSD-SP, but therapists as well as researchers are very reluctant to use exposure or CBT techniques in patients with psychotic symptoms. In a recent recruitment for a randomized clinical trial comparing psychotherapies for chronic PTSD, many enrollees (17%) reported psychotic symptoms and unfortunately were excluded from the study (50). Both researchers and therapists have non-evidence based views that for instance exposure techniques would worsen psychotic symptoms or cause patients to decompensate. However, this might not be true (57, 58). For example, a recent pilot study testing EMDR in a patient with a psychotic disorder and comorbid PTSD showed that this approach was safe (no deterioration of the psychotic symptoms) and effective in terms of a reduction of auditory hallucinations, delusions, anxiety, depressive symptoms and an improvement of self-esteem (56).

Recognition of PTSD-SP as a valid diagnostic entity will facilitate clinical research into effective treatment options for this complex and difficult to treat psychiatric condition. Our study contributes to this validation process and, hopefully, stimulates more research into highly needed treatments for PTSD-SP.

## Future research

We found important additional indications that PTSD-SP is either a distinctive nosological concept or a subtype of PTSD. We found clear evidence that PTSD-SP is different from (and the psychotic features cannot be explained by) schizophrenia, dissociative disorder, major depressive disorder with psychotic features and substance-induced disorders. However, more research is needed to further validate PTSD-SP. For example, there is a paucity of family studies (just one unreplicated

study) and there are no studies focusing on the course of the disorder. Not all subjects develop PTSD after traumatization and not all individuals with PTSD develop secondary psychotic symptoms. It remains unclear 'what makes the difference'. Nor is there convincing evidence whether PTSD-SP is fundamentally distinct from PTSD or whether it should be considered to be a subtype of PTSD. There is hardly any evidence focusing on the pathophysiology, the etiology or additional risk factors of the disorder. More neurobiological, gene-environment and psychological research is warranted to clarify these issues.

Most importantly treatment-intervention studies are still rare and further validation of PTSD-SP is necessary in order to pave the road for specific treatment intervention studies in the near future.

## Neurobiological research

A hypothetical model explaining the appearance of psychotic features in patients with PTSD-SP was developed by Hamner et al. (30). They propose that psychotic features in PTSD involve noradrenergic rather than dopaminergic hyperactivity. Studies suggest either elevated resting or exaggerated response of noradrenalin in PTSD (30, 59, 60). Furthermore, lots of studies have been conducted on noradrenergic hyperactivity and psychosis. Van Kammen et al. (1994) reported that increased central noradrenergic activity during chronic dopamine receptor blockade by haloperidol was associated with a high risk of relapse within six weeks after haloperidol withdrawal (61). Stressful events induce noradrenergic hyperactivity and even induce increased dopamine release. Finally, there is evidence that dysregulation of noradrenergic systems is induced by cortisol (62).

Quite differently, Sautter et al (22) propose a dopaminergic theory. They have shown that unlike PTSD patients without psychosis, patients with PTSD-SP have an increased secretion of hypothalamic corticotrophin-releasing hormone (CRH). Increased CRH produces increased cortisol secretion. Increased cortisol levels leads to increased dopamine synthesis and increased dopamine release in the brain (63). Cortisol augments dopamine secretion especially in the mesolimbic system which is considered nowadays to be the cause of positive psychotic symptoms in patients with a psychotic disorder (62, 64, 65). At least two aspects of this theory need further empirical evidence. First, although still disputed, evidence suggests that in PTSD basal cortisol levels are not increased, even decreased (66). Thus empirical studies are needed to assess whether indeed cortisol levels in PTSD-SP are increased compared to non-psychotic PTSD. An as yet unpublished paper by Manguno-Mire et al. (67) demonstrates that subjects with PTSD and secondary psychotic features show significantly higher baseline cortisol levels than subjects with PTSD without psychotic features and control subjects. A second aspect of this theory that needs to be clarified is what explains the increased CRH in PTSD-SP.

Psychosocial stress is associated with increased risk for developing psychosis, especially in case of cumulative exposure (68). If increased levels of basal cortisol appear before adolescence (e.g. due to childhood trauma) a cascade of events leads to a reduction of up to 33% of dopaminergic innervations of the prefrontal cortex in the brain of patients with schizophrenia (69). Maturation of the prefrontal cortex is not thought to be completed until early adulthood and might explain the severity of executive function deficits in schizophrenia (63). Since PTSD-SP develops much later in life compared to the onset of schizophrenia (Chapter 4, this thesis) and patients suffering from PTSD-SP mainly experience traumatic events in adulthood (of note: childhood traumatic experiences were not explicitly measured in our study), the prefrontal cortex is likely to be matured and thus increased cortisol levels give rise to mesolimbic dopamine hyperactivity, but prefrontal functioning is likely to be much more preserved compared to patients suffering from schizophrenia. This might explain the similarities (hallucinations and delusions) as well as the differences between patients with schizophrenia and patients with PTSD-SP (no conceptual disorganization, no negative symptoms). This model presumes that basal cortisol levels are increased in PTSD-SP patients which to date is not yet clearly established. What we do know is that in PTSD without psychosis basal cortisol levels are not increased but rather decreased. What we do not know is if and how cortisol, as well as dopamine and noradrenalin are involved in the pathophysiology of PTSD-SP. Future neurobiological studies could clarify these issues. To date neuroimaging studies are missing as far as PTSD-SP is concerned. Studies with several neuroimaging techniques (structural MRI, and PET or SPECT scans) could be useful in order to look for similarities and differences between patients with PTSD-SP and non-psychotic PTSD as well as schizophrenia. Structural neuroimaging studies with traumatized patients have reported findings similar to those in psychosis: thinning of the corpus callosum and reduced volumes in the anterior cingulate cortex and hippocampus (70-74). Of interest is what distinguishes PTSD-SP patients from patients with these other disorders, e.g. hypo- or hyperfunctioning of parts of the prefrontal cortex.

### Psychological research

There are several common psychological processes suggested in PTSD and psychosis and their relationship. Cognitive models in psychosis might explain how these processes are interrelated. Traumatized patients develop cognitions like “I am vulnerable” and “people can’t be trusted” (75, 76), which increases the risk of psychosis. Selective attention to threat is similar in paranoia and PTSD (76). Calvert et al. (75) suggest that cultural interpretations are important as well: if the interpretation of a post-traumatic intrusion is culturally acceptable both clinician and patient tend to favour PTSD as the diagnostic explanation. However if the link between symptoms and trauma is less obvious and culturally unacceptable, a diagnostic interpretation favouring psychosis is more likely (75, 76).

### Therapeutic research

Finally, of foremost concern, are studies focusing on effective treatment options, both in the area of medication and psychotherapy.

As far as medication is concerned there are several options to be considered. First of all, several studies report improvements of PTSD-symptomatology by antipsychotic medication, especially second generation antipsychotics (77, 78) both as monotherapy as well as in addition to selective serotonin reuptake inhibitors (SSRI's). However these studies present no clues as to which antipsychotics offer additional effects in PTSD-SP. None of the published pharmacological studies in PTSD-SP have been replicated and most are open label pre-post studies. Higher quality studies aimed at replication or validation are warranted. In addition trials comparing SSRI's and antipsychotics could yield important data e.g. regarding the initial step in pharmacotherapy.

If noradrenergic pathophysiology is assumed to be present, clonidine might be of interest. Clonidine is an alpha(2)-adrenoreceptor agonist and inhibits the spontaneous firing of brain norepinephrine (NE) containing neurons by its agonist action on the presynaptic alpha(2)-receptors. Alternatively, prazosine, an alpha(1)-adrenoreceptor antagonist which dampens noradrenergic function in different parts of the brain could be investigated (49).

Preliminary evidence suggests that CBT as well as EMDR might be of interest in PTSD-SP. Especially since CBT is effective in PTSD as well as in treating positive psychotic symptoms research into efficacy as well as side-effects is comprehensible. Psychotherapy trials explicitly designed to include patients suffering from PTSD-SP are warranted. This also applies for studies comparing psychotherapeutic interventions with pharmacotherapy.

### Conclusion

In currently available studies we found support for PTSD-SP as a separate diagnostic entity. Our study added new findings to support this hypothesis. We produced a more detailed description of the differences between PTSD patients with and without psychotic features than most other studies so far, and we studied a different and broader trauma cohort (male and female refugees) than in most other studies (only male war veterans). We found evidence that PTSD-SP can be delineated from other psychiatric disorders with psychotic features such as schizophrenia, major depression with psychotic features, dissociative disorder, and substance-induced psychotic disorder.

PTSD-SP and schizophrenia could be successfully differentiated by a limited set of clinical features. We found a symptom pattern in our patients with PTSD-SP that



was distinct from our patients with schizophrenia. The discrepancy between the age of onset of first psychosis in our schizophrenia group and our PTSD-SP group is an important and significant distinction. It favors the validity of PTSD-SP and helps us to delineate PTSD-SP from schizophrenia. This also applies to the fact that the symptom pattern in these patients with PTSD-SP in a multi-ethnic, mixed gender civilian population was very similar to the symptom pattern reported in studies among mainly male U.S. war veterans with PTSD-SP.

Our study also provided clinical evidence that the psychotic features in PTSD-SP were not part of a (pre-existing) major depressive disorder, both by analyzing the time of onset of PTSD, of psychosis and of major depressive disorder as well as by our findings that DBH plasma levels in PTSD-SP patients are not decreased, as is seen in patients with major depressive disorder with psychotic features. Also the psychotic features in PTSD-SP could not be accounted for by the presence of substance-induced psychotic disorders or a dissociative disorder. Although we have obtained several facts indicating that PTSD-SP should be considered as a complicated subtype of PTSD or as a separate diagnostic entity more research is needed to address a number of unresolved issues. For example, little is known about the course of PTSD-SP or about its pathophysiology. Also, there is a paucity of family studies as well as neuroimaging data, nor do we have studies about the etiology and risk factors of PTSD-SP. The potential influence of psychosocial and cultural factors in the development of PTSD-SP, as well as the pathoplastic influence of cultural idioms of distress are issues for future research. And most importantly, much more research is needed concerning adequate and effective treatments.


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**Summary**  
**Samenvatting**  
**Dankwoord**  
**Curriculum Vitae**



## Summary

The study presented in this thesis originated from a clinical observation. During our clinical work in a psychiatric inpatient treatment facility for traumatized refugees and asylum seekers in the Netherlands we encountered many patients suffering from symptoms of posttraumatic stress disorder (PTSD) in conjunction with symptoms of chronic psychosis, especially delusions and hallucinations. These patients had developed PTSD and subsequently, sooner or later, psychotic symptoms as well. They had a remarkable poor response to antipsychotic medication. Questions of referring psychiatrists about the diagnosis of these patients, as well as the repeatedly encountered treatment resistance of their chronic psychotic symptoms, paved the way for the main questions of this thesis. Before studies aimed at finding adequate and effective treatment options could be undertaken another important question emerged first: what is the diagnostic position of this manifestation of posttraumatic stress disorder and subsequent psychosis? Is it a form of (late onset) schizophrenia? Is it a complex PTSD? Is it a special kind of affective psychotic disorder? Or is it a diagnostic entity (PTSD-SP) on its own? The goal of this thesis was to find evidence for the validity of this complex clinical picture as a separate diagnostic entity or to refute it. Is PTSD with secondary psychotic features a diagnostic entity on its own or could this syndrome appropriately be described by familiar and already existing diagnostic categories?

First, in Chapter 2 and 3, we studied the present state of knowledge by an extensive survey of the literature. Twenty-four studies were identified with empirical data and minimum requirements regarding the level of evidence. From these studies PTSD-SP emerged as a syndrome that consists of posttraumatic stress disorder, joined by one or more psychotic features, especially hallucinations and delusions. The prevalence of PTSD-SP was unclear with varying rates of patients who looked for mental treatment (15-64%). The psychotic features were not confined to only the episodes of re-experiencing, but persisted continuously. The content of these psychotic features was generally paranoid in nature, and no first rank Schneiderian psychotic features appeared to be present. There was no history of psychotic episodes prior to the traumatic event(s). There was no relationship between the nature or severity of the traumatic events and the presence of PTSD-SP. In first degree relatives of PTSD-SP patients there was an increased prevalence of major depression but no increased prevalence of psychotic disorders, which would be expected in cases of schizophrenia. Positive correlations of the secondary psychotic features in PTSD-SP patients were found with ethnicity (African-American and Hispanic), with co-morbid depressive disorder, with the enzyme-activity of D $\beta$ H and with cerebrospinal fluid concentrations of CRF, blood platelet serotonin and MAO B activity. There were specific smooth

pursuit eye movement deficits. Positive and negative psychotic symptoms did respond in uncontrolled pre-post comparisons with antipsychotics in some studies but not significantly compared to placebo in another study. Olanzapine treatment resulted in larger reductions in negative symptoms and PTSD symptoms than fluphenazine.

In short, these two chapters summarized what was known about PTSD-SP and revealed the main gaps in the knowledge about this syndrome and the issues that needed additional empirical research.

Three principal research questions came forward out of this review of the literature:

1. Can chronic psychosis in PTSD-SP be distinguished from psychosis in schizophrenia by clinical features and trauma history?
2. Can the presence of psychotic features in PTSD-SP be explained by psychiatric comorbidity, by more severe PTSD re-experiencing-symptoms, or by more severe or a specific type of traumatic events?
3. Is plasma dopamine beta-hydroxylase activity increased in posttraumatic stress disorder with secondary psychotic features?

To answer these questions we designed a cross sectional study in which we recruited adult refugee patients from two mental health hospitals in the Netherlands. As previous studies were almost exclusively limited to male outpatient war veterans from the U.S. exposed to combat-related trauma, we focused on a different and more diverse population: a multi-ethnic sample of refugees, both male and female, who had been exposed to a wide range of traumas, not exclusively combat-related. And next, as previous studies revealed that patients suffering from PTSD-SP had psychotic features similar but not necessarily identical to schizophrenia, we wanted to compare the psychotic features in both groups, PTSD-SP and schizophrenia, in order to determine similarities and/or differences between the two.

This was the main objective of Chapter 4. We found that the clinical features of PTSD-SP can be distinguished from those of schizophrenia. Patients of the PTSD-SP group had considerably less negative symptoms and less disorganisation than is commonly seen in schizophrenia and furthermore they had more affective distress and more stress due to auditory hallucinations than patients in the schizophrenia group in this study. In addition, patients in the PTSD-SP group had more comorbid disorders than patients in the schizophrenia group. Patients with PTSD-SP suffered more from depressed and anxious feelings than patients who suffered from schizophrenia and they were more frequently traumatized. In males the first psychotic symptoms in PTSD-SP patients started more than 10 years later than in schizophrenia.

Major depressive disorder was the most common comorbid condition in the PTSD-SP group.

Therefore, in Chapter 5, we explored the associations between psychotic features in PTSD-SP and other comorbid psychiatric conditions, especially major depressive disorder.

Our data indicated that the presence of psychotic symptoms was not attributable to comorbid major depressive disorder since:

1. in our study, 11 of the 34 patients with PTSD-SP (32.4%) did not have a current diagnosis of major depressive disorder.
2. in the remaining patients the psychotic symptoms emerged in the majority of the patients before the onset of major depressive disorder with a mean time lag of more than three years.

In Chapter 6 we aimed to validate a previous study by Hamner and Gold who reported an increased level of blood plasma activity of dopamine- $\beta$ -hydroxylase (D $\beta$ H) in patients with PTSD and psychotic symptoms compared to healthy controls and PTSD patients without psychotic features. We wanted to validate these findings in a larger, mixed gender, multi-ethnic sample and included also patients with schizophrenia. In addition, we evaluated *DBH* -1021C>T (rs1611115) genotype because D $\beta$ H plasma levels are under strong genetic control. We found that *DBH* -1021C>T genotype was strongly associated with plasma D $\beta$ H activity in the ethnically heterogeneous sample. Mean plasma D $\beta$ H activity in patients with PTSD-SP was not different from that of patients with schizophrenia or PTSD or from that of health individuals, even after taking *DBH* -1021C>T genotype into account. The presence or absence of major depressive disorder in patients with PTSD-SP was not related to plasma D $\beta$ H activity either.

In the general discussion (Chapter 7) we reassessed our main research question whether PTSD-SP is a diagnostic entity by combining the existing literature until 2008 (at the start of our study), our own research findings and the findings from newer studies published from 2008 until 2012. We concluded that we have obtained numerous facts indicating that PTSD-SP should be considered as a (severe) subtype of PTSD or as a separate diagnostic entity. Nevertheless more studies are needed to address a number of unresolved issues. For example, little is known about the course of PTSD-SP or about its pathophysiology. And there is a paucity of family studies as well as neuroimaging data, nor do we have studies about the etiology and risk factors of PTSD-SP. This all might contribute to find more adequate and effective treatment options for this clinical syndrome.

## Samenvatting

Het onderzoek dat in dit proefschrift wordt beschreven kwam voort uit de klinische praktijk. Werkend in een psychiatrische kliniek voor getraumatiseerde asielzoekers en vluchtelingen in Nederland troffen we veel patiënten aan die leden aan de symptomen van een posttraumatische stress-stoornis (PTSS) alsook aan chronisch psychotische symptomen, met name wanen en hallucinaties. Deze patiënten hadden eerst een PTSS ontwikkeld en daarna, vroeg of laat, kwamen daar psychotische symptomen bij. Deze psychotische symptomen reageerden erg slecht op antipsychotische medicatie. Diagnostische vragen van verwijzers over dit beeld, alsook de frequente therapie-resistentie die we aantroffen bij deze patiënten gaven aanleiding tot de hoofdvragen van dit proefschrift. Alvorens in de toekomst onderzoek te kunnen doen naar adequate en effectieve behandelingen diende eerst een andere belangrijke vraag beantwoord te worden: hoe dient een posttraumatische stress-stoornis gevolgd door een psychose diagnostisch geïnterpreteerd te worden? Is het een vorm van schizofrenie (met verlaat begin)? Is het een complexe PTSS? Is het een speciaal soort van affectieve psychotische stoornis? Of is het een diagnostische entiteit op zichzelf (PTSS-SP)? Het doel van dit proefschrift is om bewijs te vinden voor de validiteit van dit complexe klinische beeld als afzonderlijke diagnostische entiteit dan wel om dit te verwerpen. Oftewel in andere woorden: is PTSS met secundaire psychotische kenmerken (PTSS-SP) een diagnostische entiteit of kan dit syndroom beschreven worden door reeds bekende en bestaande diagnostische categorieën?

In hoofdstuk 2 en 3 bestudeerden we allereerst de bestaande kennis door een uitvoerig literatuur onderzoek. Vierentwintig empirische studies met een redelijk nivo van bewijs werden gevonden. Uit deze studies kwam PTSS-SP naar voren als een syndroom dat bestaat uit een posttraumatische stress-stoornis waaraan een of meer psychotische symptomen waren gekoppeld, met name wanen en hallucinaties. De prevalentie van PTSS-SP werd niet duidelijk, het prevalentie percentage onder PTSS patiënten die psychische hulp zochten voor hun klachten varieerde van 15 tot 64%. De psychotische kenmerken beperkten zich niet tot aanvallen van herbelevingen maar waren continu aanwezig. De inhoud van deze psychotische kenmerken was veelal paranoïde gekleurd en de symptomen van de eerste orde van Schneider leken afwezig te zijn. Er was geen voorgeschiedenis van psychotische episoden die vooraf gingen aan de traumatische gebeurtenissen. Er was geen relatie tussen de aard of ernst van de traumatische gebeurtenissen en het al dan niet verschijnen van een PTSS-SP. Bij eerstegraads verwanten van patiënten met een PTSS-SP werd wel een verhoogde prevalentie van depressie in engere zin gevonden maar geen verhoogde prevalentie van psychotische stoornissen, hetgeen wel verwacht zou worden indien

deze patiënten aan schizofrenie zouden lijden. Bij PTSS-SP patiënten werden positieve correlaties gevonden tussen secundaire psychotische kenmerken met de volgende variabelen: 'ethniciteit' (Afro-Amerikaans en Spaans-Amerikaans), 'comorbide depressieve stoornissen', 'verhoogde enzymactiviteit van plasma dopamine- $\beta$ -hydroxylase' (D $\beta$ H), 'Corticotrophin Releasing Factor concentraties in de liquor cerebrospinalis' en 'serotonine' en 'MAO-B activiteit in bloedplaatjes'. Er waren specifieke oogbewegingsdefecten bij PTSS-SP patiënten. Positieve en negatieve psychotische symptomen reageerden weliswaar op antipsychotica in sommige studies met ongecontroleerde pre-post vergelijkingen echter niet in een studie die gebruik maakte van een placebo-groep. Behandeling met olanzapine leidde tot een grotere reductie van negatieve symptomen alsook van PTSS symptomen dan flufenazine. Kortom, in deze twee hoofdstukken werd samengevat wat bekend was over PTSS-SP in de literatuur en dit leidde tot een overzicht van de belangrijkste lacunes en tot de thema's die nader empirisch onderzocht moesten worden.

Drie hoofdvragen kwamen uit dit literatuuronderzoek naar voren:

1. Kan de chronische psychose in PTSS-SP onderscheiden worden van de psychose bij schizofrenie door klinische kenmerken en de traumatische voorgeschiedenis?
2. Kan de aanwezigheid van psychotische kenmerken bij PTSS-SP verklaard worden door de psychiatrische comorbiditeit, door mogelijk ernstigere symptomen uit het herbelevingen-cluster van de aanwezige PTSS of door ernstigere (of een specifiek soort van) traumatische gebeurtenissen?
3. Is de plasma dopamine beta-hydroxylase activiteit toegenomen bij posttraumatische stress stoornis met secundaire psychotische kenmerken?

Om deze vragen te beantwoorden werd een cross-sectionele studie ontworpen waarin we volwassen vluchtelingen/asielzoekers rekruteerden in twee psychiatrische ziekenhuizen in Nederland. Aangezien studies tot op heden voornamelijk werden verricht bij mannelijke, poliklinische oorlogsveteranen uit de VS die blootgesteld waren aan gevecht gerelateerde trauma's wilden wij ons richten op een andere en meer gevarieerde populatie: een multi-etnische groep van vluchtelingen en asielzoekers, zowel mannen alsook vrouwen, blootgesteld aan een breed scala van traumatische gebeurtenissen en niet louter gevecht gerelateerde trauma's. Eerdere studies hebben laten zien dat patiënten die leden aan PTSS-SP psychotische kenmerken hadden die leken op schizofrenie. Daarom wilden wij de psychotische kenmerken van schizofrene patiënten en PTSS-SP patiënten met elkaar vergelijken om de overeenkomsten en/of verschillen tussen beide te kunnen vaststellen.

Dit was de hoofddoelstelling van hoofdstuk 4. We vonden dat de klinische kenmerken van PTSS-SP onderscheiden kunnen worden van die van schizofrenie. Patiënten van de PTSS-SP groep vertoonden aanzienlijk minder negatieve symptomen

en minder desorganisatie dan men ziet bij de schizofrenie groep en verder hadden ze meer affectief onbehagen en meer stress door de auditieve hallucinaties dan patiënten uit de schizofrenie-groep. Bovendien hadden de patiënten van de PTSS-SP groep meer comorbide psychiatrische stoornissen en leden ze meer aan angst en depressieve gevoelens dan patiënten uit de schizofrenie groep en waren ze ook vaker getraumatiseerd. Bij mannen begonnen de eerste psychotische symptomen meer dan tien jaar later dan bij mannen uit de schizofreniegroep. De depressieve stoornis was de meest voorkomende comorbide stoornis in de PTSS-SP groep.

Vandaar dat we in hoofdstuk 5 zijn nagegaan of er associaties waren tussen de psychotische kenmerken bij PTSS-SP en andere comorbide psychiatrische stoornissen, met name de depressieve stoornis. Onze verkregen onderzoeksgegevens wijzen er op dat de aanwezigheid van psychotische symptomen niet toegeschreven kan worden aan een comorbide depressieve stoornis aangezien:

1. in onze studie, 11 van de 34 patiënten met PTSS-SP (32,4%) geen comorbide depressieve stoornis hadden,
2. in de resterende groep patiënten in de meerderheid van de gevallen de psychotische symptomen ontstonden voordat de depressieve stoornis ontstond, gemiddeld zat daar drie jaar tussen.

In hoofdstuk 6 stelden we ons ten doel om de studie van Hamner en Gold te valideren. Deze auteurs hadden gerapporteerd dat de plasma dopamine- $\beta$ -hydroxylase activiteit verhoogd was bij patiënten met PTSS en psychotische symptomen, vergeleken met gezonde controlepersonen en PTSS patiënten zonder psychotische kenmerken. We wilden deze bevindingen bevestigen in een grotere patiëntenpopulatie die multi-etnisch van aard was, zowel mannen alsook vrouwen bevatte en we wilden de plasma dopamine- $\beta$ -hydroxylase activiteit ook vergelijken met een groep schizofrene patiënten. Bovendien hebben we tevens het *DBH -1021C>T* (rs1611115) genotype bepaald aangezien uit eerder onderzoek bleek dat de plasma dopamine- $\beta$ -hydroxylase activiteit in hoge mate door dit genotype wordt beïnvloed. We vonden inderdaad dat ook in deze etnisch heterogene populatie het *DBH -1021C>T* genotype in hoge mate correleerde met de plasma dopamine- $\beta$ -hydroxylase activiteit. De gemiddelde plasma dopamine- $\beta$ -hydroxylase activiteit van patiënten met PTSS-SP verschilde niet van die van patiënten met schizofrenie of patiënten met PTSS zonder psychotische kenmerken en verschilde evenmin van het gemiddelde van gezonde controlepersonen. Ook niet na correctie op de invloed van het *DBH -1021C>T* genotype. De aan- of afwezigheid van een depressieve stoornis bij patiënten met een PTSS-SP was niet gerelateerd aan de plasma dopamine- $\beta$ -hydroxylase activiteit.

In de algemene discussie (hoofdstuk 7) hebben we opnieuw de vraag geëvalueerd of PTSS-SP een aparte diagnostische entiteit is, en wel deze keer door de bestaande



literatuur die bekend was bij de start van ons onderzoek in 2008 te combineren met de bevindingen uit ons eigen onderzoek en ook de bevindingen van studies van anderen die sindsdien zijn gepubliceerd (tot en met 2012). We concludeerden dat we tal van feiten hebben opgespoord die er op wijzen dat PTSS-SP beschouwd zou moeten worden als een (ernstig) subtype van de posttraumatische stress-stoornis dan wel als een aparte diagnostische entiteit. Desalniettemin is er nog meer onderzoek nodig om een aantal nog niet opgeloste kwesties te beantwoorden. Zo is bijvoorbeeld weinig bekend over het beloop van PTSS-SP of over de pathofysiologie. Ook is er een schaarste aan studies onder verwanten van PTSS-SP patiënten en ontbreekt onderzoek op het gebied van neuro-imaging. Ook is er geen onderzoek naar de etiologie en de risicofactoren die leiden tot PTSS-SP. Al met al kan dit bijdragen aan het vinden van geschiktere en effectieve behandelmogelijkheden van dit klinische syndroom.

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ers like you, suffer from traumatic experiences themselves. Hurricane Katrina hit your hospital in New Orleans. It vanished, together with your patients and research subjects, and your school had to downsize 180 faculty members in order to survive. Kartina damaged not only your career and private life, but our common research interest, psychotic PTSD, as well: I sincerely hope that you manage to rebuilt your scientific infrastructure again and continue to publish on PTSD-SP.

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## Curriculum Vitae

Mario Braakman werd geboren op 16 april 1961 te Kerkrade, Nederland. De middelbare school volgde hij in Kerkrade-West bij de scholengemeenschap Sancta Maria alwaar hij in 1979 het VWO-eindexamen Atheneum B behaalde. Hij studeerde Geneeskunde aan de Katholieke Universiteit te Nijmegen, de huidige Radboud Universiteit. Na het behalen van zijn kandidaats Geneeskunde begon hij daarnaast ook aan de studie Culturele Antropologie eveneens aan de Radboud Universiteit. Gedurende deze twee studies studeerde hij tevens aan de Leidse Universiteit een jaar "precolumbiaanse archeologie" bij etno-archeoloog Prof. Dr. Maarten Jansen en "Yucateecs Maya" bij de vergelijkende taalwetenschapper Prof. Dr. Willem Adelaar. Het antropologische veldwerk verrichte hij in 1985-86 in de staat Quintana Roo, Mexico in een klein Maya-dorp in het subtropische regenwoud van Yucatan. Hierna was hij werkzaam als student-assistent aan de Radboud Universiteit, vakgroep sociale antropologie, bij wijlen Prof. Dr. Jan Pouwer en wijlen Prof. Dr. Albert Trouwborst. Hij behaalde zijn doctoraal antropologie (cum laude) in 1989 en zijn artsenbul in 1991. Tijdens zijn studententijd had hij twee grote leermeesters in de medische antropologie: allereerst Prof. Dr. Vincent van Amelsvoort voor wie hij een liber amicorum redigeerde, en later Prof. Dr. Sjaak van der Geest.

Van 1991 tot 1996 volgde hij de opleiding tot psychiater in het voormalige APZ Wolfheze (opleider Fons Tholen) nu onderdeel van Pro Persona, Riagg Barneveld (opleider Zdravko Košutić) en ziekenhuis Overvecht te Utrecht (opleider Rolf Lanting). Vanaf 1996 werkt hij als psychiater bij de Gelderse Roos, het huidige Pro Persona, eerst als hoofd behandeling bij Phoenix, een gespecialiseerde klinisch afdeling voor asielzoekers en vluchtelingen en vanaf 2007 als hoofdopleider psychiatrie voor Arnhem en Wolfheze. Voorts was hij ondermeer hoofd zorgprogramma psychose van de Gelderse Roos en van 1993 tot 2003 redacteur van het Vlaams-Nederlandse tijdschrift Medische Antropologie. Sedert 2012 is zijn hoofdfunctie hoofdopleider psychiatrie voor Pro Persona (Arnhem, Wolfheze, Nijmegen, Ede en Tiel). Daarnaast is hij binnen Pro Persona werkzaam als coördinator interculturalisatie, hoofd opleidingen van ProCES (Pro Persona Center for Education and Science), psychiater bij het team bipolaire stoornissen te Nijmegen en verricht hij second opinions bij het DACA (Diagnose- en AdviesCentrum Allochtonen) van Pro Persona te Arnhem. Daarnaast is hij redacteur van de rubriek 'transculturele psychiatrie' van [www.psychiatrienet.nl](http://www.psychiatrienet.nl) en heeft hij nog een aantal landelijke functies. Hij woont met zijn vrouw, dochter en zoon in de Overbetuwe.



