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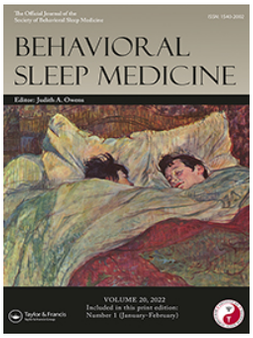

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Dissociative Symptoms are Highly Prevalent in Adults with Narcolepsy Type 1

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ABSTRACT

Introduction: The core symptoms of narcolepsy such as excessive daytime sleepiness and cataplexy are well known. However, there is mounting evidence for a much broader symptom spectrum, including psychiatric symptoms. Disordered sleep has previously been linked with dissociative symptoms, which may imply that patients with narcolepsy are more prone to develop such symptoms.

Objectives: To investigate the frequency of dissociative symptoms in adult patients with narcolepsy type 1 compared to population controls.

Methods: In a retrospective case control study, sixty adult patients fulfilling the criteria for narcolepsy type 1 and 120 matched population control subjects received a structured interview using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) to assess dissociative symptoms and disorders.

Results: A majority of narcolepsy patients reported dissociative symptoms, and even fulfilled the DSM-IV-TR criteria of a dissociative disorder (62% vs 1% in controls, $p < .001$). Most frequently reported symptoms were "dissociative amnesia" (37% vs 1%, $p < .001$) and "dissociative disorder of voluntary movement" (32% vs 1%, $p < .001$).

Conclusion: Dissociative symptoms are strikingly prevalent in adult patients with narcolepsy type 1. Although a formal diagnosis of dissociation disorder should not be made as the symptoms can be explained by narcolepsy as an underlying condition, the findings do illustrate the extent and severity of the dissociative symptoms. As for the pathophysiological mechanism, there may be symptom overlap between narcolepsy and dissociation disorder. However, there may also be a more direct link between disrupted sleep and dissociative symptoms. In either case, the high frequency of occurrence of dissociative symptoms should result in an active inquiry by doctors, to improve therapeutic management and guidance.

Introduction

Narcolepsy is a chronic neurologic sleep disorder with an estimated prevalence of 20–50 per 100.000 (Longstreth et al., 2007). It is caused by a deficiency of the hypocretin neuropeptides, most likely through an autoimmune process affecting the producing neurons in the dorsolateral hypothalamus (Kornum et al., 2017; Peyron et al., 2000; Thannickal et al., 2000).

Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy. In addition, patients with narcolepsy experience disordered sleep in terms of fragmentation and abnormal

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expressions of rapid eye movement (REM) sleep, such as rapid transitions into REM sleep, hypnagogic and hypnopompic hallucinations and sleep paralysis (Dauvilliers et al., 2007; Sturzenegger & Bassetti, 2004). Importantly, besides these "core" symptoms, patients often have other, not sleep-related complaints including obesity, fatigue, and psychiatric signs including anxiety and eating disorder symptoms (Canellas et al., 2014; Fortuyn et al., 2010, 2011, 2008; Lecendreux et al., 2015; Oosterloo et al., 2006).

Narcolepsy affects the life of patients in a broad sense, with a deleterious impact on education, recreation, driving, sexual functioning and personality, which in turn harms psychosocial wellbeing (Raggi et al., 2019). The prevalence of affective disorders in adults with narcolepsy may be as high as 35% (Fortuyn et al., 2010; Ohayon, 2013) and ADHD symptoms are often reported by both pediatric and adult patients (Kim et al., 2020; Plazzi et al., 2018).

The causes of the high prevalence of psychiatric signs and symptoms are still under discussion. First, the hypocretin system might play a direct role in the pathogenesis of psychiatric disorders. For example, most of the mood-related brain regions, such as the amygdala, striatum and prefrontal cortex, are widely innervated by hypocretin neurons and vice versa (Chen et al., 2015). Second, psychiatric symptoms may arise as a result of the burden narcolepsy poses on an individual (Stores et al., 2006).

Over the past two decades, studies have increasingly shown a relationship between disordered sleep and dissociation (Koffel & Watson, 2009; Lynn et al., 2019; Selvi et al., 2015; Van Der Kloet et al., 2013; Van Der Kloet, Giesbrecht et al., 2012; Van Heugten-van Der Kloet et al., 2014). The American Psychiatric Association defines dissociation as "a disruption of the usually integrated functions of consciousness, memory, identity or perception of the environment" (American Psychiatric Association, 2000). Several pathologic dissociative symptoms can be distinguished. These include feeling like everything is unreal (derealization) and feeling disconnected from one's body or feelings (depersonalization). In addition, they include amnesia for personal information or events that are too extensive to be explained by ordinary forgetfulness (dissociative amnesia). Dissociation may also lead to identity alteration; learning from others of activity of alternate identities, feeling possessed or controlled, and perceiving internal images and voices (identity alteration) (Korzekwa et al., 2009). The DSM-IV-TR lists four diagnoses under the category "dissociative disorder": dissociative amnesia, dissociative fugue (a sudden, unexpected travel away from one's home with an inability to recall some or all of one's past), depersonalization disorder, dissociative identity disorder. Dissociative disorder "not otherwise specified" refers to various forms of dissociation that are not fully covered by any of the specific dissociative disorder (American Psychiatric Association, 2000)

Some authors argue that dissociation is a result of the infiltration of dreamlike mentation during the day which could eventually initiate episodes of derealization or depersonalization (Lynn et al., 2019). In 2009, Koffel & Watson reviewed the relation between unusual sleep experiences and dissociation (Koffel & Watson, 2009). They suggest that dissociation and sleep experiences such as nightmares, vivid dreams and hypnagogic or hypnopompic hallucinations represent a common domain with possibly a shared etiology.

The present study hypothesizes that adult narcolepsy type 1 patients express more dissociative symptoms than population controls. In a retrospective case-control design, dissociative symptoms were assessed using a well-validated, psychiatric semi-structured interview.

Methods

Participants

Sixty adult (≥18 years old) patients with narcolepsy type 1 were recruited from September 1996 till November 2006 at the Center for Sleep Medicine "Kempenhaeghe" (Heeze, the Netherlands) and through the Dutch narcolepsy patient association. Recruitment of patients was relatively low at first, partly due to fear of stigmatization from the patients. However, especially after the hypocretin findings

sparked interest in underlying mechanisms, the interest in the topic of psychiatric comorbidity increased, and recruitment was restarted. In addition, later on the population control dataset (see below) became available.

Patients were included if they fulfilled the criteria of narcolepsy with cataplexy, and as such all met the criteria of narcolepsy type 1 according to the current standards of the International Classification of Sleep Disorders (ICSD-3) (Medicine, 2014). We only included adult patients, aged eighteen years or older. Patients were excluded when other sleep disturbances were present as a potential cause for excessive daytime sleepiness, such as sleep-related breathing disorders. Diagnoses were confirmed by review of the medical records including clinical notes, overnight sleep studies and multiple sleep latency testing.

Population controls (n = 120) were selected from the cross-sectional population-based Nijmegen-Health-Area-2 study, in which psychiatric symptoms were assessed in 368 people from the Dutch population (Hodiamont et al., 2005). Controls were matched for age, sex and urban environment (living in a community with more or less than 100.000 inhabitants). Nor in the narcolepsy group nor the population control group, participants were excluded based on their mental status.

Procedure

After approval from the medical ethical committee of the Radboud University Nijmegen Medical Center, patients were asked by their physician if they were interested to participate in a study, in which a clinical assessment about possible psychiatric complaints would take place. Patients then received further information about the study and were included after informed consent. Patients were also recruited during general information sessions about narcolepsy held by the patient organizations. In case a patient showed interest in participating in the study, they received further information and were included after they gave their written informed consent.

Measure

Symptoms of dissociation were assessed in a semi-structured interview guided by the Dutch edition of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), version 2.1 (Rijnders et al., 2000). The SCAN stems from the "Present State Examination" (PSE) and is a validated diagnostic instrument that is widely endorsed (Brugha et al., 2001; Schützwohl et al., 2007). It is not constructed explicitly for use with either ICD-10 or DSM-IV-TR but can be used for both systems. We described the presence of a variety of dissociative symptoms in patients and controls. To assess whether patients fulfilled the criteria of a dissociative disorder we used the DSM-IV-TR, which was the main reference during the time data collection took place for this study. It should be noted however that a formal diagnosis of dissociative disorder should not be made if there is an underlying somatic/neurological disease, in this case, narcolepsy. Nevertheless, fulfilling the DSM-IV-TR criteria for a dissociative disorder, does illustrate the extent and severity of dissociative symptoms.

All interviews were performed by trained and certified SCAN interviewers. DSM-IV-TR diagnostic classifications were derived from the computerized version of the SCAN 2.1 (Ishell, version 1.0.4.6).

For the current analysis, items were used from Chapter 2 ("Somatoform and dissociative disorders") augmented with items of Chapter 16 ("Perceptual disorders other than hallucinations") that contribute to the diagnosis of dissociation. Besides, Chapter 7 items "loss of concentration" and "insufficient thinking" (phrasing as used in the SCAN), were included. Table 1 shows relevant probing questions from the SCAN 2.1 interview.

Individual symptoms were scored using rating scales with the following basic format: 0: a positive rating of absence; 1: symptom occurred but uncommon or transitory; 2: symptom was present, on multiple occasions or for part of the time; 3: symptom was present more or less continuously. Ratings were then dichotomized as "absent" (score 0 or 1) or "present" (score 2 or 3).

Table 1. Key SCAN 2.1 questions probing symptoms of dissociation (Rijnders et al., 2000).

Dissociative amnesia: "You mentioned that you had memory problems, could you tell more about them, please? Are they present all the time or do they come and go?"
Amnesia centered around recent stress: "When did the memory problems start? Were you under any particular stress then? What were your personal relationships like at that time?"
Dissociative fugue: "Have you ever found yourself a long way from your usual range of travel without being able to remember how you got there?"
Dissociative stupor: "You mentioned that you had lost consciousness or experienced trances or fits, recently. Could you tell me more about that, please?"
Trance experience: "Have you experienced being in an altered state of consciousness or trance?"
Possession experience: "Have you had the experience of being taken over by some influence or power?"
Dissociative convulsions: "Have you had any faints or fits or convulsions recently?"
Dissociative sensory loss or anesthesia: "Have you had any loss of vision, hearing, vibration, or smell or touch? Can you feel heat and cold normally?"
Dissociative disorder of voluntary movement: "Have you been unable to move an arm or a leg, some part of a limb? Have you found your movements uncoordinated and that you could not stand unaided?"
Association of dissociative symptoms with stress: "When you experienced this problem were you under any particular stress?"
Multiple Personality: (1) Two or more discrete personalities: absent/ present. (2) Each personality is complete (3) Each personality is manifested by discrete periods of control of behavior (4) Extensive forgetfulness with inability to recall important personal information.
Changing perceptions: "Do things seem to change in size or shape or color in a puzzling way?"
Dulled perception: "Have things looked grey and flat; lacking their usual color and detail?"
Heightened perception: "Do sounds seem unnaturally clear or loud or objects look vividly colored or patterns seem particularly detailed and interesting?"
Changed perception of time, déja vu, jamais vu: "Does your experience of time seem to have changed?"
Derealization (things): "Have you felt recently as though the world was unreal, or only an imitation of reality, like a stage set, with cardboard cut-outs instead of real houses or trees? What was that like?"
Derealization (people): "Did other people seem to be acting a part, like actors in a play or like puppets, or even dead?"
Depersonalization: "Have you felt that you yourself were not a real person, not really part of the living world? Like living in a dream? Not really here? Like acting in a play with all the lines laid down?"
Depersonalized perception of self: "Do you seem unreal to yourself when you look in a mirror or on a photograph? Do you find that you seem to be seeing yourself from outside your body like a stranger?"
Unfamiliarity (self): "Have you felt that part of your body did not belong to you or looked unfamiliar, or the wrong size?"

Statistics

Data are presented as a frequency or as mean ± sd. For each SCAN item, frequencies were determined by considering the first two categories as being a negative score and the other categories as a positive score. Frequencies were then compared between the narcolepsy and control group using Fisher's exact test. On a symptom level, twenty-two Fisher's tests were done. In order to decrease the risk of a type 1 error, a Bonferroni correction was applied, resulting in a significance level of 0.00227. For secondary outcome measures we used a significance level of $p < .01$. Fisher's tests were also used to determine whether there was any influence of medication (both overall and per medication group) and gender on dissociative symptoms and disorders.

Results

Demographic characteristics and medication use are listed in Table 2. Narcolepsy patients and controls were well matched for gender, age and urban environment. Patients had a mean age of 43.5 (range 26.9–59.1). About half of the narcolepsy patients used stimulant medication to suppress sleepiness; less than half used antidepressant medication for cataplexy or sodium oxybate. Only 2% of the patients used antipsychotics. Less than one-third did not use any medication.

In Table 3, the symptoms assessed in SCAN Chapter 2 ("Somatoform and dissociative disorders„) and Chapter 16 ("Perceptual disorders other than hallucinations„) are summarized in order of prevalence. While only 1% of controls reported dissociative amnesia, more than a third of patients with narcolepsy reported this as a symptom. Dissociative disorder of voluntary movement was present in 32% of the patients. While none of the controls reported having experienced derealization and only

Table 2. Demographic and clinical characteristics.

	Narcolepsy Patients	Controls
N	60	120
Age (yrs)	43.5 ± 15.6	43.5 ± 15.4
Males	28 (47%)	56 (47%)
Age at onset (yrs)	20.1 ± 9.2	n.a.
Age at diagnosis (yrs)	30.6 ± 11.6	n.a.
Duration of symptoms (yrs)	23.9 ± 15.8	n.a.
Time since diagnosis(yrs)	10.5 ± 11.0	n.a.
Medication		
Stimulants	28 (47%)	0 (0%)
• Amfetamines	2 (3%)	
• Modiodal	13 (22%)	
• Methylphenidate	11 (18%)	
• Modiodal + Methylphenidate	2 (3%)	
Antidepressants	26 (43%)	5 (4%)
Sodium Oxybate	7 (12%)	0 (0%)
Antipsychotics	2 (2%)	0 (0%)
Antidepressants + Stimulants	12 (20%)	0 (0%)
Antidepressants + Sodium Oxybate	4 (7%)	0 (0%)
Stimulants + Sodium Oxybate	3 (5%)	0 (0%)
No medication	17 (28%)	115 (96%)

Table 3. Frequency of positive answers on SCAN section 2 and 16.

	Narcolepsy	Controls	P-value (Fisher Exact)
N	60	120	
Dissociative amnesia	22 (37%)	1 (1%)	<0.001
Dissociative Disorder of voluntary movement	19 (32%)	1 (1%)	<0.001
Dissociative fugue	15 (25%)	0 (0%)	<0.001
Changed perception of time, déja vu, jamais vu	15 (25%)	1 (1%)	<0.001
Trance experience	14 (23%)	0 (0%)	<0.001
Amnesia centered around recent stress	11 (18%)	0 (0%)	<0.001
Derealization (people)	9 (15%)	0 (0%)	<0.001
Derealization (things)	8 (13%)	0 (0%)	<0.001
Depersonalization	8 (13%)	1 (1%)	0.001
Dissociative sensory loss or anesthaesia	7 (12%)	0 (0%)	<0.001
Changing perception	7 (12%)	1 (1%)	0.002
Dulled perception	7 (12%)	1 (1%)	0.002
2 or more discrete personalities	6 (10%)	1 (1%)	0.006
Possession experience	6 (10%)	0 (0%)	0.001
Heightened perception	6 (10%)	0 (0%)	0.001
Association of dissociative symptoms with stress	5 (8%)	0 (0%)	0.004
Dissociative stupor	5 (8%)	0 (0%)	0.004
Depersonalized perception of self	4 (7%)	0 (0%)	0.012
Unfamiliarity (self)	4 (7%)	1 (1%)	0.043
Each personality is complete	2 (3%)	1 (1%)	0.263
Possession experience combined with trance	3 (3%)	0 (0%)	0.036
Dissociative convulsions	3 (3%)	0 (0%)	0.036

1 of the controls experienced depersonalization, these symptoms were present in respectively 15% (derealization people), 13% (derealization things) and 13% (depersonalization) of the patients. Although the prevalence was lower than the other symptoms, still 10% of narcolepsy patients reported having "2 or more discrete personalities", compared with only 1 patient in the control group. In almost half of the patients, the reported dissociative symptoms were associated with a significant disruption of their daily activities, in contrast to only 5% of the controls.

As indicated in Table 4, there were significantly more narcolepsy patients fulfilling the criteria of a dissociative disorder according to the DSM-IV-TR criteria, compared to controls. In fact, 62% of

Table 4. Number of subjects fulfilling DSM-IV-TR criteria of dissociative disorders.

	Narcolepsy	Controls	P-value (Fisher Exact)
N	60	120	
Dissociative disorders	37 (62%)	1 (1%)	<0.001
Dissociative amnesia	5 (8%)	0 (0%)	0.004
Dissociative identity disorder	0 (0%)	1 (1%)	1.000
Dissociative disorder not otherwise specified	32 (53%)	0 (0%)	<0.001

patients met the criteria of either a diagnosis of dissociative amnesia (8%) or a dissociative disorder not otherwise specified (NOS) (53%).

Significantly more women met the criteria for a dissociative disorder (25 female versus 12 male, p = .008). All patients fulfilling the criteria of dissociative amnesia (n = 5) were female. Subjectively insufficient thinking and loss of concentration were not significantly associated with a dissociative disorder (respectively 19/25 patients, p = .053 and 32/48 patients p = .014). No significant associations were found between dissociative disorders and the presence of disturbing dreams/nightmares, sleep terrors or hypnagogic hallucinations. The use of narcolepsy medication, in general, was not associated with a dissociative disorder neither were the specific use of stimulants, antidepressants, sodium oxybate or antipsychotics. On a symptom level, only dissociative fugue was significantly associated with the use of antidepressants (thirteen patients without antidepressants experienced dissociative fugue, in contrast to only one patient who was using antidepressants p = .02).

Discussion

We performed a case-control study using semi-structured formal psychiatric interviews and show for the first time that the majority of patients with narcolepsy type 1 display symptoms of dissociation. More than 60% of patients fulfilled the DSM-IV-TR criteria for a dissociative disorder versus only 1% of matched population controls. More than half of the patients met the criteria for "dissociative disorder NOS", and almost 10% the criteria for "dissociative amnesia". As mentioned before, a formal diagnosis of dissociation should not be made if symptoms can be the result of an underlying neurologic or somatic disease. However, these findings do illustrate the significant extent and severity of dissociative symptoms in narcolepsy. On the symptom level, dissociative amnesia, dissociative disorder of voluntary movement, dissociative fugue, changed perception of time, trance experience and amnesia centered around recent stress were most frequently reported. The abundant presence and wide range of dissociative symptoms is remarkable. Perhaps the most striking example of a dissociative symptom is that 10% of the patients reported the experience of harboring two or more discrete personalities, compared to none of the control subjects.

Epidemiological studies in the general population find a prevalence of dissociative disorder with rates in the order of 1–3% (Rauschenberger & Lynn, 1995; Sandberg & Lynn, 1992), in agreement with our control group. Studies regarding gender differences in dissociation were not conclusive (Spitzer et al., 2003; Vanderlinden et al., 1993). In our study, we found no gender differences on a symptom level. However, females did meet the criteria for dissociative disorders more often.

The 'formal' diagnosis based on the SCAN 2.1 interview is mainly indicating the significant presence of dissociative symptoms, but obviously, caution should be exercised regarding the underlying cause. Symptoms due to a periodic lowering of consciousness with an organic cause, as in narcolepsy, and symptoms due to a presumed functional cause of changed consciousness, as in dissociation disorder, could very well be similar. Symptoms such as dissociative amnesia and trance experience could be caused by the excessive daytime sleepiness, characteristic for narcolepsy. Moreover, automatic behavior as a result of hypersomnolence is often reported in narcolepsy, involving sometimes bizarre behavior accompanied by amnesia (Sturzenegger & Bassetti, 2004). This could very well match the description of a "dissociative fugue" according to the DSM-IV-TR or a "sleep-related dissociative disorder" according to the ICD-10.

In the past two decades, several studies highlight the importance of unusual sleep experiences in the development of dissociative symptoms (Koffel & Watson, 2009; Lynn et al., 2019); (Selvi et al., 2015; Van Heugten-van Der Kloet, Cosgrave et al., 2015; Van Heugten-van Der Kloet, Giesbrecht et al., 2015). Unusual sleep experiences in these studies were defined as nightmares, vivid dreaming, "narcolepsy symptoms" and complex nighttime behavior. Van der Kloet et al. reviewed 23 clinical and non-clinical studies, showing a correlation between unusual sleep experiences and dissociative symptoms (Van Der Kloet, Merckelbach et al., 2012). Several studies demonstrate an increase in dissociative symptoms triggered by sleep deprivation (Giesbrecht et al., 2007; Selvi et al., 2015; Van Heugten-van Der Kloet, Giesbrecht et al., 2015) whereas sleep normalization was accompanied by a reduction of dissociative symptoms (Van Heugten-van Der Kloet, Giesbrecht et al., 2015). In addition, longer REM sleep periods during the night were predictive of dissociation (Van Heugten-van Der Kloet et al., 2013). In this study, no significant associations were found between dissociative disorders and the presence of disturbing dreams or nightmares, sleep terrors or hypnagogic hallucinations, however this could be due to the fact that the prevalence of all these symptoms are very high in narcolepsy in general (Kornum et al., 2017; Pisko et al., 2014). It is evident that people with narcolepsy suffer from disordered sleep, and moreover, the mentioned "unusual sleep experiences" are part of the core symptoms of narcolepsy. In this sense, our findings strengthen the presumed link between disordered sleep, unusual sleep experiences and dissociation. Lynn et al. argue that sleep disturbances and unusual sleep experiences can persist to an attenuated degree in everyday life, and push waking consciousness more toward the dreaming end of the sleep-wake continuum (Lynn et al., 2019; Van Heugten-van Der Kloet et al., 2013).

Narcolepsy is caused by a deficiency in hypothalamic hypocretin signaling (Peyron et al., 2000; Thannickal et al., 2000). The hypocretin neurons are presumed to stabilize transitions between wake and sleep by stimulating wakefulness and preventing uncontrolled transitions between sleep states (Saper et al., 2005). Saper described two master- switches in the brainstem, controlling the sleep-wake cycle. The hypocretin deficiency causing type 1 narcolepsy results in faster and more unstable transitions between and within different sleep states, dreaming, and wakefulness (Schoch et al., 2017). Since hampered (meta)consciousness is a key element in the understanding of dissociation (American Psychiatric Association, 2000; Lynn et al., 2019), it does not seem unreasonable to suggest that a flawed regulation of consciousness ultimately results in dissociation. So, the neural circuit that is responsible for consciousness, could be responsible for the expression of dissociative symptoms as well. This would locate the source of dissociation in this brainstem circuit. So far other circuits, in the limbic system and (pre)frontal cortex have been found to be functional in producing dissociation (Brand et al., 2012; Krause-Utz et al., 2017). These circuits do not by themselves have a function in regulating consciousness but do undergo secondary changes in activity during the phases of wake, REM- and non-REM- sleep. Hypothetically, instability of the sleep-wake cycle in narcolepsy could be part of the explanation of the dissociative symptoms. Because of the breakdown of the usually strictly orchestrated sleep states, components of REM sleep express themselves independently resulting in cataplexy, sleep paralysis, hypnagogic hallucinations and automatisms. During REM sleep, the prefrontal areas of the brain are in a state of deactivation resulting in more fluid "reasoning" (Llewellyn, 2013). Excessive REM sleep pressure and the occurrence of (micro)sleep episodes during the day, could lead to more fluid and flexible reasoning, which is related to the occurrence of dissociative symptoms (Van Heugten-van Der Kloet et al., 2013). However, it should be mentioned that especially in the case of dissociative symptoms, the precise mechanisms in relation to (REM) sleep remain speculative.

Dissociative symptoms are not limited to dissociative disorders, but can occur in a variety of mental health problems such as post-traumatic stress disorder (PTSD) and schizophrenia. Often, dissociation in these other conditions has been found to be related to traumatic experiences. Because of the presence of hypnagogic hallucinations, narcolepsy patients have been misdiagnosed with schizophrenia or other psychotic disorders (Plazzi et al., 2015). However, a role for trauma in the emergence of dissociation in narcolepsy patients has not been established, nor have there been reports of an

overrepresentation of PTSD in narcolepsy patients. So, although there seems to be some overlap in symptoms between schizophrenia and narcolepsy, phenotypically the hypnagogic hallucinations in narcolepsy have been shown to be different from hallucinations of schizophrenic patients. Moreover, delusions are exceptional in narcolepsy patients, but hallmarks in schizophrenic patients (Fortuyn et al., 2009).

The results of the present study show that patients with narcolepsy type 1 are more prone to develop dissociative symptoms. Whatever the underlying cause, the high prevalence of dissociative symptoms implicates that patients and their close family members should be educated about the possible occurrence and should be given the opportunity to discuss these symptoms with their treating health professionals. Not only can the presence of dissociative symptoms in narcolepsy patients aggravate the burden that narcolepsy patients experience, it can also lead to significant functional impairment at school, work or in social interaction. In our study, narcolepsy medication in terms of stimulants, antidepressants, antipsychotics or sodium oxybate did not affect the occurrence of dissociative symptoms, nor dissociative disorders. Therefore, adjusting narcolepsy medication is not likely to have a direct effect. Psychological treatment recommendations for dissociative symptoms or disorders are often based on the assumption of an underlying trauma causing the symptoms (International Society for the Study of Trauma and Dissociation, 2011). As there is no evidence in the literature that narcolepsy patients are more traumatized compared to the general population, treatment focusing on an underlying trauma is probably not beneficial. Nevertheless, it is recommended to explore the possibility of trauma during the diagnostic process. Treatment of dissociative symptoms or disorders in patients with narcolepsy which are not related to trauma, could be part of a cognitive behavioral therapy, focusing on optimizing sleep and lifestyle, psycho-education, and enhancing coping skills. Since narcolepsy is usually treated in a multidisciplinary way, a psychologist should be involved in the care of these patients, with specific expertise in narcolepsy. It should be noted that, effects of these interventions in narcolepsy patients are hypothetical and lack scientific evidence at this time.

More and more it is becoming clear that the spectrum of narcolepsy is much broader than the "narcoleptic pentad" (Canellas et al., 2014; Droogleever Fortuyn et al., 2012; Fortuyn et al., 2010; Zhang et al., 2018). From a clinical point of view, this might lead to difficulties not to miss symptoms, or having "blind spots". From a research perspective, it also raises the question if these, perhaps less obvious, symptoms have interdependencies and could possibly be clustered. Longitudinal monitoring of the broad spectrum of narcolepsy symptoms may be useful to discover such relations and to increase our understanding of the course of symptoms. Modern tools may help in such studies, for example, with the Narcolepsy Monitor, a recently developed mobile app enabling long-term monitoring of the subjective severity of a wide range of narcolepsy symptoms (Quaedackers et al., 2020).

In this study we used the DSM-IV-TR criteria to assess the presence of dissociative disorders. The DSM-IV-TR was replaced by the DSM-5 in 2013, so the new system was not yet available during data collection. However, since the purpose of this study is to emphasize the presence of dissociative symptoms rather than diagnosis, in patients with narcolepsy, the precise diagnostic classification system is less relevant. Also, given the adult age of the narcolepsy patients included in this study, we have no information about the prevalence of dissociative symptoms in children or adolescents with narcolepsy. Another issue which could be addressed in future prospective studies is the lack of polysomnographic data and detailed information about the dose and timing of medication. While some studies have suggested an association between sleep deprivation or sleep fragmentation and the occurrence of dissociative symptoms, our data did not suffice to either confirm or refute this hypothesis. Future research could employ a prospective design with detailed registration of medication use and new technologies to monitor sleep architecture over longer time periods and correlate this to the presence of dissociative symptoms. Future studies could also consider contrasting narcolepsy type 1 versus type 2 with respect to the presence of dissociative symptoms, to gain more insight in the specific role of hypocretin deficiency. Assessing relation with the severity or frequency of cataplexy would need a longitudinal follow up design which would not be easy, but very interesting.

In summary, the results of this study show a high prevalence of dissociative symptoms in patients with narcolepsy type 1. Although there might be an overlap between symptoms of dissociation and symptoms of narcolepsy, the proportion of narcolepsy patients suffering from dissociative symptoms is strikingly high and may impact a broader sense of wellbeing and quality of life. Dissociation in narcolepsy type 1 could be a more serious and more frequent symptom than is currently assumed. Caregivers should actively inquire not only after the classical symptoms of narcolepsy, but also after the presence of less obvious symptoms, such as dissociation.

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References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed ed.). text rev.

Brand, B. L., Lanius, R., Vermetten, E., Loewenstein, R. J., & Spiegel, D. (2012). Where are we going? An update on assessment, treatment, and neurobiological research in dissociative disorders as we move toward the DSM-5. *Journal of Trauma & Dissociation*, *13*(1), 9–31. https://doi.org/10.1080/15299732.2011.620687

Brugha, T. S., Jenkins, R., Taub, N., Meltzer, H., & Bebbington, P. E. (2001). A general population comparison of the composite international diagnostic interview (CIDI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). *Psychological Medicine*, *31*(6), 1001–1013. https://doi.org/10.1017/s0033291701004184

Canellas, F., Lin, L., Julià, M. R., Clemente, A., Vives-Bauza, C., Ollila, H. M., Hong, S. C., Arboleya, S. M., Einen, M. A., Faraco, J., Fernandez-Vina, M., & Mignot, E. (2014). Dual cases of type 1 narcolepsy with schizophrenia and other psychotic disorders. *Journal of Clinical Sleep Medicine*, *10*(9), 1011–1018. https://doi.org/https://doi.org/10.5664/jcsm.4040

Chen, Q., De Lecea, L., Hu, Z., & Gao, D. (2015). The hypocretin/orexin system: An increasingly important role in neuropsychiatry. *Med Res Rev*, *35*(1), 152–197. https://doi.org/10.1002/med.21326

Dauvilliers, Y., Arnulf, I., & Mignot, E. (2007). Narcolepsy with cataplexy. *Lancet*, *369*(9560), 499–511. https://doi.org/10.1016/s0140-6736(07)60237-2

Droogleever Fortuyn, H. A., Fronczek, R., Smitshoek, M., Overeem, S., Lappenschaar, M., Kalkman, J., Renier, W., Buitelaar, J., Lammers, G. J., & Bleijenberg, G. (2012). Severe fatigue in narcolepsy with cataplexy. *Journal of Sleep Research*, *21*(2), 163–169. https://doi.org/10.1111/j.1365-2869.2011.00943.x

Fortuyn, H. A., Lappenschaar, G. A., Nienhuis, F. J., Furer, J. W., Hodiamont, P. P., Rijnders, C. A., Lammers, G. J., Renier, W. O., Buitelaar, J. K., & Overeem, S. (2009). Psychotic symptoms in narcolepsy: Phenomenology and a comparison with schizophrenia. *General Hospital Psychiatry*, *31*(2), 146–154. https://doi.org/10.1016/j.genhosppsych.2008.12.002

Fortuyn, H. A., Lappenschaar, M. A., Furer, J. W., Hodiamont, P. P., Rijnders, C. A., Renier, W. O., Buitelaar, J. K., & Overeem, S. (2010). Anxiety and mood disorders in narcolepsy: A case-control study. *General Hospital Psychiatry*, *32*(1), 49–56. https://doi.org/10.1016/j.genhosppsych.2009.08.007

Fortuyn, H. A., Mulders, P. C., Renier, W. O., Buitelaar, J. K., & Overeem, S. (2011). Narcolepsy and psychiatry: An evolving association of increasing interest. *Sleep Medicine*, *12*(7), 714–719. https://doi.org/10.1016/j.sleep.2011.01.013

Fortuyn, H. A., Swinkels, S., Buitelaar, J., Renier, W. O., Furer, J. W., Rijnders, C. A., Hodiamont, P. P., & Overeem, S. (2008). High prevalence of eating disorders in narcolepsy with cataplexy: A case-control study. *Sleep*, *31*(3), 335–341. https://doi.org/10.1093/sleep/31.3.335

Giesbrecht, T., Smeets, T., Leppink, J., Jelicic, M., & Merckelbach, H. (2007). Acute dissociation after 1 night of sleep loss. *Journal of Abnormal Psychology*, *116*(3), 599–606. https://doi.org/10.1037/0021-843X.116.3.599

Hodiamont, P. P., Rijnders, C. A., Mulder, J., & Furer, J. W. (2005). Psychiatric disorders in a Dutch Health Area: A repeated cross-sectional survey. *Journal of Affective Disorders*, *84*(1), 77–83. https://doi.org/10.1016/j.jad.2004.09.001

International Society for the Study of Trauma and Dissociation. (2011). Guidelines for treating dissociative identity disorder in adults, third revision. *Journal of Trauma & Dissociation*, *12*(2), 115–187. https://doi.org/10.1080/15299732.2011.537247

Kim, J., Lee, G. H., Sung, S. M., Jung, D. S., & Pak, K. (2020). Prevalence of attention deficit hyperactivity disorder symptoms in narcolepsy: A systematic review. *Sleep Medicine*, *65*, 84–88. https://doi.org/10.1016/j.sleep.2019.07.022

Koffel, E., & Watson, D. (2009). Unusual sleep experiences, dissociation, and schizotypy: Evidence for a common domain. *Clinical Psychology Review*, *29*(6), 548–559. https://doi.org/10.1016/j.cpr.2009.06.004

Kornum, B. R., Knudsen, S., Ollila, H. M., Pizza, F., Jennum, P. J., Dauvilliers, Y., & Overeem, S. (2017). Narcolepsy. *Nature Reviews Disease Primers*, *3*(1), 16100. https://doi.org/10.1038/nrdp.2016.100

Korzekwa, M. I., Dell, P. F., & Pain, C. (2009). Dissociation and borderline personality disorder: An update for clinicians. *Current Psychiatry Reports*, *11*(1), 82–88. https://doi.org/10.1007/s11920-009-0013-1

Krause-Utz, A., Frost, R., Winter, D., & Elzinga, B. M. (2017). Dissociation and alterations in brain function and structure: Implications for borderline personality disorder. *Current Psychiatry Reports*, *19*(1), 6. https://doi.org/10.1007/s11920-017-0757-y

Lecendreux, M., Lavault, S., Lopez, R., Inocente, C. O., Konofal, E., Cortese, S., Franco, P., Arnulf, I., & Dauvilliers, Y. (2015). Attention-deficit/hyperactivity disorder (ADHD) symptoms in pediatric narcolepsy: A cross-sectional study. *Sleep*, *38*(8), 1285–1295. https://doi.org/10.5665/sleep.4910

Llewellyn, S. (2013). Such stuff as dreams are made on? Elaborative encoding, the ancient art of memory, and the hippocampus. *Behavioral and Brain Sciences*, *36*(6), 589–607. https://doi.org/10.1017/S0140525X12003135

Longstreth, W. T., Jr., Koepsell, T. D., Ton, T. G., Hendrickson, A. F., & Van Belle, G. (2007). The epidemiology of narcolepsy. *Sleep*, *30*(1), 13–26. https://doi.org/10.1093/sleep/30.1.13

Lynn, S. J., Maxwell, R., Merckelbach, H., Lilienfeld, S. O., Kloet, D. V. H., & Miskovic, V. (2019). Dissociation and its disorders: Competing models, future directions, and a way forward. *Clin Psychol Rev*, *73*, 101755. https://doi.org/10.1016/j.cpr.2019.101755

Lyssenko, L., Schmahl, C., Bockhacker, L., Vonderlin, R., Bohus, M., & Kleindienst, N. (2018). Dissociation in psychiatric disorders: A meta-analysis of studies using the dissociative experiences scale. *American Journal of Psychiatry*, *175*(1), 37–46. https://doi.org/10.1176/appi.ajp.2017.17010025

Medicine, A. A. O. S. (2014). International classification of sleep disorders—third edition (ICSD-3). *AASM Resource Library*.

Ohayon, M. M. (2013). Narcolepsy is complicated by high medical and psychiatric comorbidities: A comparison with the general population. *Sleep Medicine*, *14*(6), 488–492. https://doi.org/10.1016/j.sleep.2013.03.002

Oosterloo, M., Lammers, G. J., Overeem, S., De Noord, I., & Kooij, J. J. (2006). Possible confusion between primary hypersomnia and adult attention-deficit/hyperactivity disorder. *Psychiatry Research*, *143*(2–3), 293–297. https://doi.org/10.1016/j.psychres.2006.02.009

Peyron, C., Faraco, J., Rogers, W., Ripley, B., Overeem, S., Charnay, Y., Nevsimalova, S., Aldrich, M., Reynolds, D., Albin, R., Li, R., Hungs, M., Pedrazzoli, M., Padigaru, M., Kucherlapati, M., Fan, J., Maki, R., Lammers, G. J., Bouras, C., Kucherlapati, R., … Mignot, E. (2000). A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Medicine*, *6*(9), 991–997. https://doi.org/10.1038/79690

Pisko, J., Pastorek, L., Buskova, J., Sonka, K., & Nevsimalova, S. (2014, August). Nightmares in narcolepsy: Underinvestigated symptom? *Sleep Medicine*, *15*(8), 967–972. https://doi.org/10.1016/j.sleep.2014.03.006

Plazzi, G., Clawges, H. M., & Owens, J. A. (2018). Clinical characteristics and burden of illness in pediatric patients with narcolepsy. *Pediatric Neurology*, *85*, 21–32. https://doi.org/10.1016/j.pediatrneurol.2018.06.008

Plazzi, G., Fabbri, C., Pizza, F., & Serretti, A. (2015). Schizophrenia-like symptoms in narcolepsy type 1: Shared and distinctive clinical characteristics. *Neuropsychobiology*, *71*(4), 218–224. https://doi.org/10.1159/000432400

Quaedackers, L., De Wit, J., Pillen, S., Van Gilst, M., Batalas, N., Lammers, G. J., Markopoulos, P., & Overeem, S. (2020). A mobile app for longterm monitoring of narcolepsy symptoms: Design, development, and evaluation. *JMIR Mhealth Uhealth*, *8*(1), e14939. https://doi.org/10.2196/14939

Raggi, A., Plazzi, G., & Ferri, R. (2019). Health-related quality of life in patients with narcolepsy: A review of the literature. *The Journal of Nervous and Mental Disease*, *207*(2), 84–99. https://doi.org/10.1097/NMD.0000000000000918

Rauschenberger, S. L., & Lynn, S. J. (1995). Fantasy proneness, DSM-III-R axis I psychopathology, and dissociation. *Journal of Abnormal Psychology*, *104*(2), 373–380. https://doi.org/10.1037//0021-843x.104.2.373

Rijnders, C. A., Van Den Berg, J. F., Hodiamont, P. P., Nienhuis, F. J., Furer, J. W., Mulder, J., & Giel, R. (2000). Psychometric properties of the schedules for clinical assessment in neuropsychiatry (SCAN-2.1). *Social Psychiatry and Psychiatric Epidemiology*, *35*(8), 348–352. https://doi.org/10.1007/s001270050249

Sandberg, D. A., & Lynn, S. J. (1992). Dissociative experiences, psychopathology and adjustment, and child and adolescent maltreatment in female college students. *Journal of Abnormal Psychology*, *101*(4), 717–723. https://doi.org/10.1037//0021-843x.101.4.717

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437* (7063), 1257–1263. https://doi.org/10.1038/nature04284

Schoch, S. F., Werth, E., Poryazova, R., Scammell, T. E., Baumann, C. R., & Imbach, L. L. (2017). Dysregulation of sleep behavioral states in narcolepsy. *Sleep*, *40*(12), 12. https://doi.org/10.1093/sleep/zsx170

Schützwohl, M., Kallert, T., & Jurjanz, L. (2007). Using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) as a diagnostic interview providing dimensional measures: Cross-national findings on the psychometric properties of psychopathology scales. *European Psychiatry*, *22*(4), 229–238. https://doi.org/10.1016/j.eurpsy.2006.10.005

Selvi, Y., Kiliç, S., Aydin, A., & Güzel Özdemir, P. (2015). The effects of sleep deprivation on dissociation and profiles of mood, and its association with biochemical changes. *Noro Psikiyatri Arsivi*, *52*(1), 83–88. https://doi.org/10.5152/npa.2015.7116

Spitzer, C., Klauer, T., Grabe, H. J., Lucht, M., Stieglitz, R. D., Schneider, W., & Freyberger, H. J. (2003). Gender differences in dissociation. A dimensional approach. *Psychopathology*, *36*(2), 65–70. https://doi.org/10.1159/000070360

Stores, G., Montgomery, P., & Wiggs, L. (2006). The psychosocial problems of children with narcolepsy and those with excessive daytime sleepiness of uncertain origin. *Pediatrics*, *118*(4), e1116–1123. https://doi.org/10.1542/peds.2006-0647

Sturzenegger, C., & Bassetti, C. L. (2004). The clinical spectrum of narcolepsy with cataplexy: A reappraisal. *Journal of Sleep Research*, *13*(4), 395–406. https://doi.org/10.1111/j.1365-2869.2004.00422.x

Thannickal, T. C., Moore, R. Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M., & Siegel, J. M. (2000). Reduced number of hypocretin neurons in human narcolepsy. *Neuron*, *27*(3), 469–474. https://doi.org/10.1016/S0896-6273(00)00058-1

Van Der Kloet, D., Giesbrecht, T., Franck, E., Van Gastel, A., De Volder, I., Van Den Eede, F., Verschuere, B., & Merckelbach, H. (2013). Dissociative symptoms and sleep parameters—an all-night polysomnography study in patients with insomnia. *Comprehensive Psychiatry*, *54*(6), 658–664. https://doi.org/10.1016/j.comppsych.2012.12.025

Van Der Kloet, D., Giesbrecht, T., Lynn, S. J., Merckelbach, H., & De Zutter, A. (2012). Sleep normalization and decrease in dissociative experiences: Evaluation in an inpatient sample. *Journal of Abnormal Psychology*, *121*(1), 140–150. https://doi.org/10.1037/a0024781

Van Der Kloet, D., Merckelbach, H., Giesbrecht, T., & Lynn, S. J. (2012). Fragmented sleep, fragmented mind: The role of sleep in dissociative symptoms. *Perspectives on Psychological Science*, *7*(2), 159–175. https://doi.org/10.1177/1745691612437597

Van Heugten-van Der Kloet, D., Cosgrave, J., Merckelbach, H., Haines, R., Golodetz, S., & Lynn, S. J. (2015). Imagining the impossible before breakfast: The relation between creativity, dissociation, and sleep. *Frontiers in Psychology*, *6*, 324. https://doi.org/10.3389/fpsyg.2015.00324

Van Heugten-van Der Kloet, D., Giesbrecht, T., & Merckelbach, H. (2015). Sleep loss increases dissociation and affects memory for emotional stimuli. *Journal of Behavior Therapy and Experimental Psychiatry*, *47*, 9–17. https://doi.org/10.1016/j.jbtep.2014.11.002

Van Heugten-van Der Kloet, D., Merckelbach, H., Giesbrecht, T., & Broers, N. (2014). Night-time experiences and daytime dissociation: A path analysis modeling study. *Psychiatry Res*, *216*(2), 236–241. https://doi.org/10.1016/j.psychres.2013.12.053

Van Heugten-van Der Kloet, D., Merckelbach, H., & Lynn, S. J. (2013). Dissociative symptoms and REM sleep. *Behavioral and Brain Sciences*, *36* (6), 630–631. discussion 634–659. https://doi.org/10.1017/S0140525X13001453

Vanderlinden, J., Van Dyck, R., Vandereycken, W., & Vertommen, H. (1993). Dissociation and traumatic experiences in the general population of The Netherlands. *Hospital & Community Psychiatry*, *44*(8), 786–788. https://doi.org/10.1176/ps.44.8.786

Zhang, Z., Mayer, G., Dauvilliers, Y., Plazzi, G., Pizza, F., Fronczek, R., Santamaria, J., Partinen, M., Overeem, S., Peraita-Adrados, R., Da Silva, A. M., Sonka, K., Rio-Villegas, R. D., Heinzer, R., Wierzbicka, A., Young, P., Högl, B., Bassetti, C. L., Manconi, M., Feketeova, E., … Khatami, R. (2018). Exploring the clinical features of narcolepsy type 1 versus narcolepsy type 2 from European Narcolepsy Network database with machine learning. *Scientific Reports*, *8*(1), 10628. https://doi.org/10.1038/s41598-018-28840-w