Similar but different

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Cognitive functioning in patients with chronic fatigue and fibromyalgia syndrome

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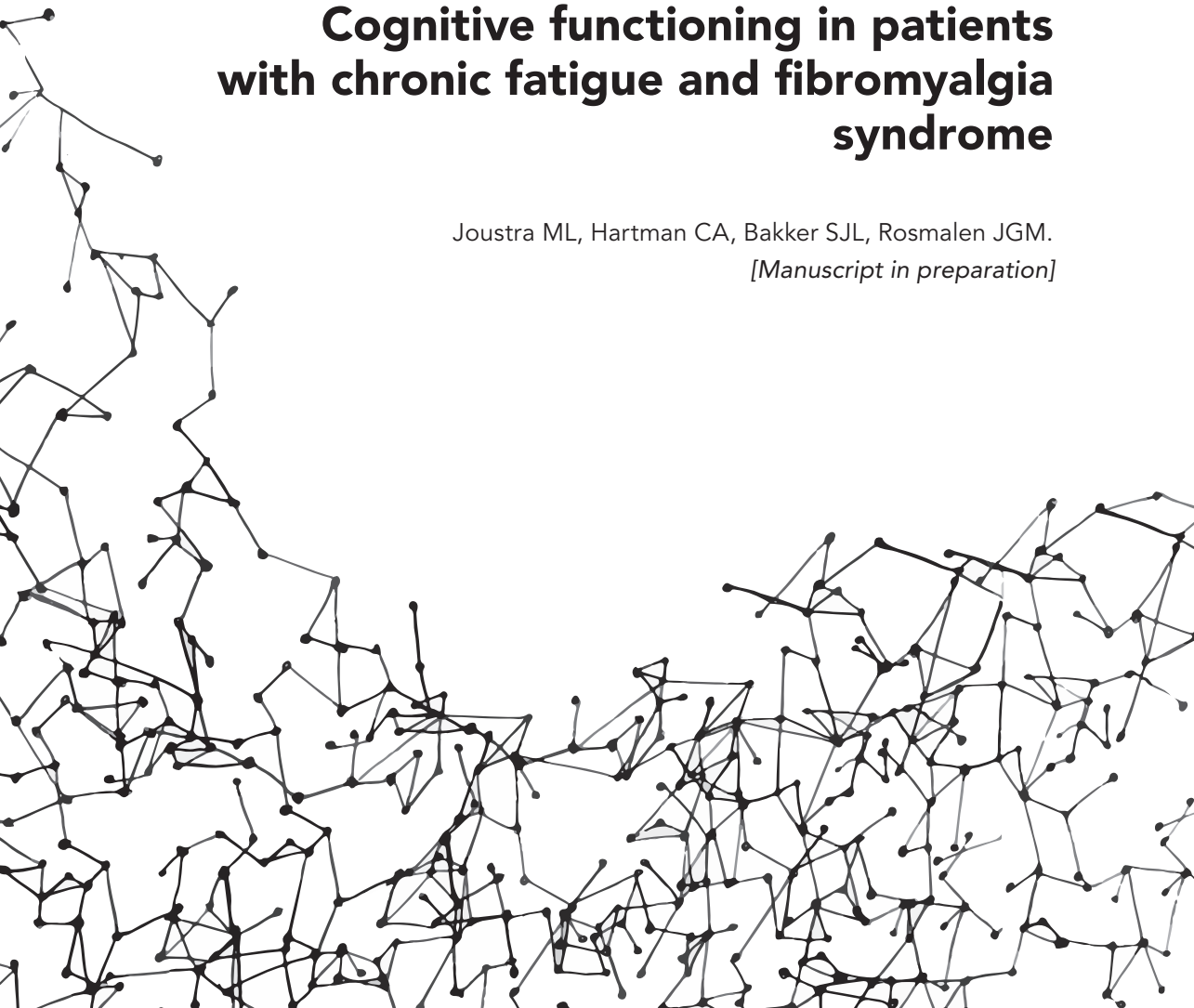
[Manuscript in preparation]



ABSTRACT

Background: The aims of this study were to examine cognitive functioning in patients with chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS) compared to controls and patients with well-defined medical diseases, and to investigate their relationship with mood or anxiety disorders, and somatic symptomatology.

Methods: This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Diagnostic criteria for CFS and FMS were assessed by questionnaire. Objective cognitive functioning was determined using the CogState computerized cognitive battery, while subjective cognitive functioning was assessed using items from the Checklist Individual Strength.

Results: Patients with CFS (n=2,461) and FMS (n=4,626) reported significantly more subjective cognitive impairments compared to control participants and patients with well-defined medical diseases. Objective cognitive impairments were particularly present in patients with CFS, although they were rather mild. These differences remained essentially the same when excluding participants with comorbid mood or anxiety disorders. In addition, the associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between the groups. General symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups.

Conclusions: Subjective cognitive impairments are more prevalent than objective cognitive impairments in patients with CFS or FMS compared to control participants and patients with well-defined medical diseases. Importantly, these impairments do not appear to be the consequence of mood or anxiety disorders.

INTRODUCTION

Functional somatic symptoms are persistent physical symptoms that cannot be adequately explained in the context of a well-defined medical disease. The term functional somatic syndromes (FSS) refers to specific combinations of persistent functional somatic symptoms. FSS are serious disabling health conditions that are associated with a reduced quality of life and reduced social participation (Collin *et al* 2011, Dickson *et al* 2009, Hoffman and Dukes 2008, Joustra *et al* 2015). Two well-known FSS are chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS).

FSS are symptom-based diagnoses, since they require the presence of specific clusters of somatic symptoms (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). The diagnostic criteria for FSS include a description of the main symptom and additional symptoms. FSS diagnostic criteria attempt to distinguish these syndromes from well-defined medical diseases that present with comparable symptoms, but they also require the absence of detectable pathological explanations for these symptoms (Drossman 2006, Drossman 2016, Fukuda *et al* 1994, Wolfe *et al* 2010). The main and additional symptoms in CFS and FMS partly overlap; for example, both patient groups can suffer from cognitive symptoms, unrefreshing sleep, fatigue or post-exertional malaise (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). Commonalities among these FSS have resulted in a discussion on whether or not these syndromes share etiological pathways, also known as the lumper-splitter discussion (Wessely *et al* 1999).

Cognitive impairment is one of the most frequently reported symptoms in both CFS and FMS (Fukuda *et al* 1994, Teodoro *et al* 2018, Thomas and Smith 2009, Wolfe *et al* 1990, Wolfe *et al* 2010). In 2010, *Psychological Medicine* published a meta-analysis of research examining cognitive functioning in patients with CFS (Cockshell, Susan Jayne and Mathias 2010). This meta-analysis found that studies examining objective cognitive impairments reported inconsistent results. The authors suggested that these inconsistencies could be explained by methodological differences, since the studies used a wide variety of cognitive tasks that could not be directly compared. They also identified several limitations of the existing literature: most studies contained small samples, did not include a control group, or did not report the diagnostic algorithm that was used to select

the patient group (Cockshell, Susan Jayne and Mathias 2010). Similar conclusions were drawn in a review focusing on cognitive functioning in patients with FMS (Glass 2009). In particular, the authors recommend a study with a large sample of subjects with varying levels of mood and anxiety disorders, pain, fatigue, and sleep disruption, which would allow for assessment of the contribution of these comorbid symptoms to cognitive functioning. Therefore, larger studies investigating both subjective and objective cognitive functioning in CFS and FMS patients and controls are needed.

In the current study, we will examine cognitive functioning in patients with CFS and patients with FMS in a large population-based cohort study of over 79,000 participants. First, we will examine whether patients with CFS and patients with FMS differ significantly from each other and from controls or patients with a well-defined medical disease with the same core symptoms (CFS versus multiple sclerosis (MS) and FMS versus rheumatoid arthritis (RA)), on the subjectively and objectively measurable aspects of cognitive functioning. We will additionally explore the effects of current mood and anxiety disorders on cognitive functioning. Lastly, the relationship between somatic symptomatology and objective cognitive functioning will be examined, and whether it differs between patient groups.

METHODS

Sampling frame

This study was conducted within the sampling frame of the LifeLines cohort study (Scholtens *et al* 2015). LifeLines is a multi-disciplinary, prospective (three-generational) population-based cohort study examining health and health-related behaviors of more than 167,000 persons living in the North East part of The Netherlands. LifeLines employs a broad range of investigative procedures in assessing biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics.

Participants

Participants of LifeLines were recruited in two ways. First, a number of general practitioners from the three northern provinces of the Netherlands invited all

their listed patients between 25 and 50 years of age to participate. If they agreed to participate, these participants were asked to invite their partner(s), parents, parents in law, and children to participate as well. In this way participants of all ages were included. Eligibility for participation was evaluated by general practitioners. To ensure the reliability of the study, persons with severe psychiatric or physical illness, and those not being able to visit the general practitioner, to fill out the questionnaires, and/or to understand the Dutch language, were excluded. Parents and children were not excluded in case of the mentioned criteria, when a representative was willing to assist these participants in the performance of the study. Inclusion of pregnant women was rescheduled until six months after pregnancy or three months after breastfeeding. Second, persons who were interested to participate could register themselves via the LifeLines website and then participate.

All participants received written information on the purpose and methods of the study and written informed consent was obtained after the procedure was fully explained. All data are kept confidential and are only used for medical research. Approval by the Medical Ethical Committee of the University Medical Center Groningen was obtained for the study.

Data collection

The first participants were included at the end of 2006, and the recruitment period was closed after reaching the target number of participants in 2013. Participants who were included in the LifeLines study will be followed for at least 30 years. At baseline, participants visited one of the LifeLines research sites for a physical examination. Prior to these baseline visits, two extensive baseline questionnaires were completed at home. Follow-up questionnaires were administered to all participants approximately every 18 months, and participants have been invited for a renewed physical examination at the LifeLines research site on average every five years. At the time of writing, data from baseline assessment, first and second follow-up questionnaires and data from the second assessment were available. During the second assessment, general physical examination was first performed, followed by medical examinations (e.g. ECG, lung function), and lastly, the CogState computerized cognitive battery and psychiatric assessment were conducted respectively.

Functional somatic syndromes and medical or psychiatric health conditions
The diagnostic criteria for CFS and FMS were assessed by questionnaire. The diagnosis for CFS was assessed using the 1994 Centers for Disease Control and Prevention criteria (CDC) (Fukuda *et al* 1994), and for FMS using the 2010 American College of Rheumatology criteria (ACR) (Wolfe *et al* 2010) (Appendix A: scoring algorithm, chapter 4).

MS and RA were assessed by questionnaire. CFS with comorbid MS (n=29), and FMS with comorbid RA (n=496) were excluded from the analyses. Controls were defined as participants that did not fulfill the diagnostic criteria for CFS and FMS and did not report MS or RA.

Psychiatric health conditions, including current mood (i.e. major depressive disorder, dysthymia) or anxiety disorders (i.e. panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, generalized anxiety disorder) were assessed with a standardized instrument, which was completed by participants at the LifeLines location. This instrument was a digitalized self-report version of the Mini International Neuropsychiatric Interview (MINI). The MINI is a brief structured instrument for diagnosing psychiatric disorders as defined by the DSM-IV and ICD-10 (Sheehan *et al* 1998).

Objective cognitive functioning
The CogState computerized cognitive battery was used to measure cognitive functioning, because it measures multiple domains of cognitive functioning and is brief, using automated data processing and scoring. It is suitable for research among people from the general population with a wide range of ages and educational levels (Fredrickson *et al* 2010, Maruff *et al* 2009). Furthermore, the CogState battery has shown to have good test-retest reliability (Darby *et al* 2002) and validity (Hammers *et al* 2012).

The CogState Brief Battery is a collection of four short card tasks. Different cognitive functioning domains are tested: 1) speed of processing (Detection task (DET); 2 min), visual attention/vigilance (Identification task (IDN); 2 min), working memory (One back (OBK); 2 min), and visual learning & memory (One Card Learning task (OCL); 5 min). During the CogState Brief Battery, a supervisor was available in case participants needed assistance.

Detection task
The DET is a simple reaction time task that measures speed of processing. In this task, the participant is instructed to attend to the center of the screen and follow the rule "Has the card turned face up? Subjects were instructed to press the "Yes" key as soon as the card turned face up. The task ended after 35 correct trials had been recorded. The primary outcome measure was reaction time (in milliseconds), which was normalized using log10 transformation.

Identification task
The IDN is a choice reaction task that measures visual attention. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question: "Is the card red"? Participants were instructed to press the "Yes" key if it is and the "No" key if it is not. This task continued until 30 correct responses had been recorded. Reaction time (in milliseconds and log10 transformed) was the primary outcome measure.

One back
The OBK is a measure of attention and working memory. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question "Is this card the same as that on the immediately previous trial"? If the answer was yes, participants were instructed to press the "Yes" key, and the "No" key if the answer was no. The task ends after 30 correct trials. The primary outcome measure was the proportion of correct answers, which was normalized using arcsine transformation.

One Card Learning task
The OCL is a visual learning and memory task. In this task, the participant is instructed to attend to the card in the center of the screen and respond to the question "Have you seen this card before in this task"? If the answer was yes, participants were instructed to press the "Yes" key, and the "No" key if the answer was no. The task ended after 42 trials. The primary outcome measure was the proportion of correct answers, normalized using arcsine transformation.

Subjective cognitive functioning
The Checklist Individual Strength (CIS) is a 20-item self-report questionnaire that covers four domains of the subjective fatigue experience, including fatigue

severity (8 items; e.g. physically I feel exhausted), concentration (5 items; e.g. thinking requires effort), motivation (4 items; e.g. I don't feel like doing anything), and physical activity levels (3 items; e.g. I think I do very little in a day) (Vercoulen *et al* 1994). Participants were asked to indicate how they recognize themselves in the mentioned statements during the past two weeks on an (1) "No, that is not true" to (7) "Yes, that is true" scale. A CIS total score (ranging from 20 to 140) can be obtained by adding the individual scores on the 20 questions. Furthermore, the summary scores can be calculated for the four domains (fatigue severity range 8-56, concentration range 5-35, motivation range 4-28, physical activity level range 3-21). Higher scores indicate a higher degree of fatigue severity, more concentration problems, reduced motivation, or less physical activity. Since motivation is also known to reflect cognitive functioning (Avlar *et al* 2015), the CIS-concentration and motivation scale were used to reflect subjective cognitive functioning.

Fatigue, pain, and general symptom severity

Fatigue severity was assessed using the results of the CIS-fatigue severity subscale (Vercoulen *et al* 1994). To assess subjective pain, participants were asked to indicate in which of 19 mentioned body areas they had pain during the last week using the Widespread Pain Index (WPI; Appendix A, chapter 4) (Fukuda *et al* 1994, Wolfe *et al* 1990, Wolfe *et al* 2010). The WPI score was determined by counting the number of body areas in which the participant reported pain during the last week.

To determine general symptom severity, the 12-item somatization scale of the Symptom Checklist-90 (SCL-90 SOM) was used (Derogatis *et al* 1974). This scale consists of 12 somatic symptoms, including: headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach, soreness of your muscles, numbness or tingling in your body, hot or cold spells, feeling weak in parts of your body, heavy feelings in arms or legs, a lump in your throat, and trouble getting your breath. Participants were asked to what extent they had been limited by these symptoms in the past seven days. Items were scored on a 5-point scale ranging from (0) "Not at all" to (4) "Extremely". The outcomes of 12 items of the SCL-90-SOM were summed (total scale ranging 0-48).

Covariates

Age, sex and educational level were included as covariates due to their associations with FSS and cognition. Educational level was assessed using the question: "What is your highest completed education?", resulting in information about low (lower secondary education or less), middle (higher secondary education), and high (tertiary education) educational level.

Statistical analyses

All analyses were performed using SPSS version 22. First, the characteristics of the different study groups were described. For continuous outcomes, means ± standard deviations (SDs) were calculated. One-way analyses of variance (ANOVA) were performed for continuous data, to test the differences in sample characteristics. In addition, $\chi 2$ tests were performed for categorical data. Cohen's *d* effect sizes were calculated for the differences between study groups in objective and subjective cognitive functioning, based on the estimated means and standard deviations using ANCOVA analysis adjusted for age, sex, and educational level. To determine 95% CIs for effect sizes, the following formulas were used (Cohen 1988, Hedge and Olkin 2014):

$$\sigma\,(d) = \sqrt{\frac{N1 + N2}{N1 \times N2} + \frac{d^2}{2(N1 + N2)}}$$

$$95\%\ CI\ d = [d - 1{,}96 \times \sigma(d), d + 1{,}96 \times \sigma(d)]$$

Effect sizes of 0.2, 0.5, 0.8, and 1.3 were interpreted to reflect small, medium, large, and very large effects, respectively (Cohen 1988, Cohen 1992). If applicable, effect sizes were reversed to ensure that a positive effect reflected better cognitive function, as reflected in better performance on a cognitive task or less subjective cognitive symptoms. Lastly, to investigate whether fatigue severity, pain severity and general symptom severity were related to objective cognitive functioning, multivariable linear regression analyses were performed using standardized variables, adjusted for age, sex and educational level. Cases with missing data were deleted listwise. To investigate whether the regression coefficients differed significantly between groups (i.e. b1 ≠ b2), a dummy variable for group and the interaction term (independent variable*dummy) were added to the regression models. Statistical significance was defined as $p<0.05$.

RESULTS

Sample characteristics

This study was performed in 79,966 participants (age: 52.9±12.6 years, 59.2% female) of the general-population cohort LifeLines. Of the included participants, 3.1% (n=2,461) fulfilled the CDC criteria for CFS, 0.2% reported MS (n=339), 5.8% fulfilled the ACR criteria for FMS (n=4,626), 3.0% reported RA (n=4,440), and 89.4% were considered controls since they did not fulfil the diagnostic criteria for CFS or FMS and did not report MS or RA (n=71,466). An overview of the general sample characteristics is presented in Table 1. Patients with CFS or FMS reported significantly higher fatigue severity, subjective cognitive problems, pain complaints, and general symptom severity compared to both controls and patients with MS or RA. Lastly, both patients with CFS and FMS had significantly higher current comorbid mood or anxiety disorder than controls and patients with MS or RA.

Cognitive functioning in CFS and FMS as compared to controls, MS and RA

In the current sample, 74% of the control group (n=52,914), 65.4% of patients with CFS (n=1,609), 71.8% of patients with MS (n=112), 68.7% of patients with FMS (n=3,179), and 62.2% of patients with RA (n=1,470) completed the CogState computerized cognitive battery. Figure 1 shows the differences between groups in objective and subjective cognitive functioning. Patients with CFS had a significantly slower reaction time on the IDN task (visual attention), and had significantly less correct answers on the OBK (attention/working memory) and OCL tasks (visual learning/memory), compared to controls with only small effect sizes (Figure 1A). Patients with FMS performed significantly less on the OCL task compared to controls with small effect size, while no significant differences were found for the other three tasks. Furthermore, patients with CFS or FMS reported significantly more subjective cognitive problems compared to controls with large to very large effect sizes.

Table 1. General characteristics of the study groups.

	Controls	CFS	MS	FMS	RA
N (%)	71,466 (89.4)	2,461 (3.1)	156 (0.2)	4,626 (5.8)	2,362 (3.0)
Female n (%)	41,178 (57.6)	1,823 (74.1)[1]	121 (77.6)	3,541 (76.5)[1,3,4]	1,531 (64.8)
Age (years), mean (SD)[#]	52.7 (12.6)	54.2 (11.8)[1]	51.9 (9.8)	52.1 (11.4)[1,3,4]	61.2 (11.9)
Education (% low-middle-high)[$]	2.4 – 65.2 – 30.2	4.8 – 72.6 – 19.6[1,2]	1.9 – 69.2 – 26.9	3.5 – 73.5 – 20.3[1,3,4]	5.5 – 70 – 21.1
CIS-fatigue, mean (SD)[#]	21.1 (10.5)	44.2 (8.0)[1,2]	33.2 (11.5)	40.3 (9.5)[1,3,4]	24.6 (11.6)
CIS-concentration, mean (SD)[#]	12.0 (6.3)	21.7 (7.4)[1,2]	16.2 (7.4)	19.9 (7.3)[1,3]	12.5 (6.4)
CIS-motivation, mean (SD)[#]	10.3 (5.0)	17.2 (5.5)[1,2]	13.9 (5.4)	15.5 (5.5)[1,3,4]	11.5 (5.4)
CIS-physical activity, mean (SD)[#]	6.9 (3.9)	13.1 (4.7)[1,2]	10.5 (5.0)	11.0 (5.0)[1,3,4]	7.8 (4.4)
WPI, mean (SD)[#]	2.0 (2.1)	7.6 (4.1)[1,2]	2.9 (2.7)	8.6 (3.0)[1,3,4]	3.4 (2.9)
General symptom severity, mean (SD)[#]	1.3 (0.4)	2.1 (0.6)[1,2]	1.5 (0.4)	2.0 (0.5)[1,3,4]	1.5 (0.5)
DET, mean (SD)[#]	2.57 (0.18)	2.59 (0.19)[1]	2.61 (0.21)	2.58 (0.18)[3,4]	2.63 (0.21)
IDN, mean (SD)[#]	2.69 (0.094)	2.70 (0.096)[1]	2.70 (0.087)	2.69 (0.095)[3,4]	2.72 (0.11)
OBK, mean (SD)[#]	1.29 (0.23)	1.26 (0.25)[1]	1.28 (0.22)	1.29 (0.23)[3,4]	1.24 (0.26)
OCL, mean (SD)[#]	0.95 (0.12)	0.93 (0.13)[1]	0.93 (0.12)	0.94 (0.13)[1,3]	0.93 (0.13)
Current mood disorder n (%)[$]	1,400 (2.0)	544 (22.1)[1,2]	3 (1.9)	682 (14.7)[1,3,4]	69 (2.9)
Current anxiety disorder n (%)[$]	4,141 (5.8)	754 (30.6)[1,2]	14 (9.0)	1098 (23.7)[1,3]	134 (5.7)

CFS = chronic fatigue syndrome; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis; CIS = checklist individual strength; WPI = widespread pain index.
[#] using ANOVA; [$] using $\chi 2$ tests.
[1] $p<0.01$ versus controls, [2] $p<0.05$ versus MS, [3] $p<0.01$ versus RA, [4] $p<0.01$ versus CFS.

When comparing patients with FSS and patients with well-defined medical diseases (Figure 1B), patients with FMS had significantly more correct answers on the OBK task (attention and working memory) compared to patients with RA with a small effect size. No significant differences were found for the other tasks between patients with CFS or FMS compared to patients with MS or RA. For subjective cognitive functioning, patients with CFS or FMS reported significantly

more concentration and motivation problems compared to patients with MS or RA with medium to large effect sizes.

Lastly, when comparing patients with CFS and FMS (Figure 1C), patients with CFS scored significantly lower on the DET (speed of processing) and OBK (attention/working memory) tasks compared to patients with FMS with a small effect size. In addition, patients with CFS reported significantly more concentration and motivation problems compared to FMS patients with small effect sizes.

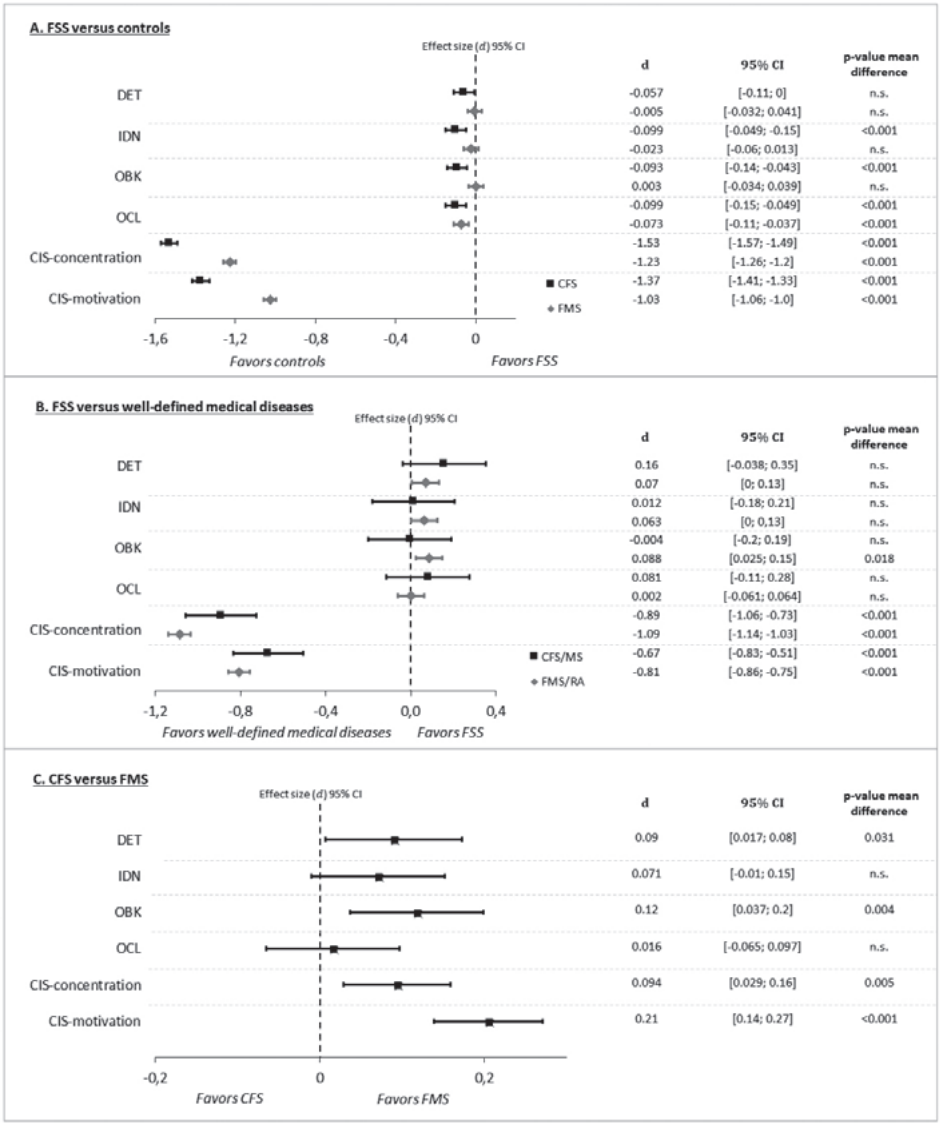


Figure 1. Effect sizes objective and subjective cognitive functioning.
Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms.
Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level.
CFS = chronic fatigue syndrome; FSS = functional somatic syndromes; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis.

The effects of comorbid mood or anxiety disorder

The influence of comorbid mood or anxiety disorder on objective and subjective cognitive functioning was tested by repeating the analyses excluding participants with comorbid mood or anxiety disorders. Among all comparisons, the results with regard to differences between groups in cognitive functioning remained essentially the same (Figure 2). In contrast to the main analyses, the exclusion of participants with mood or anxiety disorders resulted in significantly lower scores on the DET task (speed of processing) in patients with CFS compared to controls (Figures 2A&B). When comparing patients with FSS and patients with well-defined medical diseases (Figure 2C&D), the effect sizes of concentration problems for the comparison CFS/MS and the effect sizes of motivation problems for the comparison FMS/RA reduced from large to medium.

Lastly, scores on the IDN task became significantly lower in patients with CFS compared to FMS, whereas the difference in the OBK task (attention and working memory) between patients with CFS and FMS lost significance when excluding participants with anxiety disorders (Figure 2E&F).

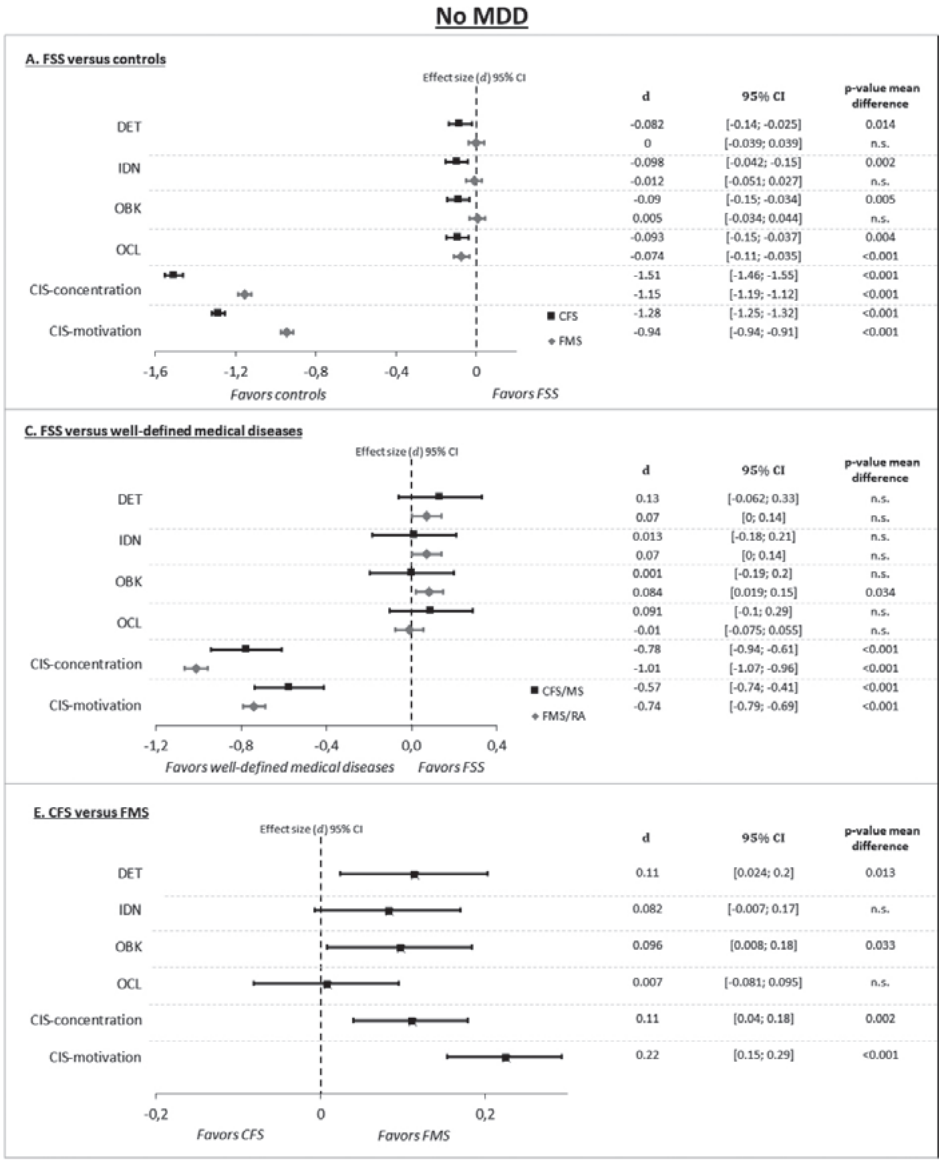


Figure 2. Effect sizes objective and subjective cognitive functioning, when excluding comorbid major depressive disorder or generalized anxiety disorder.

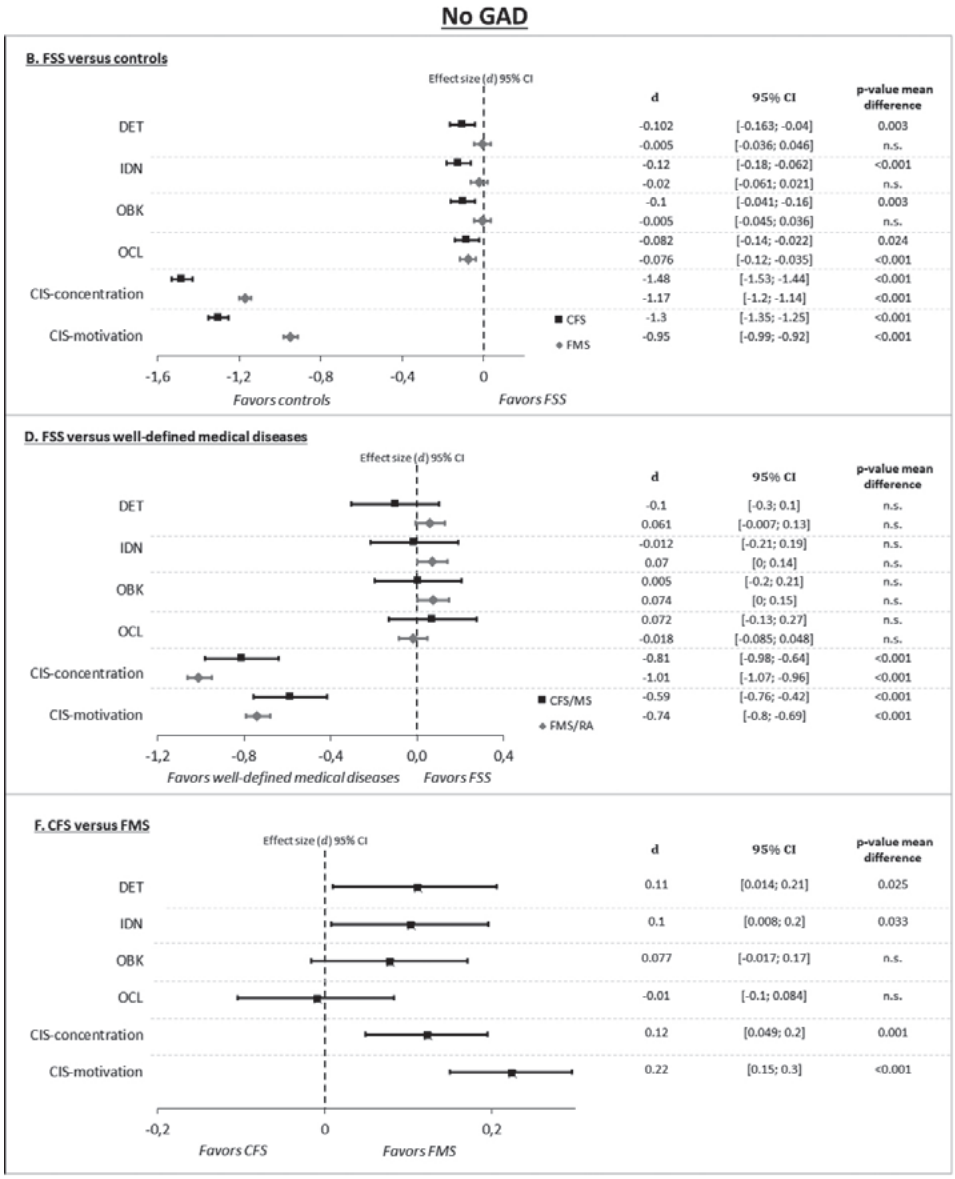


Figure 2. Continued.
Favors represent a positive effect for the corresponding group reflecting better performance on a cognition task or less subjective symptoms.
Effect sizes based on the estimated means and standard deviations adjusted for age, sex, and educational level.
CFS = chronic fatigue syndrome; FSS = functional somatic syndromes; GAD = generalized anxiety disorder; MDD = major depressive disorder; MS = multiple sclerosis; FMS = fibromyalgia syndrome; RA = rheumatoid arthritis.

Associations between symptom severity and objective cognitive functioning

Results of the multivariable regression analyses investigating the association between fatigue, pain or general symptom severity and objective cognitive functioning can be found, per patient group, in Table 2. In controls, severity of fatigue and pain were significantly negatively associated with DET, but not significantly associated with IDN, OBK or OCL scores. General symptom severity was positively associated with all four tasks. In CFS patients, severity of fatigue was significantly negatively associated with DET, and general symptom severity was significantly positively associated with DET, IDN, and OBK. Lastly, general symptom severity was significantly positively related to all four tasks in FMS patients.

Statistical tests of differences in regression coefficients between groups (see note under Table 2), indicated some differences between groups. Although one association was significantly different in patients with CFS from that in controls, and two from those in patients with MS, the estimates were very small and mainly non-significant. In patients with FMS, a few associations were significantly different from controls, and one association was significantly different from patients with RA. However, estimates were again very small and in one case non-significant within the group of FMS patients.

Table 2. Associations between symptom severity and objective cognitive functioning.

	DET	IDN	OBK	OCL
Controls				
CIS-fatigue	-0.016 [-0.026, -0.007]	0.001 [-0.008, 0.01]	0.007 [-0.003, 0.016]	0.007 [-0.003, 0.017]
WPI	-0.013 [-0.024, -0.002]	-0.011 [-0.022, 0]	-0.002 [-0.014, 0.009]	-0.001 [-0.013, 0.01]
SCL-90 SOM	0.012 [0.001, 0.023]	0.018 [0.007, 0.029]	0.032 [0.021, 0.044]	0.026 [0.015, 0.038]
CFS				
CIS-fatigue	-0.09 [-0.16, -0.023][1,2]	0.005 [-0.066, 0.076][2]	-0.029 [-0.11, 0.048]	-0.042 [-0.12, 0.032][3]
WPI	-0.011 [-0.043, 0.02]	0.015 [-0.018, 0.049]	-0.004 [-0.04, 0.032]	0.018 [-0.017, 0.053]
SCL-90 SOM	0.037 [0.002, 0.071]	0.042 [0.006, 0.078]	0.048 [0.009, 0.088]	0.032 [-0.006, 0.07]
MS				
CIS-fatigue	0.15 [-0.054, 0.35]	0.20 [0.031, 0.38]	-0.12 [-0.31, 0.07]	0.069 [-0.12, 0.26]
WPI	-0.048 [-0.26, 0.16]	0.011 [-0.17, 0.19]	-0.043 [-0.24, 0.15]	0.076 [-0.12, 0.27]
SCL-90 SOM	0.22 [0.002, 0.43]	0.10 [-0.082, 0.29]	-0.052 [-0.24, 0.13]	0.01 [-0.18, 0.21]
FMS				
CIS-fatigue	-0.03 [-0.07, 0.011]	-0.002 [-0.044, 0.04]	0.01 [-0.033, 0.052]	-0.034 [-0.076, 0.008][1,4]
WPI	-0.002 [-0.033, 0.028]	0.009 [-0.023, 0.04]	-0.003 [-0.035, 0.029]	0.012 [-0.02, 0.044]
SCL-90 SOM	0.043 [0.016, 0.07][1]	0.052 [0.024, 0.08][1]	0.043 [0.014, 0.071]	0.047 [0.076, 0.19]
RA				
CIS-fatigue	0.001 [-0.055, 0.057]	0.034 [-0.023, 0.091]	0.054 [-0.005, 0.11]	0.053 [0, 0.11]
WPI	-0.037 [-0.093, 0.02]	0.023 [-0.035, 0.08]	0.032 [-0.028, 0.092]	0.016 [-0.038, 0.07]
SCL-90 SOM	0.004 [-0.05, 0.058]	0.039 [-0.017, 0.094]	0.065 [0.007, 0.12]	0.075 [0.023, 0.13]

Multivariable regression analyses, adjusted for age, sex, and educational level. Reported as standardized B [95%CI]. Significant associations are underlined. A positive association indicates that the experience of more symptoms was associated with worse performance on the objective cognitive tasks. CFS = chronic fatigue syndrome, FMS = fibromyalgia syndrome, MS = multiple sclerosis, RA = rheumatoid arthritis, DET = detection task, IDN = identification task, OBK = one back, OCL= one card learning task, CIS-fatigue = fatigue subscale of the checklist individual strength, WPI = widespread pain index, SCL-90 SOM = 12-item somatization scale of the Symptom Checklist-90.

[1,2,3,4] refer to associations that differed between groups [1] $p < 0.05$ versus controls, [2] $p < 0.05$ versus MS, [3] $p < 0.05$ versus FMS, [4] $p < 0.01$ versus RA.

DISCUSSION

This is the first large population-based study that assessed both subjective and objective cognitive functioning in patients with CFS and FMS compared to patients with MS and RA and a control group, including relevant confounding variables. We found that subjective cognitive impairments are more prevalent in both patients with CFS and FMS than in controls and patients with MS and RA, respectively. Patients with CFS had significantly more subjective and objective cognitive impairments compared to patients with FMS, which could not be attributed to the presence of comorbid mood or anxiety disorders. In addition, associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between patients with FSS and controls or patients with well-defined medical diseases. General symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups.

The main strength of the current study is that it was performed in a large population-based sample, in which data were collected on subjective and objective cognitive functioning and relevant confounding variables. This enabled comparing patients with FSS and patients with well-defined medical diseases in a single cohort, avoiding differences in selection procedures or measurement. Since we selected the groups from the general population, it was possible to examine subjective and objective cognitive functioning of the different study groups irrespective, help-seeking behavior, referral by clinicians, and differences in diagnostic assessment. Lastly, FSS were based on the official positive diagnostic criteria instead of the self-reported diagnoses.

There are also limitations of the current study. First, we used a brief battery covering only basic domains of cognitive functioning. We therefore may have missed some differences in objective cognitive functioning between patients with FSS and controls or patients with well-defined medical diseases. In addition, cognitive tasks assess specific cognitive functions, while questionnaires cover more global cognitive functions, which makes it difficult to compare results on objective cognitive functioning and subjective cognitive functioning. Second, FSS diagnoses were based on the responses to a questionnaire, without an assessment by a physician. Because LifeLines is a large population cohort study

that aims to study a wide spectrum of mental and somatic disorders, it was not feasible to determine whether participants met the diagnostic criteria for FSS based on clinical examinations. We excluded patients that fulfilled the criteria for one of the FSS and reported the corresponding well-defined medical disease, but we cannot fully exclude the presence of other somatic pathology explaining the symptoms.

Our study supports previous findings that cognitive impairments are more prevalent and severe in both patients with CFS and FMS compared to controls (Teodoro *et al* 2018, Thomas and Smith 2009). Furthermore, we found that patients with CFS had reduced visual learning and working memory, and both patients with CFS or FMS had reduced visual attention scores compared to controls. Patients with CFS or FMS did not differ from controls in speed of processing, so differences in this most basic cognitive process cannot serve as an explanation for the differences in other, more complex cognitive functions. These findings are in accordance with a recent meta-analysis that concluded that patients with FSS have primarily cognitive impairments in the domains of attention, memory, and tasks requiring working memory (Cockshell, Susan Jayne and Mathias 2010, Glass 2009). In contrast to earlier research, we found only small effect sizes for the differences, and we found that the objective cognitive impairments of FSS patients are comparable to those in patients with MS and RA (Krupp *et al* 1994). A possible explanation for these differences might be that we have addressed some limitations of previous research, including the use of small samples and self-report diagnoses. In addition, previous research mostly recruited referred patients, while we selected patients from the general population. Thus, the results in previous research might be the affected by help-seeking behavior, referral practices by clinicians, or differences in diagnostic assessment.

This study found that subjective cognitive impairments were more prevalent in patients with FSS compared to control participants and patients with well-defined medical diseases, while differences in objective cognitive performance between the groups were rather mild. Similar findings have been reported in previous studies, investigating both healthy participants as well as patients with FSS (Ray *et al* 1993, Stulemeijer *et al* 2007, Tucker-Drob 2011). The difference between the outcomes of subjective and objective cognitive functioning may be due to the fact that questionnaires measure different domains of cognitive function than cognitive

tasks (Cockshell, Susan Jayne and Mathias 2010, Ray *et al* 1993). Questionnaires cover more global and overarching cognitive functions, whereas tasks assess much smaller and specific functions. In addition, the CogState brief battery covered four basic domains of cognitive functioning, while adequate cognitive functioning in daily life requires much more, and more complex, processing. Furthermore, in accordance with previous research, the presence of comorbid mood or anxiety disorders did not explained the differences in cognitive performance between groups (Cockshell, Susan J. and Mathias 2013). Thus, although mood or anxiety disorders are relatively common in patients with FSS (Janssens *et al* 2015), we found no evidence to suggest that they contribute to cognitive impairments. We also found that the associations between somatic symptomatology and cognitive functioning were in most cases not significantly different between patients with FSS and controls or patients with well-defined medical diseases. Moreover, general symptom severity, but not the main symptoms fatigue or pain, were in most cases significantly associated with the performance on the cognitive tasks in all groups. The associations between the experience of somatic symptoms and the performance on the cognitive tasks were therefore not unique to patients with FSS, as shown by the results in controls or the MS/RA groups.

Lastly, we investigated differences between patients with CFS and patients with FMS in the context of the lumper-splitter discussion (Wessely *et al* 1999). We found that patients with CFS patients had significantly more subjective cognitive impairments and performed significantly worse on tasks measuring speed of processing and attention/working memory, compared to patients with FMS. Since we found both similarities and differences between CFS and FMS, our results support suggestions that FSS have both specific and general characteristics (Lacourt *et al* 2013).

While our study addresses many limitations of previous research, our cross-sectional design provides only a first step. Future studies will be necessary to understand the causes of and contributors to impaired subjective cognitive functioning in FSS patients. Furthermore, the fluctuations that occur in FSS symptoms (e.g. pain, fatigue) may result in unstable results on objective cognitive tasks (Fuentes *et al* 2001). We recommend to use a more extensive cognitive battery that measures more aspects of cognitive functioning, in correctly diagnosed CFS and FMS patients compared to a well-matched control group, including relevant confounding variables and taking into account the fluctuations of symptoms experienced.

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