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ORIGINAL PAPER

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The spectra of neurasthenia and depression: course, stability and transitions

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Abstract *Background* Neurasthenia has had a chequered history, receiving changing labels such as chronic fatigue or Gulf war syndrome. Neurasthenia is recognized by ICD-10, but not by DSM-IV. Its course, longitudinal stability and relationship to depression is not well understood. *Methods* In a stratified community sample (n = 591), representative of 2600 persons of the canton of Zurich, Switzerland, neurasthenia and depression were assessed in six structured interviews between ages 20 and 41. Course, stability and comorbidity were examined. A severity spectrum of neurasthenia and depression from symptoms to diagnosis was taken into account. *Results* The annual prevalence of a neurasthenia diagnosis increased from 0.7% to 3.8% from age 22–41, while mere symptoms became less prevalent. Intra-individual courses improved in 40% and deteriorated in about 30% of symptomatic cases. The most frequent symptoms overall, besides criterial exhaustion, were increased need for sleep, over-sensitivity, nervousness and difficulty concentrating. Cross-sectional associations and overlap with depression were strong. Longitudinal stability of ICD-neurasthenia was low. *Conclusions* Neurasthenia is intermittent, overlaps significantly with depression, and shows improvement and deterioration over time to roughly equal measures.

Key words neurasthenia · depression · prevalence · course · comorbidity · spectrum

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Introduction

Neurasthenia is operationally defined by ICD-10 [39] as a syndrome of mental fatigue and/or physical exhaustion with a minimum duration of 3 months. Its world-wide significance was definitely established by the large prospective transcultural study of the WHO in general health care [25, 32]. In the United States it is dealt with mainly as the neurological disorder chronic fatigue syndrome (see review by Wessely [37]) and is absent from the psychiatric classification of DSM-IV (discussed by Morey and Kurtz [22]).

The history of neurasthenia has been summarised by Steiner [30], Fischer-Homberger [14], Gosling [16], Shorter [29], Wessely [36], Taylor [31] and Schäfer [26, 27]. According to Schäfer [26], neurasthenia was an element of melancholia until the 17th century. In the 18th century it was regarded as an element of hypochondriasis, and became an independent neuropsychiatric syndrome with Beard [8] and Van Deusen [33]. Over the past two decades it has continued to change its labels in a chameleon-like fashion in order to be socially acceptable and not stigmatising, overlapping with chronic fatigue syndrome, myalgic encephalomyelitis [36], Gulf War syndrome [18], burn-out syndrome [15], as well as with atypical depression [6].

Most research has focussed on *chronic* fatigue, and its symptoms have been studied internationally [38]. But it is plausible that a large number of patients also suffer from *acute*, shorter and impairing fatigue syndromes, as shown by earlier reports from the Zurich Study [1, 7, 21]. Such a dimensional neurasthenia spectrum was also proposed early by Sharpe et al. [28] and Pawlikowska et al. [23].

In the Zurich Study of a community sample the neurasthenic syndrome was one of 30 psychological and functional somatic syndromes assessed in six interviews from the ages of 20–41 [3]. The data make it possible to analyse symptoms of neurasthenia on a

continuum from tiredness to severe physical and mental fatigue and exhaustion (neurasthenia spectrum), its longitudinal development over 20 years and its association with depression.

Methods

Sample

The initial Zurich Study sample consisted of 4547 subjects (2201 men, 2346 women) representative of the canton of Zurich in Switzerland, who were screened with the Symptom Checklist 90-R (SCL-90-R; (17)). In order to increase the probability of including individuals at risk for psychiatric syndromes, a stratified subsample of 591 subjects (292 males, 299 females) was selected for interview, with 66% comprising individuals who scored above the 85th percentile on the SCL-90-R Global Severity Index ('high-risk group'), and 33% comprising a random sample of those scoring below the 85th percentile ('low-risk group'). The 591 subjects are representative of 2600 persons from the canton of Zurich. The initial screening was conducted in 1978, when the subjects were aged 19 (men) and 20 (women). Full interviews were conducted in 1979, 1981, 1986, 1988, 1993, and 1999, by trained clinical psychologists or psychiatrists in the participants' homes. A broad spectrum of 30 psychiatric and somatic syndromes was assessed, including exhaustion/fatigue and depression [3]. The interviewers all had a degree in psychopathology. They were trained in group interviews and by learning from experienced interviewers during interviews in the participants' homes.

Neurasthenia interview

The stem questions were adapted to current ICD concepts of neurasthenia and were in 1993/1999: 1) "in the last 12 months, did you experience being physically exhausted, washed out, done in, shattered, even in situations of marginal physical effort?", and 2) "in the last 12 months, did you sometimes experience a pronounced mental exhaustion and fatigue, even in situations of marginal mental effort?" If one of the questions was answered with yes, 20 symptoms were checked and an open question asked for possible other symptoms; the symptoms are listed in Table 2 of the results section.

Validity and reliability of interview

While we do not have data on the reliability of the interview section on neurasthenia, we have such data for the section on depression, which includes the "neurasthenic" items fatigue, lack of energy and motor slowing. In 1993, at the 5th interview of the Zurich study, an interrater-reliability analysis was conducted in eight raters who rated 22 participants using the depression section of the SPIKE interview. The percent interrater agreement on the presence/absence of symptoms was 95.6%. The corresponding mean value of Kappa was 0.89, indicating almost perfect agreement [5].

In 1984, after the 2nd interview, the sensitivity of the stem question for depression was calculated in 90 outpatients, against two gold standards: (1) the presence/absence of an ICD diagnosis for depression in the patient's medical history, and (2) the patient's BDI score, with scores >7 indicating depression [20]. Sensitivity was 0.93 in the first, and 0.98 in the second case. Since the answer to the stem question decides on who will be questioned further on the particular syndrome, these sensitivities indicate that the SPIKE stem question captured almost all patients who had a confirmed diagnosis of depression.

Taken together, we conclude that the SPIKE section on depression picks up the large majority of subjects at risk for depression, and that the assessment of these subjects' symptoms by the interviewers was reliable and consistent. We cannot answer the question for the neurasthenia section of the interview, but given the results for depression, we have no reason to doubt the reliability of the assessment of neurasthenic symptoms by our interviewers.

Diagnoses

Neurasthenia was defined by ICD-10 criteria [39] as a syndrome of mental fatigue and/or physical exhaustion with at least one of six criterial symptoms and a minimum duration of 3 months. No exclusion criteria were applied in order to allow us to study the associations with other syndromes. In the first interview (1979) 3-months neurasthenia was not yet assessed, only 1-month neurasthenia and shorter manifestations.

No somatic examinations were conducted to ascertain potential somatic causes of neurasthenia. Only *attributions* of somatic causes by the participants were recorded, which are known not to be a reliable guide to the presence of objective somatic causes. Inspection of the somatic causes reported by the subjects identified roughly three subjects per interview who might qualify for an organic cause for neurasthenic manifestations. None of these causes belonged to those listed in the ICD's exclusion criteria. Due to their small number and to the unreliability of causal attributions we did not exclude these subjects from analysis.

Our *neurasthenic spectrum* consists of: (1) 3-months neurasthenia according to ICD-10, (2) 2-weeks neurasthenia [7], (3) recurrent brief neurasthenia (RBN) [1] and (4) neurasthenic symptoms. RBN required the presence of a neurasthenic syndrome of short duration (<2 weeks) occurring at least 12 times in the previous year. Our spectrum concept arose from the systematically collected data in all syndromal sections of the interview; after the stem questions and list of symptoms, the duration (maximum, average) and frequency of neurasthenic episodes were assessed for the last 12 months as well as the estimated number of days/year with neurasthenic symptoms. Neurasthenia subgroups were formed according to different duration, frequency and severity criteria and the resulting spectrum was validated using clinical indicators such as treatment and suicide attempt rates, comorbidity, work and social impairment [2, 7, 21].

Major depressive episodes (MDE) were defined according to DSM-III R and dysthymia according to DSM-IV, without the application of any exclusion criteria. Our definition of minor depression was strict, i.e. requiring not two but three to four of the nine criterial symptoms of depression and a duration of at least 2 weeks. Recurrent brief depression was defined by about monthly or more frequent episodes of depression lasting <2 weeks, by the presence of five or more of the nine criterial symptoms, plus work impairment (ICD-10).

The diagnosis of bipolar I disorder was similar to the original definition of Dunner et al. [12], i.e. the presence of mania requiring hospitalisation was necessary; bipolar II disorder required the presence of a major depressive episode (DSM-III R) and episodes of overactivity plus two of seven criterial hypomanic symptoms [4]. A diagnostic group of minor bipolar disorder (MinBP) was included in the bipolar spectrum concept, comprising dysthymia, minor and recurrent brief depression in association with two of seven criterial hypomanic symptoms, and the chronic form, cyclothymic disorder [4].

Statistics

Prevalence rates were corrected for stratified sampling and weighted back to the population of 2600 subjects. We sometimes report "cumulative prevalence" rates, which is the prevalence cumulated over six interview years, i.e. the prevalence of ever having had a given syndrome/symptom in the 12 months preceding any of the interviews. Frequencies were compared across groups using χ^2-tests; Kruskal-Wallis tests were used for continuous data. For the analysis of symptom frequency (Table 2), in which several independent tests were carried out, we indicate which tests would be significant after Bonferroni correction.

Table 1 One-year and cumulated one-year prevalences (95% confidence intervals) of subgroups of neurasthenia across six interviews

Age (m/f)	Symptoms	RBN	2-weeks	3-months
20/21	24.6 (19.9–30.1)	5.4 (3.3–8.8)	2.4 (1.2–4.9)	–
22/23	19.1 (14.5–24.9)	1.9 (1.0–3.5)	0.9 (0.2–3.2)	0.7 (0.2–3.4)
27/28	7.1 (4.4–11.4)	4.8 (2.6–8.5)	1.8 (0.7–4.5)	1.3 (0.5–3.3)
29/30	8.1 (5.0–12.8)	3.1 (1.5–6.2)	3.0 (1.3–6.7)	3.0 (1.4–6.1)
34/35	6.8 (4.0–11.6)	4.0 (2.0–7.9)	1.0 (0.3–3.6)	2.0 (0.8–4.9)
40/41	5.8 (3.1–10.5)	4.7 (2.4–8.8)	7.4 (4.3–12.5)	3.8 (1.8–7.7)
Cumulative	28.4 (23.3–34.1)	12.1 (8.8–16.3)	9.7 (6.7–13.8)	6.0 (3.9–9.2)

To assess the longitudinal relationship between neurasthenia and depression, we ran a number of regression models. First, generalized estimating equations (GEE) models with dichotomous dependent and independent variables were run. GEE models include the data from all time points of a longitudinal study. Our first model included 3-months neurasthenia as the dependent variable; the predictor variables were: 3-months neurasthenia at any previous interview, a major depressive episode (MDE) at the same interview, and MDE at any previous interview. A second model included MDE as the dependent variable and the predictors were: 3-months neurasthenia at the same interview, 3-months neurasthenia at any previous interview, and MDE at any previous interview.

Variants of the two models were computed by replacing the predictor variables referring to *any* previous interview with predictors referring only to the *preceding* interview (1st-order lag variables). Sex, risk group and time were additional predictors in all GEE models.

As a simple test for the adequacy of the models, we compared the results of running these models with and without requiring robust Standard Errors, and found very good agreement, i.e. no more than 10% difference in SEs, and identical patterns of statistical significance.

The GEE models accommodate the longitudinal dependence of observations by directly modeling the within-subject correlation structure of the data. In this case, we chose an independent correlation structure that assumes independent correlations of observations within a single individual between adjacent points in time, as recommended by Diggle et al. [11] for transition models.

Results

Frequency and prevalence of diagnostic sub-groups

Table 1 shows that there was an increase of the one-year prevalence of 3-months neurasthenia from 0.7% to 3.8% from the second to the sixth interview (ages 22–41 years), and a decrease in the group with neurasthenic symptoms. RBN did not change clearly (from 5.4% to 4.7%), whereas 2-weeks neurasthenia increased from 2.4% to 7.4%. Across 20 years the cumulative incidence rate of 3-months neurasthenia was 6.0%, 5.5% for men and 6.5% for women (gender ratio F:M = 1:2:1). Restricted to cases with work and/or social impairment the cumulative incidence rate of 3-months neurasthenia remained 5.6%. The prevalence rate of treated 3-months neurasthenia was 3.2%, which represents 53.1% of all cases.

Stem questions

The two stem questions of criterion A of ICD-10 (physical and mental exhaustion/fatigue) were assessed separately in 1993 and 1999. Women complained of suffering from both symptoms slightly more often than men (prevalence rates 14.7% vs. 10.3%; $P = 0.32$); they reported physical exhaustion twice as often as men (16.5% vs. 7.9%; $P = 0.007$), whereas mental exhaustion was reported to a similar extent by women and men (10.2% vs. 9.1%; $P < 0.77$).

Symptoms

About 20 symptoms of neurasthenia, assessed during the third to the sixth interview (age 28–41), are listed in Table 2 for four groups: 3-months neurasthenia, 2-weeks neurasthenia, RBN and neurasthenic symptoms. 3-months neurasthenia generally had the highest load of symptoms, whereas subjects with only neurasthenic symptoms had the smallest load. The profiles of RBN and 2-weeks neurasthenia were roughly similar.

Apart from the characteristic symptoms of physical and mental exhaustion with increased need for sleep, the most frequent symptoms were over-sensitivity to external stimuli and to critical remarks, tension and difficulty concentrating. Over-sensitivity was also accompanied by lower stress tolerance.

Longitudinal overlap between neurasthenia and depression

The longitudinal overlap was strong. Fourty-four (68.5%) of the 64 subjects who ever reported 3-months neurasthenia in any of the interviews also ever reported MDE (OR = 4.5, 95% C.I. 2.5–7.9, $P < 0.001$; Fig. 1). Sixty to 79% of the subjects with 3-months neurasthenia had a previous or subsequent episode of subthreshold or threshold mood disorder. Twelve (18.8%) of the 64 cases with 3-months neurasthenia overlapped with dysthymia, minor depression or recurrent brief depression. 3-months neurasthenia without anxiety (panic or GAD) or mood disorder occurred in only 1.4% of the sample. Thirty-seven (55.2%) of the 67 subjects who ever suffered from 2-weeks neurasthenia ever had MDE (OR = 3.3, 95% C.I. 2.0–5.4, $P < 0.001$). If we include all subjects who ever reported symptoms, 316 (82.7%) of the 382 who ever reported neurasthenic symptoms also at some time reported depressive symptoms (OR = 6.9, 95% C.I. 3.6–13.5, $P < 0.001$).

Table 2 Frequency of symptoms of neurasthenia in different subgroups

	Groups	Neurasthenia 1	2	3	4	p (1–4)	p (2–4)
	Diagnosis	Symptoms	RBN	2-weeks	3-months		
	Subjects	68	69	47	63		
	Symptoms	%	%	%	%		
1	Low energy	10.3	30.4	23.4	39.7	0.02	0.04
2	Exhaustion	80.9	88.4	89.4	92.1	0.25	0.002
3	Physical weakness	52.9	60.9	74.5	74.6	0.03	0.002
4	Excessive physical fatigue	52.9	60.9	74.5	81.0	0.004	0.0001*
5	Excessive mental fatigue	52.9	60.9	44.7	47.6	0.04	0.05
6	Fatigue after marginal physical effort	52.9	60.9	47.5	81.0	0.004	0.0001*
7	Increased need for sleep	58.8	85.2	87.2	92.1	0.0001*	0.0001*
8	Disturbed sleep	14.7	30.4	23.4	36.5	0.03	0.07
9	Oversensitive to external stimuli (noise, light)	61.8	73.9	61.7	76.2	0.17	0.09
10	Oversensitive to critical remarks	55.9	71.0	74.5	81.0	0.02	0.007
11	Tense, irritable	72.1	92.8	85.1	85.7	0.01	0.18
12	Unable to relax	17.4	34.8	31.9	46.0	0.007	0.03
13	Muscle pain or heavy limbs	39.7	59.4	36.2	52.4	0.04	0.30
14	Difficulty concentrating	61.8	79.1	61.7	74.6	0.06	0.52
15	Easily distracted	23.5	40.6	46.8	41.3	0.05	0.27
16	Difficulty thinking/memory problems	48.5	73.9	44.6	63.5	0.004	0.09
17	General performance impaired	41.2	49.3	59.6	61.9	0.08	0.007
18	Diminished need for social contacts	8.8	21.7	21.3	30.2	0.03	0.12
19	Less able to withstand stress	58.8	71.0	70.2	77.8	0.13	0.03
20	Sensitive to weather	19.1	30.4	40.4	34.9	0.08	0.54

* Significant after Bonferroni correction (40 tests)

Age and order of onset

Overall the age of onset of neurasthenic symptoms was 20.1 ± 6.9 years; the four groups of neurasthenia did not differ significantly in this respect ($P < 0.34$). The onset of depressive symptoms occurred on average four years earlier (15.9 ± 5.8 years). In 99 cases (18.3%), the age of onset of neurasthenic and depressive symptoms was the same (including an error margin of ±1 year), in 237 cases (43.7%) depression preceded neurasthenia, in 71 cases (13.1%) neurasthenia preceded depression, while another 121 cases (22.3%) suffered only from depression and 14 cases (2.6%) only from neurasthenia.

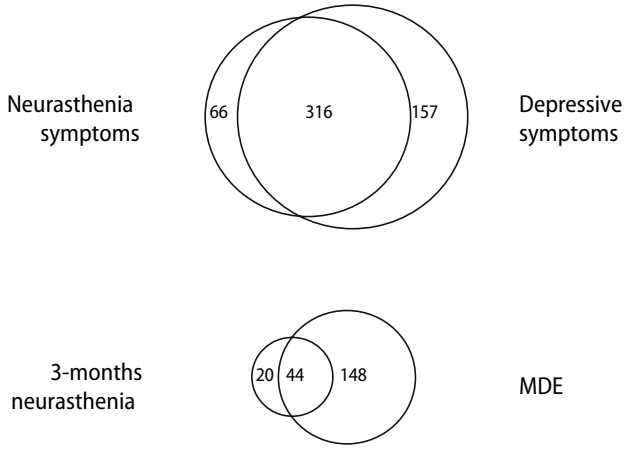

Fig. 1 Longitudinal overlap of neurasthenia and depression

Course of diagnostic subgroups: changes on the severity spectrum

We compared each subject's first and last completed interview (the first being for all subjects the one completed at age 20, the last varying according to the subject). 105 (27.3%) of all subjects who had ever experienced any kind of neurasthenic manifestations stayed in the same diagnostic subgroup, i.e. there was no change in severity of the manifestation. 124 subjects (32.3%) switched to a more severe subgroup between their first and last interviews and 155 (40.4%) to a less severe subgroup.

In a more fine-grained analysis, we investigated the change of neurasthenia subgroup between the first and last completed interview, quantifying the change in terms of units, with one unit corresponding to one step up to the next, more severe, subgroup of neurasthenia or down to the next, less severe, subgroup. Subgroups in order of ascending severity were "no neurasthenia", "neurasthenia symptoms", "recurrent brief neurasthenia", "two-week neurasthenia", and "3-month neurasthenia". For example, a subject who changed from recurrent brief neurasthenia at the first interview to 3-months neurasthenia at the last interview would be assigned a change in severity of +2. Figure 2 shows the histogram of severity changes. It is evident that by far the most frequent classes were those subjects who stayed in their neurasthenia subgroup, and those who changed to the next lower (less severe) subgroup. While overall, more subjects got better than worse, considerably more "jumped" up two or

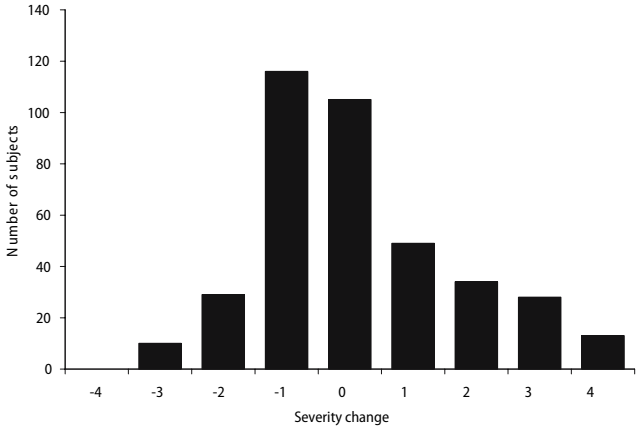

Fig. 2 Histogram of changes in severity of neurasthenia subgroup between first and last completed interview. One unit corresponds to a change into the next higher or lower subgroup. See text for further explanation

more subgroups than "jumped" down two or more subgroups.

Transitions between and diagnostic stability of subgroups of neurasthenia

We first analysed the intra-individual diagnostic stability of neurasthenia across all interviews, merging the interviews at t_1 and t_2 (age 21 and 23) as well as those at t_3 and t_4 (age 28 and 30) and comparing them with t_5 (age 35) and t_6 (age 41). In general, none of the subgroups of neurasthenia showed high longitudinal stability (Fig. 3). On average, only about 15% of the subjects remained in their subgroup across two adjacent time points. A similar proportion changed to other subgroups of neurasthenia. Most subjects in any subgroup, however, changed to the symptom-free group at the next time point.

In addition, we examined the history and follow-up of the individually last and first episodes of 3-months neurasthenia, respectively. Cumulatively, all changes across the interviews were taken into account, not just the first and last interview as in section 3.6 (for more details, see legend to Fig. 4). Figure 4 shows subgroup changes from and to 3-months neurasthenia. The stability of 3-months neurasthenia was low: the first episode was followed by the same diagnosis in only 23% of cases, and only 16% of last observed episodes had a history of a previous episode. Over 75% of subjects with 3-months neurasthenia had a previous or subsequent symptom-free period. Combining 3-months and 2-weeks neurasthenia into one group resulted, as expected, in a slightly higher stability: in this case one fourth of the subjects ever had a previous, and one third ever had a subsequent episode of neurasthenia. GEE confirmed the low stability of 3-months neurasthenia: the OR of prediction of current by previous neurasthenia was non-significant.

GEE models of associations between 3-months neurasthenia and MDE

In the "cumulative exposure" GEE model (Table 3a), 3-months neurasthenia was predicted neither by a previous diagnosis of 3-months neurasthenia, nor by a previous diagnosis of MDE. It was, however, strongly associated with concurrent MDE. MDE was predicted by previous diagnoses of MDE and 3-months neurasthenia, and was also strongly related to concurrent 3-months neurasthenia.

The first-order lag model (Table 3b) differed from the cumulative exposure model in that MDE in the previous interview predicted 3-months neurasthenia, while 3-months neurasthenia in the preceding interview did not predict current MDE. Thus, whereas cumulative previous exposure to MDE did not predict current 3-months neurasthenia, exposure in the preceding interview did. Furthermore, whereas cumulative previous exposure to 3-months neurasthenia predicted current MDE, exposure in the preceding interview did not.

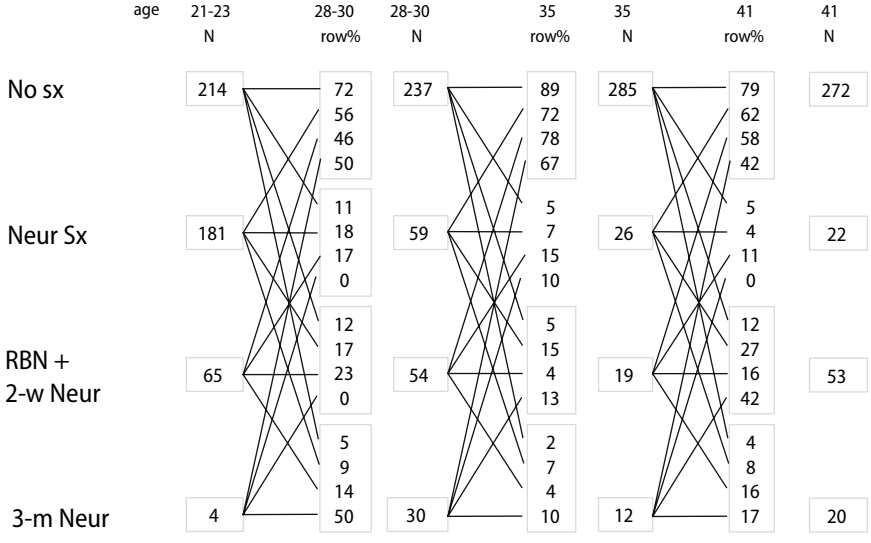

Fig. 3 Temporal shifts between subgroups of neurasthenia between two successive time points. An example for how to read this figure: at ages 21–23, 181 particpants reported neurasthenic symptoms ("Neur sx"), and of these, 56% became symptom-free ("No sx") at ages 28–30. This can readily be seen by following the uppermost line originating from the box reading "181". "No sx" = no neurasthenic symptoms, "Neur sx" = neurasthenic symptoms. "RBN" = Recurrent Brief Neurasthenia. "2-w Neur" = 2-weeks neursthenia, "3-m Neur" = 3-months neurasthenia (ICD-10)

Table 3 GEE models of neurasthenia and depression: odds ratios

Dependent variable	Explanatory variables						
	3-months neurasthenia (ICD-10)		MDE		Male	Risk	Time
	Previous[a]	Same[a]	Previous	Same			
a. Cumulative exposure model							
3-months neurasthenia (ICD-10)	1.8	–	1.1	6.4***	0.5*	2.3*	1.0
MDE	2.0*	6.4***	2.0***	–	0.9	1.7**	0.98
b. First-order lag model							
3-months neurasthenia (ICD-10)	1.3	–	1.9*	5.9***	0.5**	2.2*	1.1**
MDE	1.5	5.8***	2.1***	–	0.7*	1.9***	1.0

[a] 'previous' indicates presence of explanatory variable at any previous interview (cumulative exposure); 'same' indicates presence of explanatory variable at same interview
[b] '–' indicates explanatory variable not included in model
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$
[a] 'previous' indicates presence of explanatory variable at the preceding interview (first-order lag); 'same' indicates presence of explanatory variable at same interview
[b] '–' indicates explanatory variable not included in model
***$P < 0.001$, **$P < 0.01$, *$P < 0.05$

Female sex increased the risk for neurasthenia and for MDE in the first order lag model. The risk group for stratified sampling was significant, indicating that high-risk status entailed a higher risk for neurasthenia and depression. Time was not a clinically significant predictor (ORs close to 1).

Discussion

This paper presents prospective data on the course and diagnostic stability of neurasthenic syndromes/symptoms across 20 years and their associations with depressive syndromes/symptoms.

Symptoms

Among cases of 3-months neurasthenia two major syndromes could be found, the typical fatigue syndrome (exhaustion, weakness, increased need for sleep) and a syndrome of reduced stress tolerance (including oversensitivity to external stimuli and to critical remarks, tension and irritability). Together they correspond to the original concept of "excessive irritable weakness" of [9].

Prevalence

Three-months neurasthenia was clearly age-related: from age 22 to 41 there was a systematic several-fold increase of the one-year prevalence of 3-months

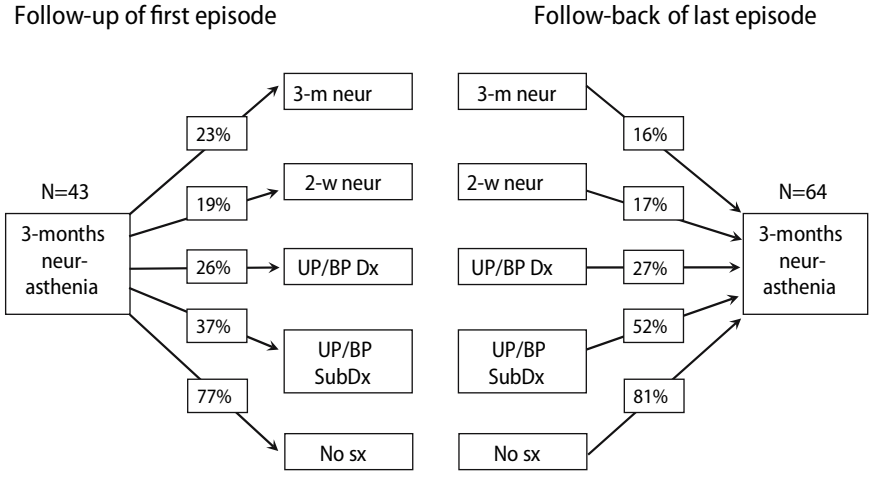

Fig. 4 Follow-up of the first and follow-back of the last episode of 3-months neurasthenia. The first and last episode of 3-m neurasthenia is identified in each subject (these episodes can be in different years for different subjects). The right side of the figure shows the percentages of subjects with a last episode of 3-month neurasthenia belonging to any of the listed subgroups in *any* previous interview. Percentages do not sum to 100% because the subgroups are not mutually exclusive: A subject may have belonged to more than one subgroup prior to the last episode of 3-months neurasthenia. Analogous considerations hold for the left side of the figure, which shows the percentages of subjects with a first episode of 3-months neurasthenia belonging to any of the listed subgroups in any subsequent interview. "3-m neur" = 3-months neurasthenia, "2-w neur" = 2-weeks neurasthenia, "UP/BP Dx" = uni- or bipolar mood disorder, "UP/BP SubDX" = uni- or bipolar subthreshold mood disorder, "No sx" = no neurasthenic symtpoms

neurasthenia, while neurasthenic symptoms prevailed at age 20–22 and decreased thereafter. A representative twin study of adolescents found a lifetime prevalence of neurasthenia of 2.3%, which is compatible with our assumption of an increase with age [13]. Cumulatively up to age 41, we found 6.0% 3-months neurasthenia.

Gender differences

Women reported physical exhaustion twice as often as men, whereas mental exhaustion was reported to a similar extent by women and men. Nonetheless, the prevalence of 3-months neurasthenia was only slightly higher for women than for men (gender ratio F:M = 1:2:1, whereas it was about 2:1 in the study of Farmer et al. 2004). In this context our findings on atypical depression are of interest, because there we found a clear preponderance of women with a cumulative prevalence rate of 6.3% for women versus 1.6% for men (ratio F:M = 3:9:1), explaining the gender difference in prevalence rates for major depressive episodes [6]. These results also illustrate that the two syndromes, neurasthenia and atypical depression, differ substantially although they share certain diagnostic symptoms.

Course of neurasthenic spectrum

Overall, there was a moderate decrease in severity of neurasthenic manifestations from the first to the last individual interview: 27% of the subjects stayed the same, 40% got better and 32% got worse. Analysis of temporal shifts revealed that the increase of 3-months neurasthenia with age was not generally at the cost of neurasthenic symptoms, since most cases with neurasthenic symptoms became symptom-free, and only a total of 13% ever changed to 3-months neurasthenia (data not shown).

A main finding is that neurasthenia, in contrast to depression, was a rather unstable diagnosis. For each point in time, the majority of cases with any neurasthenic manifestation switched to the symptom-free group at the next interview. In the GEE model, previous 3-months neurasthenia did not predict subsequent 3-months neurasthenia.

The cross-sectional and longitudinal association of neurasthenia and depression

The cross-sectional association of neurasthenia with depression is well-established [10, 13, 17, 19, 22, 24, 34, 35, 37]. In cases of co-occurrence the diagnosis of depression often took precedence over that of neurasthenia [25]. In our data cross-sectional associations between neurasthenia and depression were strong and statistically significant. Longitudinally, previous depressive states on all diagnostic levels consistently predicted subsequent depression whereas, as we have seen, neurasthenic syndromes were temporally unstable. The prediction of 3-months neurasthenia by MDE and vice versa was weak and inconsistent between the two GEE models.

Limitations

With fatigue being an ubiquitous and unspecific symptom of many illnesses, the question of etiological heterogenetiy becomes particularly relevant. In particular, a fatigue syndrome due to a somatic illness or an accident may have a different etiology than "non-organic" neurasthenia. But then again, it may not. Fatigue may have a proximal cause that is the same or very similar everywhere it occurs, and different illnesses may trigger this proximal cause through a variety of different causal pathways. While this is an open question, it would have been desirable to exclude subjects with known organic causes of fatigue from our analysis, since at best, this would have resulted in a more homogeneous group of neurasthenics. However, we could not exclude organically-caused fatigue because no physical examination to objectively ascertain organic causes had been carried out. Only participants' subjective causal attributions were available, but these cannot in general be taken to reflect true somatic causes, and thus are not a reliable basis for exclusions.

Analysing the associations between 3-months neurasthenia and depression one has to be aware that MDE requires a minimum duration of only 2 weeks. This large time difference reduces comparability and may explain some controversional findings. Sample sizes were partly small, and might also account for some of the inconsistencies. They may limit the generalizability of our findings to the general population or to patient populations. The empirical and conceptual overlap between neurasthenia and depression confounds the issue of diagnostic stability, but this limitation is inherent and unavoidable.

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