Digging into the construct of fibrofog: Psychometric properties of the Spanish version of the Multidimensional Inventory of Subjective Cognitive Impairment (MISCI) in patients with fibromyalgia

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Introduction

Fibromyalgia (FM) is a syndrome characterized by a broad range of symptoms such as chronic widespread musculoskeletal pain, fatigue, stiffness, sleep problems, psychological distress (depression and anxiety) and cognitive disturbances (Häuser et al., 2015). Indeed, over 50% of patients with FM present a subjective perception of impaired cognitive abilities (Katz, Heard, Mills & Leavitt, 2004) and this has been ranked as one of the top five major contributors to distress in FM (Bennett, Jones, Turk, Russell & Matallana, 2007), associated with negative impact on health-related quality of life, perceived disability (Arnold et al., 2008), impaired job performance, and increased health care utilization (Wilson, Robinson & Turk, 2009). Perceived dyscognition involves complaints about memory, concentration, verbal expression, activity management and scheduling, mental agility, and generally experiencing life through a haze (Arnold et al., 2008). Altogether, these cognitive complaints have been popularly termed *fibrofog* (from fibromyalgia and brain-fog).

Although pain has been the main focus of research and clinical care in FM, more recently, fibrofog has been proposed as a core domain for FM assessment in randomized controlled trials and clinical practice (Mease et al., 2009), and is one component of the current diagnostic criteria for FM (Wolfe et al., 2010). Research has shown that perceived dyscognition is related to objective cognitive impairments in memory, verbal fluency, attention/concentration and executive functioning (Kravitz & Katz, 2015; Park, Glass, Minear & Crofford, 2001; Tesio et al., 2015). However, in addition to objective cognitive difficulties, other contributing factors, such as emotional distress, have demonstrated appreciable effects on fibrofog (Ambrose, Gracely & Glass, 2012; Gelonch, Garolera, Valls, Rosselló & Pifarré, 2016; Glass, Park, Minear & Crofford, 2005).

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Core FM symptoms such as fatigue, unrefreshing sleep and mood alterations may contribute to fibrofog (Williams, Clauw & Glass, 2011). Although some authors reported normal results on neuropsychological tests in persons with FM, methodological limitations of the research so far (e.g., narrow range of cognitive domains, small sample size, poor ecological validity of tests) may also call into question the findings regarding normality of objective cognitive performance in patients with FM (Ambrose, Gracely & Glass, 2012).

Perceived cognitive disturbances are not only reported by people with FM, but also by patients with other chronic pain conditions and mood and anxiety disorders (American Psychiatric Association, 2013; Iverson & McCracken, 1997). Perceived dyscognition may be indicative of truly impaired cognitive functioning or represent a patient's perception of impairment where none exists. However, evidence shows that, irrespectively of real objective impairment, fibrofog can contribute to perceived functional impairment (McCracken & Iverson, 2001; Pedrelli, Baer, Losifescu & Fava, 2010; Saffer, Lanting, Koehle, Klonsky & Iverson, 2015). Actually, around 42% of patients with chronic pain report at least one cognitive complaint (Iverson & McCracken, 1997). Causal and maintaining mechanisms of objective and subjective cognitive impairment in FM are largely unknown. One hypothesis suggests that cognitive impairment in chronic pain may be due to the interference of pain in cognitive processes, since it could compete for attentional resources and so restrict available mental resources for cognitive tasks (Dick, Verrier, Harker & Rashiq, 2008). Hypervigilance to pain and to pain-related information has already been extensively described in patients with FM (Häuser et al., 2015). In this regard, higher catastrophizing or pain-related fear/anxiety can be related to more difficulties in diverting attention away from a painful event, so limiting the available attentional resources (Roth et al., 2005). In previous studies in patients with chronic pain or FM, despite heterogeneous results, cognitive complaints have been linked to pain intensity, depression (Gelonch et al., 2017; McCracken & Iverson, 2001), anxiety, sleep problems and fatigue (Kravitz et al., 2015). As proposed by Williams, Clauw & Glass (2011), perceived dyscognition in FM may be part of a "symptom cluster" (Dodd, Miaskowski & Paul, 2001) with other FM symptoms, such as fatigue, sleep and mood disturbances (which are in turn commonly associated with many chronic illnesses), heightening respective intensity with their co-ocurrence. As one might expect, several studies have reported strong positive correlations between measures of cognitive impairment, and mood or fatigue in FM (Ambrose, Gracely & Glass, 2012). Since both subjective and objective cognitive impairment have been widely reported in patients with depression (McIntyre, et al., 2013) and depressive symptoms are very frequent in

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patients with FM (Häuser et al., 2015), cognitive complaints in FM are frequently attributed to depressive symptoms. Such neurobehavioral features may reflect disturbed centrally mediated processes in FM. In this regard, FM substantially overlaps with other syndromes characterized by impaired pain regulation of central origin such as irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint disorder or vulvodynia syndrome, which are classed together under the Central Sensitivity Syndromes (CSS) umbrella (Woolf, 2011; Yunus, 2007). Thus, objective and subjective cognitive problems, even after excluding correlates with other symptoms as contributing factors, may be indicative of real alterations at the brain level (Ceko, Bushnell & Gracely, 2012). In this regard, accelerated brain gray matter loss has been reported in FM suggesting premature aging in this disorder (Kuchinad, Schweinhardt, Seminovitcz, Wood, Chizh & Buschnell, 2007). In fact, a pattern of local abnormalities of gray matter (i.e., reductions or increments) involving areas related to pain processing, stress response, and cognitive control have been described in patients with FM (Wallit, et al., 2016). However, it is not yet clear whether these alterations may be causative or just an epiphenomenon of FM.

Although current recommendations indicate the need to include fibrofog as an outcome in FM clinical research (e.g., Mease et al., 2009), most studies do not assess fibrofog as a variable of interest. Consequently, very little is known about the impact of available treatments for fibrofog in FM. In a recent network meta-analysis focusing on pain and quality of life, small effects of questionable clinical relevance for some pharmacological treatments (i.e., pregabalin, SNRIs) and more ubiquitous effects of small-moderate magnitude for non-pharmacological programs (such as multicomponent therapy, aerobic exercise and cognitive-behavior therapy) were reported (Nüesch et al., 2013). Further studies should test whether these interventions are also effective in reducing fibrofog. A promising intervention (Adler-Neal & Zeidan, 2017) for targeting fibrofog and other core symptoms in FM is Mindfulness-Based-Stress Reduction (MBSR; Kabat-Zinn, 1990). Mindfulness training has been related to ameliorations of FM symptoms in previous studies (see Lauche, Cramer, Dobos, Langhorst & Schmidt, 2013 for a review) and also to improvements in cognitive function (Chiesa, Calati & Serretti, 2011; Lao, Kissane & Meadows, 2016).

Examination of fibrofog in clinical research may be hindered by the fact that most instruments for assessing cognitive dysfunction are very lengthy, non-FM-specific and do not evaluate all domains of perceived cognitive impairment in FM (such as the *Multiple Abilities Self-report Questionnaire* or MASQ; Seidenberg, et al., 1994). In response to these limitations, the *Multidimensional Inventory of Subjective Cognitive Impairment* (MISCI; Kratz et al., 2016) was devised to be a brief

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yet comprehensive self-report measure of multi-faceted cognitive functioning for use in both clinical and research practice.

The MISCI is a 10-item patient-reported instrument aimed at assessing the construct of perceived cognitive function in patients with FM and is composed of a selection of the most informative items from the cognitive functioning item banks of the Patient Reported Outcomes Measurement Information System and the Quality of Life in Neurological Disorders initiatives (PROMIS®/NQ; Cella et al., 2010). This inventory covers five main clinically-relevant cognitive functioning domains: 1) memory, 2) verbal language ability, 3) general mental clarity, 4) attention/concentration and 5) executive functioning. To develop this instrument, factorial analyses were completed and Item Response Theory analyses were performed to identify the two most discriminating items for each clinically-relevant cognitive domain. The original English version of the MISCI showed excellent internal consistency, low ceiling/floor effects, and good convergent validity with FM impact severity and the MASQ (Seidenberg et al., 1994) a classical (and longer) measure of perceived cognitive abilities which evaluates non-FM-specific domains such as language, verbal memory, attention, visual perceptual and visual memory (Kratz et al., 2015; Williams & Kratz, 2016).

The main objective of the present study was to assess the psychometric properties of the Spanish version of the MISCI in a sample of patients with FM. Specifically, we evaluated the dimensionality, internal consistency, test-retest reliability, construct (convergent and known-groups) validity, and sensitivity to change of this instrument. Structural neuroimaging measurements were also used to evaluate the convergence between MISCI scores and brain-derived objective data. To our knowledge, this is the first study that surveyed the psychometric properties of a non-English version of the MISCI outside the U.S. Given the well-known contributive effect of depressive symptoms on fibrofog reported by many authors (e.g. Gelonch et al., 2017), known-groups validity of the MISCI and the putative additive effect of depression on fibrofog were tested by comparing MISCI scores in three clinical samples: 1) Patients with FM without depression, 2) with FM and comorbid depression, and 3) patients without FM reporting residual depressive symptoms. Sensitivity to change of the MISCI was also assessed after a MBSR program using early-stage data from the EUDAIMON study, a randomized controlled trial (RCT) examining the cost-effectiveness of mindfulness-based stress reduction in patients with FM (Feliu-Soler et al., 2016). Finally, in order to test for potential symptom cluster contributors to fibrofog, a hierarchical regression analysis was performed with core FM symptoms as predictors of MISCI scores.

Methods

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Participants

The FM study sample was composed of 120 adult patients with a FM diagnosis according to American College of Rheumatology (ACR) 1990 criteria (98.3% women, mean age=53.8 years, SD=6.9, Range=36−65 years) recruited at the Rheumatology service of Sant Joan de Déu Hospital (St. Boi de Llobregat, Spain). MISCI was administered (together with the other paper-and-pencil measures) as part of the evaluation protocol of the EUDAIMON study (Feliu-Soler et al., 2016). All recruited patients in this study were selected following a multi-stage recruitment process. A health psychologist screened potential participants through a phone interview and then made an appointment for those patients that met inclusion/exclusion criteria and agreed to participate in the study. Face-to-face interviews were performed once written consent had been obtained. A detailed description of the study protocol can be found elsewhere (Feliu-Soler et al., 2016). The following inclusion/exclusion criteria were applied: Patients of both genders between 18–65 years-old, provision of written informed consent to participate, able to understand and read Spanish, not participating in other studies, not receiving psychological treatment during the last twelve months, not reporting previous mindfulness training, not having comorbidity (according to their hospital medical record) with severe medical illness, psychotic symptoms or substance abuse, nor being involved in ongoing litigation relating to FM. The sample size of 120 patients available for psychometric analyses of the MISCI was considered appropriate to validate the MISCI since the classic criteria of ≥10 cases per item was met (Kass & Tinsley, 1979). Nearly half of these patients (n= 56) presented current comorbid Major Depressive Disorder (64 did not present) according to the Structured Clinical Interview for DSM Axis I Disorders (SCID-I; First, Spitzer, Gibbon & Williams, 1997) administered by a health psychologist. Additionally, to test the known-groups validity of the MISCI, a sample of 45 non-FM adult primary care patients (83.7% women, mean age=52.2 years, SD=17.2, range=23−87 years) in partial/total remission from Major Depressive Disorder according to clinical records (Residual Depressive Symptomatology group, RDS) were also invited to complete the MISCI. See Table 1 for more detailed information. This last sample was participating in a 12-month non-randomized controlled trial on the cost-effectiveness of active monitoring (vs. stand-alone antidepressant treatment) in mild-moderate major depression (the INFAP study, Rubio-Valera et al., 2015). Signed informed consent was obtained from all patients before initiating their participation in the study and the EUDAIMON and INFAP study protocols were approved by the Clinical Research Ethics Committee at the Sant Joan de Déu Foundation (CEIC reference numbers: PIC-33-11 and EPA-24-12).

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Procedure

Items corresponding to the 10-item original MISCI instrument were drawn from the NIH PROMIS®/Neuro-QOL item banks, which underwent a rigorous forward and back-translation procedure (English-Spanish-English) with multiple expert reviews and cognitive debriefing with a sample of native Spanish-speakers (Eremenco, Cella & Arnold, 2005). As stated above, a paper-and-pencil version of the MISCI and sociodemographic data were completed by all the patients as part of the EUDAIMON and INFAP studies. To evaluate the construct validity of the MISCI, a subsample of 96 patients with FM also completed a battery of self-report measures. Additionally, to extend the evaluation of construct validity of the MISCI with brain-based objective variables, anatomic brain measurements from 61 patients were obtained and grey matter volumes of specific regions of interest potentially related to fibromyalgia (Lin, Lee & Weng, 2016; Wallit, Ceko, Gracely & Gracely, 2016) were calculated. To evaluate MISCI sensitivity to change, 59 patients from the EUDAIMON study [37 allocated to MBSR and 22 to Treatment-as-usual (TAU)] also completed the MISCI pre- and post- intervention (8 weeks). MBSR is an 8-week program which includes meditative training (e.g., body-scan, breath focusing, walking meditation or mindful eating), mindful-stretches and psycho-educative content aimed at increasing more adaptive responses in the context of stress, pain and illness (Adler-Neal & Zeidan, 2017; Kabat-Zinn, 1990). Since little clinical change has been reported in patients allocated to TAU in other RCTs with similar samples and equivalent measurement time frames (e.g., Luciano et al., 2011), pre-post data from the 22 patients allocated to TAU was also used to test the temporal stability of the MISCI. TAU, as it is commonly provided in Spanish health-care settings, mainly consists of pharmacological treatment adjusted to the symptomatic profile of the patients and counselling on aerobic exercise adjusted to patients' physical limitations is usually provided. Participants from the INFAP study also completed a paper-and-pencil version of the MISCI. The Patient Health Questionnaire (PHQ-9, Kroenke & Spitzer, 2002) was only used in this last sample to describe severity of depressive symptoms. All data were obtained in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent updates. The FSJD Research Committee Board evaluated and approved both study protocols (PIC-102-15 and EPA-24-12, respectively).

Study measures

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All study participants completed a socio-demographic and clinical questionnaire with gender, date of birth, marital status, educational level, employment status and years with FM (when applicable).

The following measures, including the MISCI, were administered in the FM sample:

- *The Multidimensional Inventory of Subjective Cognitive Impairment* (MISCI; Kratz et al., 2015) is a 10-item instrument with a 5-point Likert scale (from 1 "*Not at all/Never*" to 5 "*Very much/Always*") to evaluate subjective cognitive function in patients with FM. It is composed of six positively-worded items reflecting perceived cognitive abilities (e.g., "*I have been able to think clearly without extra effort*") and four negatively-worded items for perceived cognitive difficulties (e.g., "*I had trouble planning out the steps of a task*"), including items for the following cognitive domains (2 per domain): mental clarity, memory, attention/concentration, executive functioning, and language. The time frame is "the past 7 days". The 4 negatively-worded items from the MISCI were reverse scored. Items were summed so that higher total scores (ranging from 10 to 50) are indicative of better subjective cognitive functioning.

- *The Revised Fibromyalgia Impact Questionnaire* (FIQR; Bennett, Friend, Jones, Ward, Han & Ross, 2009; Luciano, Aguado, Serrano-Blanco, Calandre & Rodriguez-Lopez, 2013) is a primary efficacy endpoint measure in FM clinical trials and is the "gold standard" assessment measure for multidimensional functional status in patients with FM. It includes 21 items rated on an 11-point Likert scale (from 0 to 10), with higher scores reflecting greater impairment. FIQR items are distributed into three domains: "physical function" (9 items); "overall impact" (2 items); and "severity of symptoms" (10 items). A total score for the FIQR (from 0-minimum impact- to 100-maximum impact) can be calculated by dividing the physical function subscore by 3 and the severity of symptoms domain by 2 and then summing both values to the overall impact subscore (unchanged). Cronbach's α of the FIQR in our sample was excellent (α=.92). The sixth item from the "severity of symptoms" section (i.e., 3f item) is related to fibrofog: "Please rate your level of memory problems" (ratings range from 0-good memory- to 10-very poor memory). This item has been also used in the present study as a variable of perceived cognitive impairment.

- *Fibromyalgia Survey Diagnostic Criteria* (FSDC; Carrillo-de-la-Peña et al., 2015; Häuser et al., 2012): A 6-item self-administered questionnaire aimed at evaluating key symptoms of FM according to the latest ACR revision. FSDC includes two domains: 1) the Widespread Pain Index (WPI) identifying 19 body areas where pain/tenderness was felt during the previous week (with

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scores ranging from 0–19), and 2) the Symptom Severity Scale (SSS; with scores ranging from 0−12) composed of three items on major FM symptoms (i.e., fatigue, trouble thinking/remembering and waking up tired or unrefreshed) scored from 0= no problem to 3= severe, continuous, life-disturbing problems, and three additional items on other somatic complaints (i.e., pain/cramps in lower abdomen, depression, and headache) coded as present= 1 or absent= 0. A total score of fibromyalginess ranging from 0 to 31 can also be obtained by summing the WPI and the SSS scale. Cronbach's α of the SSS subscale in our sample was considered to be adequate (α=.66). The item on the presence of cognitive symptoms (i.e., attention, concentration or memory problems) from the SSS (ranging from 0= "No problem" to 3= "Severe: pervasive, continuous, life disturbing problems") was also studied separately as an additional convergent measure of perceived cognitive impairment.

- The *Hospital Anxiety and Depression Scale* (HADS; Luciano et al., 2014; Zigmond & Snaith, 1983): Originally developed to assess anxiety and depressive symptom severity in non-psychiatric hospital patients and includes 14 items on a 4-point Likert scale (from 0=not at all to 3=very often) in two subscales: HADS-A: Anxiety and HADS-D: Depression). Possible scores range from 0 to 21 for both anxiety and depressive subscales, with higher scores suggesting greater severity. Cronbach's αs of the HADS-A and HADS-D subscales in our sample were good (.87 and .86, respectively).

- The *Perceived Stress Scale* (PSS-10; Cohen & Williamson, 1988; Remor, 2006): IA 10-item self-administered 5-point Likert scale (from 0=Never to 4=Very often) instrument to assess the degree to which situations in one's life are considered stressful in the previous month. Scores range from 0 to 40. Cronbach's α of the PSS in our sample was considered to be excellent (α=.91).

- The *Pain Catastrophizing Scale* (PCS; García-Campayo, Rodero, Alda, Sobradiel, Montero & Moreno, 2008; Sullivan, Bishop & Pivik, 1995) is a 13-item instrument using a 5-point Likert scale (0= not at all to 4= all the time) that evaluates 3 cognitive dimensions related to pain catastrophizing: Rumination (4 items) or the inclination to focus excessively on pain sensations, Magnification (3 items) understood as the tendency to amplify the threat value of pain sensations and, finally, Helplessness (6 items), the inclination to perceive oneself as unable to control the intensity of pain; a PCS total score (score range between 0−52) and three subscale scores (with scores ranging from 0−16, 0−12 and 0−24, respectively) can be computed through the algebraic sum of ratings, with higher scores indicating greater pain catastrophizing. The internal consistency of the PCS was excellent in our FM sample (Cronbach's α=.94).

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- The *Structured Clinical Interview for DSM Axis I Disorders* (SCID-I; First, Spitzer, Gibbon & Williams, 1997) was used to diagnose current Major Depressive Episode in the FM sample.

- Structural neuroimaging data were collected on a Philips Ingenia 3.0 T whole body system equipped with a 12-element receive-only head matrix coil. High-resolution anatomical T1-weighted scans were obtained using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following scanning parameters: repetition time (TR) = 9 ms, echo time (TE) = 4 ms, inversion time = 1000 ms, flip angle = 8°, field of view (FOV) = 240 × 240 × 170 mm, matrix size = 240 × 240, number of slices = 170, and acceleration factor (SENSE) = 2 with an isotropic resolution of 1 × 1 × 1 mm3. All images were analyzed with SPM12 (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) running under MATLAB (Release 2012b, The MathWorks, Inc., Natick, MA, USA). Gray matter, white matter and cerebrospinal fluid were segmented from the T1 images of the participants employing the CAT toolbox (http://www.neuro.uni-jena.de/cat) for SPM12. The following specific gray matter regions were selected in accordance with a recent review and meta-analysis (Lin, Lee & Weng, 2016; Wallit, et al., 2016): prefrontal cortex, orbitofrontal cortex, cingulate cortex, insula, precuneus, superior temporal gyrus, cerebellum, brain stem, and subcortical structures. Volumes for the regions of interest were automatically calculated according to the Neuromorphometrics atlas (http://www.neuromorphometrics.com). Total brain volume was obtained by summing the volumes of the gray matter, white matter and cerebrospinal fluid segments.

Data analyses

Sociodemographic information and available clinical characteristics were reported with descriptive statistics of frequencies, means and standard deviations (SD). T-tests and χ^2 were used to test for differences between FM total sample and the sample without FM with Residual Depressive Symptomatology (RDS) in sociodemographic data. All data were analyzed with SPSS v22.0 and Mplus v7.2.

Dimensionality: Data from the full FM sample (N=120) were used to test the factor structure in a Confirmatory Factorial Analysis (CFA) with all MISCI items loading on one latent factor (Model 1). Since psychological instruments composed of both positively and negatively formulated items tended to obtain worse fit for unidimensional models because positively phrased items are prone to load on one factor and negatively phrased items on another (Woods, 2006), a one-factor model with "method effects" (Model 2) as a respecification of Model 1 was also tested. Model 2

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incorporated correlated error terms on the negatively phrased items of the MISCI (items 7, 8, 9, and 10). Therefore, six correlated residuals were specified. Moreover, items situated in a separate instrument section are likely to covary (Luciano et al., 2013). The maximum likelihood estimation with robust standard errors was applied to test the fit of the two alternative factor models and the following model fit indices were examined (the values in parentheses denote goodness-of-fit standards): the χ^2 test (non-significant value), the Tucker–Lewis index, the comparative fit index (TLI and CFI ≥ .95 indicate an acceptable fit, and ≥ .97 indicate a good fit), and the root mean square error of approximation with 90% confidence intervals (RMSEA ≤ .08 indicates an acceptable fit and ≤ .05 indicates a good fit).

Internal consistency: Cronbach's α coefficient was calculated in the FM sample with acceptable α values fof .60 for exploratory research and of .70 for confirmatory research (Hair, Anderson, Tatham & Black, 1998). Additionally, we assessed homogeneity of the MISCI by inspecting the corrected item-total correlation (correlation of the item designated with the summed score for all other subscale items). A common rule-of-thumb is that these values should be at least .30 (Nunnally & Bernstein, 1994).

Test-retest reliability: To determine the stability over time of the MISCI, test-retest reliability was explored uing the Intraclass Correlation Coefficient (ICC; 2-way random, absolute agreement with 95% CI; Trevethan, 2017) using data from the TAU group (around 2 months elapsed between pre-post assessments). The common cut-off points for reliability assessment are > .90 (excellent), .75−.90 (good), .60−.75 (moderate), and < .60 (low).

Convergent construct validity of the MISCI was studied by means of Pearson's moment correlations between MISCI and clinical variables related to FM-related symptoms (FIQR, FSCD, HADS subscales and PSS) and Pain Catastrophizing (PCS). Associations with FIQR item "memory problems" and the FSCD-item "problems with attention, concentration or memory" were also evaluated as specific perceived cognitive-impairment items. Since these specific items are considered "legacy measures" of fibrofog, high correlations are expected (r>.60). Pearson correlations between MISCI scores and specific brain areas volumes were also evaluated. Effect size of correlations were interpreted in the light of the Ferguson (2009) paper where *r*s between .20 and .49 mean a minimum effect representing a "practically" significant effect for social science data, .50 to .79 correspond to a "moderate effect" and ≥.80 to a strong effect size. Since total brain volume, age and years with FM may be theoretically related to specific brain area volumes,

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partial correlations controlling for these variables were also performed for those specific regions presenting significant zero-order correlations with MISCI.

Known-groups construct validity: The known-groups validity approach is founded on the basis that specific subgroups of patients might be expected to score differently from others. T-test comparisons were performed to assess the validity of the MISCI to discriminate among FM patients without depression (according the SCID-I), patients with FM with depression and patients without FM with residual depressive symptoms. We calculated between-groups effect sizes using Cohen's d (rule of thumb for Cohen's *d*: .20= small, .50= medium, and .80= large effect sizes). As cognitive complaints are usually associated with depressive symptomatology, an additive effect of MDD and FM diagnosis on MISCI scores (i.e., lower scores) was expected to be found. In this regard, better results in the MISCI (i.e., higher scores) were expected in patients with FM without MDD and even better in those patients with residual depressive symptoms (without FM or current MDD diagnosis).

Sensitivity to change: To determine the usefulness of the MISCI as an outcome measure of interventions in FM, sensitivity to change was explored with repeated-measures ANOVA comparing patients allocated to MBSR and those whom received TAU. Partial eta squared (η_p^2) for group x time effect size calculation was used (interpreted as follows: .04–.24=minimum, .25–.63=moderate, ≥ .64=strong effect sizes; Ferguson, 2009). Paired samples T-Test and Cohen's *d* correcting for dependence between means using Morris and DeShon's (2002) equation were used for posthoc analyses. To evaluate the clinical effectiveness of the MBSR intervention, statistical significance and effect size of changes in FIQR were evaluated.

Finally, to test for symptoms in FM which are potential contributors to perceived cognitive impairment, a hierarchical multiple regression of MISCI scores using FIQR items for pain, energy/fatigue, stiffness, sleep quality, tenderness to touch, depression, anxiety, problems with balance, and environmental sensitivity as predictors was performed. This analysis was carried out controlling first (with stepwise method at $p < .05$) for sociodemographic variables (gender, age and years of schooling) and medical data (i.e., years with FM, use of the following psychotropic drugs: narcotic analgesics, benzodiazepines, antidepressants, hypnotics, anti-epileptics) and selected FIQR items as the second step (entry method).

Results

Dimensionality

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The χ^2 value for both models was significant (model 1 = 157.093, p< .001; model 2 = 49.031, p< .001). The other fit indices of model 1 did not indicate adequate fit to the data (CFI= .79; TLI= .73 and RMSEA= .17, 90% CI: .14–.20). The inclusion of correlated residuals in model 2 substantially improved model fit (CFI = .97; TLI = .95 and RMSEA = .08 (90% CI: .04–.11). In addition, the four correlated residuals were statistically significant ($\theta_{7,8}$= .49, $\theta_{7,9}$= .36, $\theta_{7,10}$= .25, $\theta_{8,9}$= .51, $\theta_{8,10}$= .43, $\theta_{9,10}$= .67; all p< .05). Therefore, model 2 yielded support for the unidimensional model of the MISCI when method effects were taken into account. All standardized factor loadings ranged from .53 to .87 in model 2 (lambda coefficients), were statistically significant (all p< .001) and in the fair to excellent range (Comrey, 1973). See Table 2 for standardized factor loading estimates.

ADD TABLE 2 ABOUT HERE

Reliability

Cronbach's α coefficient was .91, indicating excellent internal consistency of the MISCI (Cicchetti, 1994). Removal of any of the MISCI items did not lead to a significant increase in the inventory's α coefficient values and all corrected item-total correlations were above the minimum cut-off of .30 recommended by Nunnally and Bernstein (1994), reflecting satisfactory scale homogeneity. For more details see Table 2. Intraclass correlation coefficient (ICC) was .88 (95% CI= .71– .95) suggesting good test-retest reliability for the MISCI (Portney & Watkins, 2000).

Convergent validity

As expected, significant negative correlations (all p< .01) with moderate effect size (Ferguson, 2009) were found between the MISCI and FIQR-item on memory problems (r= -.74) and the FSDC-item on cognitive symptoms (r= -.69) suggesting good evidence of convergent validity of the MISCI. Moderate correlations were also found between MISCI and instruments measuring FM impact (as reported by FIQR; r= -.60), fibromyalginess (FSDC; r= -.45), anxiety (HADS-A; r= -.59), depression (HADS-D; r= -.62), perceived stress (PSS; r= -.62) and pain catastrophizing (PCS-Total; r= -.58). See Table 3 for more details. A significant correlation between MISCI scores and years with FM was also found (r= -.22, p= .03).

ADD TABLE 3 ABOUT HERE

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Significant (p< .05) zero-order correlations between brain structure volumes and MISCI scores were found with rs ranging from .30 to .46 (i.e., left anterior cingulate cortex (lACC), left middle cingulate cortex (lMCC), left lateral orbitofrontal gyrus, left medial orbitofrontal gryus, left inferior orbitofrontal gyrus, right posterior cingulate, left superior temporal gryus, and right superior temporal gyrus). When controlling for age, years with FM and total brain volume, only lACC and lMCC were significantly associated with MISCI scores (r= .30, p= .04, and r= .38, p= .009, respectively). See Figure 1 for more details regarding these areas. No significant associations were observed regarding MISCI scores and other cortical and subcortical volumes.

ADD FIGURE 1 ABOUT HERE

Known-groups validity

Table 4 displays the MISCI mean scores for subsamples of patients with FM, with or without Major Depressive Disorder comorbid diagnosis, and the comparative sample of patients without FM reporting residual depressive symptomatology [i.e., mild depression severity according to PHQ-9 scores (Mean= 9.03, SD= 6.71); Kroenke & Spitzer, 2002]. Univariate ANOVA showed significant between-group differences ($F_{[2,162]}$= 17.35; p< .001) with posthoc analyses indicating worse perceived cognitive performance (i.e., lower MISCI scores) in the FM with depression group compared to FM without depression (p< .001; d= .74) and to patients without FM and with Residual Depressive Symptomatology (RDS group) (p< .001; d= -1.09) with medium and large effect sizes, respectively. The FM sample without depression also showed lower MISCI scores compared to the RDS group (p= .02; d= -.45).

ADD TABLE 4 ABOUT HERE

Sensitivity to change

Greater changes in MISCI scores were observed in MBSR group ($F_{[1,57]}$= 10.92; p= .002; η_p^2= .16) as suggested by main and posthoc analyses, with effect sizes suggesting a large effect of MBSR on MISCI scores (d= .98). Similarly, an effect of treatment on FIQR scores was also observed ($F_{[1,54]}$= 4.70; p= .03) in the MBSR group. Results are shown in Table 5.

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ADD TABLE 5 ABOUT HERE

FM-inherent contributors to fibrofog

After controlling for years with FM (the only confounding variable significantly related to MISCI scores), hierarchical regression analysis was highly significant (p< .001) with Depressive symptoms, Anxiety symptoms and Balance problems from the FIQR accounting for 43.6% of MISCI variance [with standardized β= -.21 (p=.049), β= -.21 (p=.036) and β= -.28 (p= .018), respectively]. In this regard, higher scores in these three predictors were related to worse perceived cognitive functioning (i.e., lower MISCI scores). Pain, energy/fatigue, sleep quality, stiffness, tenderness to touch, and hypersensitivity to external stimuli were not significant predictors of MISCI scores in the final model (all p> .05). Other confounding variables entered in the first step such as age, gender, years of schooling, and use of psychotropic drugs (i.e., narcotic analgesics, benzodiazepines, antidepressants, hypnotics, anti-epileptics) were not significant predictors of MISCI scores (all p> .05). Regarding psychotropic medication (not reported in Table 1): 25.8% (n= 31) of the FM sample were under treatment with narcotics, 44.2% (n= 53) with benzodiazepines, 36.7% (n= 44) with antidepressants, 3.3% (n= 4) with hypnotics and 13.3% (n= 16) with anti-epileptics. The mean number of psychotropic medications was 1.23 (SD= 1.24) and 38.3% of the sample (n= 46) did not take any.

Additionally, a linear regression model (enter method) was computed including the three significant predictors only (i.e., anxiety, depressive symptoms and balance difficulties); this model yielded a slightly lower percentage of total explained variance (37.6%) with the three predictors remaining significant. See Table 6 for more detailed information.

ADD TABLE 6 ABOUT HERE

Discussion

Despite the serious impact of perceived dyscognition on quality of life and functionality in those with FM, this construct is not usually assessed in clinical research and is not typically a focus of clinical care. Bearing in mind the broad range of symptoms that require assessment in FM, measures that are reliable, valid and brief yet sufficiently comprehensive are greatly needed. The psychometric properties of the MISCI, which was designed specifically to assess the broad range of cognitive problems that are common in FM, have only been published in English. Though items from the MISCI were translated into Spanish by Eremenco, Cella & Arnold (2005), the psychometric properties of the Spanish adaptation of the MISCI have not previously been

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published. The present work presents the psychometric properties of the Spanish version of the MISCI for the first time and expands its potential application to Spanish-speaking individuals.

The MISCI (Kratz et al., 2015) comprises 5 domains (with 2 items each) covering common symptoms of fibrofog (i.e., memory, verbal language ability, general mental clarity, attention/concentration, and executive functioning). Since MISCI was not devised to evaluate each of these distinct domains but to provide a single comprehensive measure on subjective cognitive dysfunction idiosyncratic to FM (Kratz et al., 2015), the CFA conducted with the Spanish version of the MISCI aimed to test the unidimensionality of the MISCI. In this regard, adequate fit indexes, especially when controlling for method effects and high factor loadings (all $\lambda > .50$) were obtained, confirming the unidimensionality of the MISCI. Since a better fit was obtained after controlling for method effects, future versions of the MISCI may consider not using items with reverse wording (Van Sonderen, Sanderman & Coyne, 2013). In common with the English version, excellent internal consistency was observed in our stdy ($\alpha = .91$). Test-retest reliability of the MISCI was evaluated for the first time, showing very good temporal stability over time (ICC= .88), even more so when considering the long period between test and retest (i.e., 2 months). No significant changes in either FIQR or MISCI scores were reported in the TAU group (6.4%, $d = .28$, $p > .05$, and 4.9%, $d = .20$, $p > .05$, respectively), thus ensuring that the test-retest reliability of the MISCI was evaluated only in a subset of patients in whom the variable measured (i.e., MISCI scores) has not changed. The sensitivity of the MISCI to change was also tested by evaluating pre-post changes after a MBSR program in comparison to treatment-as-usual. We corroborated, by means of pre-post changes in FIQR scores (main outcome measure), ≥20% that MBSR was clinically effective (Bennett, 2005) (MBSR: 22%, $d = .74$, $p < .001$). Moreover, even larger pre-post improvements (large effect size) in MISCI scores were found (MBSR: 29%, $d = .98$, $p < .001$), indicating a great impact of MBSR on fibrofog. This finding provides preliminary evidence of the effectiveness of mindfulness-based interventions for managing fibrofog symptoms. Previous studies on mindfulness reported some positive effects on pain and quality of life (Lauche, Cramer, Dobos, Langhorst & Schmidt, 2013) but to date none tracked perceived cognitive functioning. In fact, there is a striking lack of information regarding the specific effects of pharmacological and non-pharmacological interventions on objective and, especially, subjective cognitive impairment in FM. Since fibrofog is ranked as one of the top contributors to distress in patients with FM, its specific evaluation −as recommended by OMERACT-9 in 2009 (Mease et al., 2009)− should be incorporated and reported in all studies

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performed in the field. The incorporation into clinical and research practice of a reliable, short measure of perceived cognitive functioning, such as the MISCI, could contribute to filling this gap.

As expected, we found a significant association between MISCI and FIQR scores, although this relationship was slightly lower compared to findings for the English version (Kratz et al., 2015): FIQR-Physical Function *r*= -.51 vs. *r*= -.60; FIQR-Impact *r*= -.39 vs. *r*= -.60; FIQR-Symptom *r*= -.65 vs. *r*= -.64; and FIQR-Overall score *r*= -.60 vs. *r*= -.70). As legacy measures for fibrofog, we used single items of cognitive complaints from the FIQR and FSDC, finding good convergence with MISCI scores (with *r*= -.74 and *r*= -.69, respectively). A high correlation (*r*= -.70) between MISCI scores and FIQR cognitive complaints was also reported in the original validation of the instrument (Kratz et al., 2015). No significant associations between MISCI scores and sociodemographic variables (age, gender, years of schooling) or psychotropic medication use were observed (data not reported; all *p*> .05). However, a significant negative correlation between chronicity (i.e., years living with FM) and MISCI scores was found (*r*= -.22, *p*< .05) and this association was also significant after controlling for age (data not shown; *p*< .05), suggesting that fibrofog may worsen due to a sustained and cumulative effect of the syndrome over time. These results are in contrast with those reported by McCracken & Iverson (2001) in a study with 275 chronic pain patients where chronicity had no association with perceived dyscognition. Correlations with other relevant clinical measures were even higher than with FIQR scores, including HADS-A (anxiety) and HADS-(depression) subscales (with *r* of -.59 and -.62, respectively), PSS (perceived stress; *r*= -.62) and PCS global score (pain catastrophizing, *r*= -.58), confirming a negative association between perceived cognitive function and mood status and negative cognitive–affective response to anticipated or actual pain. These findings are in congruence with other studies suggesting that fibrofog may be part of a symptom cluster in FM (Williams, Clauw & Glass, 2011), meaning that fibrofog can increase in intensity with the co-occurrence with other FM symptoms. In this regard, depression, anxiety and distress would not only be related to perceived cognitive disturbances in FM but also to cognitive complaints in chronic pain in general (McCracken & Iverson, 2001).

In a recent study incorporating objective measures of cognitive performance, depression together with working memory, and everyday physical functioning predicted (32% of the total variance) subjective cognitive complaints (Gelonch et al., 2017), indicating that perceived subjective dyscognition may be partially related to objective cognitive impairments but also to affective symptomatology. Regarding the contributing role of depression to fibrofog in our results, in the known-groups validity analyses, significant differences in mean MISCI scores were found among

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samples of patients with FM with or without comorbid depression and a clinical comparative group without FM suffering residual depressive symptoms. According to these findings, there could be an additive effect of FM and major depression on perceived cognitive impairment. Interestingly, in our study, depressive symptomatology in the group *without* FM (assessed by means of PHQ-9) was also significantly correlated with MISCI scores despite the small sample size (n= 38; r= -.34; p= .03) giving extra support to the hypothesis regarding an independent relationship between depression and perceived cognitive impairment assessed with the MISCI. Significant associations between mood status (together with pain, fatigue and sleep) and fibrofog were also reported by Williams, Clauw & Glass (2011) in a sample of 24 patients with FM. Furthermore, in a recent large cross-sectional study (n= 681) by McAllister and colleagues (2016), depression and anxiety were predictors of fibrofog, together with pain intensity, autonomic function and fatigue.

A positive relationship between perceived cognitive deficits and pain catastrophizing was also previously reported in chronic pain samples (Roth, Geisser, Theisen-Goodvich & Dixon, 2005). In this regard, higher catastrophizing and pain-related fear/anxiety can be related to more difficulties in diverting attention away from a painful event, disengaging from a pain stimulus, or shifting attention away from pain-related thoughts (Roth et al., 2005). Given that attentional resources are limited, such increased attentional focus on pain could be at the expense of other competing cognitive demands (Eccleston & Crombez, 1999; Moore, Keogh & Eccleston, 2013), so impairing cognitive performance. Thus, it seems that pain intensity alone may not be sufficient in all cases to produce cognitive deficits and that high pain catastrophizing and pain-related anxiety may be key mediating factors in some cases (McCracken and Iverson, 2001; Roth et al., 2005).

Regarding the association between fibrofog and neuroimaging data, negative associations between lACC and lMCC volumes with MISCI scores were found. Given that ACC and MCC seem to be imvolved in integrating negative affect, pain and cognitive control (Shackman, Salomons, Slagter, Fox, Winter & Davidson, 2011) and that reduced volumes in these areas have previously been described in patients with FM (Wallit et al., 2016), our findings provide deeper insight into the nature of fibrofog and its overlap with pain and affective processing. At the same time, these findings also provide valuable data on the convergent validity of the MISCI with brain-derived markers.

In the hierarchical regression analysis predicting MISCI scores, depression and anxiety FIQR-items were significant predictors (with β= -.21 both) of lower MISCI scores. Surprisingly, in a greater

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measure than the two aforementioned predictors, a higher beta value (β= -.28) was observed regarding the specific FIQR item on perceived problems in balance. The regression model, including all FIQR-items controlling for FM chronicity (i.e., years with FM) as a first step, predicted 44% of MISCI variance. A more parsimonious model using only the three significant predictors from the first model (i.e., depression symptoms, anxiety symptoms and problems with balance FIQR-items) accounted for a slightly lower value with 38% of the MISCI variance predicted.

Gender, age, years of schooling and psychotropic use in the first step of the model, and pain, fatigue, stiffness, tenderness to touch, sleep problems, and environmental sensitivity in the second one, although that all were significantly related to MISCI scores (with *r*s ranging between -.21 and -.45), did not contribute significantly to the prediction of MISCI scores. In contrast to our findings, McCracken & Iverson (2001), in their study with chronic pain patients, found that being more educated, of male gender, and using narcotics or antidepressants were related to higher cognitive complaints. In fact, antidepressant use in this study, together with pain-related anxiety and depression symptoms, as assessed by the FIQR, predicted 36% of variance in MISCI scores. Methodological differences from these other studies may also explain divergence of our results. In this regard, FM symptoms (i.e., FIQR items) in our regression analyses were entered as a second step after controlling for the effect of chronicity and different measures have been also used (e.g., items vs. complete scales). Related to this latter point, it should be pointed out that Williams and colleagues (2011) used the MASQ to evaluate perceived cognitive functions and found significant associations between pain and perceived language deficits but not between pain and perceived attention or concentration. Given that MISCI is an amalgamation of main fibrofog domains, including language (Kratz et al., 2015), the strength of association between specific domains of perceived dyscognition and pain (or other FM symptoms) could be "diluted" in our results. Regarding unrefreshing sleep and fatigue, we did not find any predictive effect of these FM symptoms on MISCI as other authors such as Williams, Clauw & Glass (2011) reported with specific domains of perceived dyscognition (i.e., memory). The same explanation of potential dilution of correlations due to the single scoring of the MISCI could be applicable.

Regarding the main predictor of fibrofog in our regression analysis, perceived balance problems is one of the four new symptoms (i.e., balance, memory, tenderness to touch, and environmental sensitivity) that were added to the revised version of the Fibromyalgia Impact Questionnaire (Bennett et al., 2009) and this is reported as one of the top 10 most debilitating symptoms in FM, with a prevalence between 45% and 68% (Katz, Ferbert & Leavitt, 2007). In the FIQR validation,

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the item on balance problems provided good discriminant validity between the FM group and the other three groups (i.e., healthy controls, a mixed clinical sample with lupus erythematosus/rheumatoid arthritis and a sample with Major Depressive Disorder; Bennett et al., 2009) and presented good convergence with the total FIQR score. More recently, Jones and colleagues (Jones, Horak, Winters, Morea & Bennett, 2009; Jones, King, Mist, Bennett & Horak, 2011), evidenced both impaired objective and subjective balance and postural functionality in patients with FM.

Balance control is a complex task which involves a quick and dynamic integration of multiple sensory, motor and cognitive inputs to execute the adequate neuromuscular response needed to maintain balance, requiring executive function and attention as well as judgment of external and internal cues (Segev-Jacubovski, Herman, Yogev-Seligmann, Mirelman, Giladi & Hausdorff, 2011). Impairments in balance and more falls are frequent among the elderly population, especially among patients with common neurological diseases (Segev-Jacubovski et al., 2011). In this regard, in the most recent study by Jones et al. on this subject (2011), postural stability was predicted by perceived cognitive impairment (assessed with the MASQ), together with FIQR scores and body-mass index. Interestingly, Jones et al. (2009) observed a significant slowing of walking in patients with FM when dividing attention to a secondary cognitive task, which may be suggestive of increased attentional resources devoted to balance and gait control, which are usually regulated automatically. This lost automatism may also be due to impaired functioning of central, sensory and/or musculoskeletal systems in FM. Performance in dual motor-cognitive tasks is better in younger compared to older individuals (Hollman, Kovash, Kubik & Linbo, 2007), so patients with FM would display a similar pattern to that which occurs with aging. In this regard, premature aging has been described in patients with FM and chronic pain (Hasset, Clauw & Williams, 2015) with mounting neuropsychological (Park et al., 2001), neuroimaging (Kuchinad et al., 2007) and even cellular evidence (Hasset et al., 2012). Thus, reported problems in balance and cognitive function may both be related to this premature aging process. Given the significant and moderate association between subjective cognitive dysfunction and problems in balance, future studies testing multicomponent treatments for fibrofog might also explore the potential benefit of including a module of training balance and postural control.

Limitations

This study has some issues that deserve a comment to adequately interpret the scope of the findings. Firstly, because the study was conducted in a single hospital and with a relatively small –

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even though more than sufficient for the analyses conducted– and homogenous sample, the generalizability to patients with different socio-demographic or clinical characteristics needs to be determined by future research. Secondly, standardized objective measures of cognitive performance were not used to assess neurofunctional impairment. This is not necessarily a limitation in psychometric studies of a patient-reported measure of perceived cognitive functioning. In any case, discrepancies between reports from patients with FMS and neuropsychological testing have been described (e.g., Kravitz and Katz, 2015; Walitt et al., 2016). Finally, although a gold standard self-reported measure of perceived cognitive dysfunction in fibromyalgia is not available, the present study did not include other validated self-report questionnaires –such as the MASQ (Seidenberg, et al., 1994) or the Mental Clutter Scale (Leavitt & Katz, 2011)– to at least partially assess this construct. Nevertheless, two FIQR and FSDC items measuring perceived cognitive dysfunction were used to evaluate the convergent construct validity of the MISCI.

In conclusion, the Spanish version of the MISCI demonstrated good to excellent psychometric properties. The fact that the MISCI is very brief (i.e., only 10 items) while providing information about a range of perceived cognitive problems commonly reported by patients with FM, confirms its potential usefulness to FM researchers and clinicians. The MISCI showed a one-factor structure and excellent psychometric properties including internal consistency, test-retest reliability, and high convergence with cognitive-specific items from FIQR and FSDC, severity of FM, depression, anxiety, stress and pain catastrophizing, suggesting a positive association between global severity in this disease and fibrofog. Interestingly, significant correlations between MISCI scores and grey matter volumes of pain-related brain areas (i.e., ACC and MCC) have been reported. Significantly different scores in MISCI were also found when comparing samples with FM with or without comorbid depression and the clinical sample without FM, suggesting an additive effect of FM and major depression on fibrofog intensity. We also found significant and large improvements in perceived dyscognition after an MBSR program, indicating at the same time that MISCI displays good sensitivity to change. Although we could not establish causal relationships in our study, we found strong correlations between anxiety, depression, and perceived balance problems with MISCI scores, and in hierarchical regression model these three variables were the main predictors of MISCI (over pain intensity, stiffness, tenderness to touch, fatigue, environmental sensitivity or impaired sleep) with a predicted variance around 40%.

Conflict of Interest Statement

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All authors declare that this study was conducted in the absence of any conflict of interest.

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Table 1. Characteristics of the study samples (i.e., FM with and without depression groups and sample with residual depressive symptoms and FM negative).

Socio-demographic variables	FM Total (*n*=120)	FM (*n*=64)	FM + MDD (*n*=56)	RDS (*n*=45)	*P**
Gender, n females (%)	**118 (98.3)**	62 (96.9)	56 (100.0)	**36 (83.7)**	**.001**
Age, M (SD)	**53.79 (6.88)**	53.06 (7.07)	54.67 (6.60)	**52.19 (17.16)**	***n.s.***
Years of schooling, M (SD)	**9.78 (2.45)**	10.22 (2.23)	9.29 (2.63)	**9.16 (4.17)**	***n.s.***
Living with (spouse/partner/relatives), n (%)	**117 (97.5)**	63 (98.4)	54 (96.4)	**40 (93.0)**	***n.s.***
Marital status, n (%)					***n.s.***
Single	**6 (5.0)**	2 (3.2)	4 (7.1)	**2 (4.7)**	-

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Married/Living with a partner	**91 (76.5)**	51 (81.0)	30 (71.4)	**36 (83.7)**	-
Separated/divorced	**16 (13.4)**	8 (12.7)	8 (14.3)	**4 (9.3)**	-
Widowed	**6 (5.0)**	2 (3.2)	4 (7.1)	**1 (2.3)**	-
Work status, n (%)					***n.s.***
Homemaker	**13 (10.9)**	7 (11.1)	6 (10.7)	**4 (9.3)**	-
Paid employment	**40 (33.6)**	24 (38.1)	16 (28.6)	**17 (39.5)**	-
Paid employment but on sick leave	**8 (6.7)**	4 (6.3)	4 (7.1)	**7 (16.3)**	-
Unemployed with allowance	**7 (5.9)**	7 (11.1)	0 (0.0)	**3 (7.0)**	-
Unemployed without allowance	**23 (19.3)**	12 (19.0)	11 (19.6)	**3 (7.0)**	
Retired/pensioner	**14 (11.8)**	7 (11.1)	7 (12.5)	**8 (18.6)**	-
Temporally disabled	**3 (2.5)**	0 (0.0)	3 (5.4)	**0 (0.0)**	-
Others (e.g., student)	**11 (9.2)**	2 (3.2)	0 (0.0)	**1 (2.3)**	-
Clinical variables, M (SD)					-
Years with FM	**11.77 (8.11)**	10.80 (7.18)	12.89 (8.99)	**-**	-
FIQR-Total (0-100)	**61.12 (20.11)**	51.03 (18.95)	72.29 (14.84)	**-**	-
Function (0-30)	**18.43 (6.14)**	16.45 (5.69)	20.62 (5.92)	**-**	-
Overall impact (0-20)	**10.29 (7.17)**	7.06 (6.96)	13.98 (5.46)	**-**	-
Severity of symptoms (0-50)	**32.41 (9.22)**	27.79 (9.06)	37.69 (6.05)	**-**	-
FSDC-Total (0-31)	**22.38 (5.13)**	20.82 (5.44)	24.27 (4.04)	**-**	-
FSDC-WPI (0-19)	**13.73 (3.64)**	13.12 (3.87)	14.43 (3.25)	**-**	-
FSDC-SSS (0-12)	**8.64 (2.42)**	7.68 (2.39)	9.81 (1.91)	**-**	-
HADS-Total (0-42)	**18.41 (8.43)**	14.11 (7.02)	23.25 (7.20)	**-**	-
HADS-A (0-21)	**10.80 (4.50)**	9.22 (4.18)	12.57 (4.20)	**-**	-
HADS-D (0-21)	**7.61 (5.12)**	4.92 (4.13)	10.68 (4.38)	**-**	-
PSS (0-40)	**21.71 (9.31)**	17.69 (9.11)	26.38 (7.17)	**-**	-
PCS-Total (0-52)	**22.03 (13.16)**	18.70 (13.39)	25.93 (11.86)	**-**	-
PCS-Rumination (0-16)	**7.39 (4.93)**	6.42 (5.06)	8.53 (4.55)	**-**	-
PCS-Magnification (0-12)	**4.59 (3.07)**	4.14 (3.14)	5.11 (2.92)	**-**	-
PCS-Helplessness (0-24)	**10.01 (6.35)**	8.05 (6.12)	12.29 (5.87)	**-**	-
PHQ-9 (0-27)	**-**	-	-	**9.03 (6.71)**	-

Note: *T-tests were used to explore differences in continuous measures between FM total sample and the RDS group; χ^2 was used for categorical variables.

FIQR= Fibromyalgia Impact Questionnaire Revised; FSDC= Fibromyalgia Survey Diagnostic Criteria questionnaire – WPI: Widespread Pain Index, – SSS= Symptom Severity Scale; FM= Fibromyalgia; HADS= Hospital Anxiety and Depression Scale; MDD= Major Depressive Disorder; PCS= Pain Catastrophizing Scale; PHQ-9= Patient Health Questionnaire; PSS= Perceived Stress Scale; RDS= Sample with Residual Depressive Symptomatology without a FM diagnosis.

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Table 2. Item Content, Mean (M), Standard Deviation (SD), Factor Loadings of the MISCI Items in the FM sample (λ of Model 1 and Model 2 – respecification of model 1 with correlated error terms on the negatively phrased items–), corrected item-total correlation (rtot) and Cronbach's *α* if item deleted.

MISCI items	M (SD)	λ Model 1	λ Model 2	r_{tot}	Cronbach's *α* if item deleted
1. *I have been able to think clearly without extra effort*	3.14 (1.07)	.62	.64	.57	.91
2. *My mind has been as sharp as usual*	2.80 (1.12)	.66	.68	.62	.90
3. *I have been able to remember things as easily as usual without extra effort*	2.82 (1.06)	.77	.81	.72	.90
4. *I have been able to learn new things easily, like telephone numbers or instructions.*	2.57 (1.18)	.73	.75	.67	.90
5. *My ability to concentrate has been good.*	2.62 (1.14)	.85	.87	.78	.89
6. *I have been able to pay attention and keep track of what I was doing without extra effort.*	2.79 (1.07)	.85	.85	.79	.89
7. *I have had trouble shifting back and forth between different activities that require thinking*	3.14 (1.01)	.63	.56	.63	.90
8. *I had trouble planning out the steps of a task*	2.57 (1.09)	.63	.54	.63	.90
9. *I have had to work harder than usual to express myself clearly*	2.73 (1.20)	.64	.53	.66	.90
10. *I have had trouble finding the right word(s) to express myself*	2.96 (1.15)	.67	.58	.67	.90

Note: MISCI= Multidimensional Inventory of Subjective Cognitive Impairment.

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Table 3. Pearson correlations between the MISCI and Study Measures in the FM sample (*n*=96).

	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1.MISCI	-.74**	-.69**	-.22*	-.60**	-.51**	-.39**	-.65**	-.45**	-.25*	-.62**	-.59**	-.62**	-.62**	-.58**
2.FIQR-*Memory problems*		.72**	.21*	.59**	.49**	.31**	.65**	.43**	.25*	.60**	.37**	.41**	.48**	.39**
3.FSDC-*Cognitive*			.19	.52**	.45**	.28**	.57**	.57**	.31**	.80**	.49**	.41**	.52**	.40**
4.Years with FM				.32**	.36**	.30**	.26**	.08	.05	.13	.17	.20*	.16	.19
5.FIQR-*Total*					.89**	.81**	.92**	.66**	.50**	.69**	.62**	.69**	.68**	.70**
6.FIQR-*Function*						.63**	.74**	.60**	.48**	.56**	.48**	.55**	.53**	.63**
7-FIQR-*Impact*							.60**	.46**	.36**	.48**	.52**	.67**	.57**	.59**
8-FIQR-*Symptom*								.65**	.47**	.73**	.66**	.65**	.68**	.66**
9.FSDC-*Fibromyalginess*									.91**	.78**	.52**	.41**	.47**	.53**
10.FSDC-*WPI*										.46**	.34**	.25*	.27**	.42**
11.FSDC-*SSS*											.64**	.53**	.61**	.53**
12.HADS-Anxiety												.70**	.80**	.62**
13.HADS-Depression													.77**	.61**
14.PSS														.61**
15.PCS-*Total*														

Note: FIQR= Fibromyalgia Impact Questionnaire Revised; FSDC= Fibromyalgia Survey Diagnostic Criteria questionnaire; MISCI= Multidimensional Inventory of Subjective Cognitive Impairment; WPI= Widespread Pain Index; SSS= Symptom Severity Scale; HADS= Hospital Anxiety and Depression Scale; PCS= Pain Catastrophizing Scale; PSS= Perceived Stress Scale.

*p< .05; **p< .01.

Table 4. Known-groups validity of the MISCI: FM without Major Depressive Disorder (MDD) vs. FM with MDD vs. Sample with Residual Depressive Symptoms (RDS).

	FM total (*n*=120)	FM (1) (*n*=64)	FM + MDD (2) (*n*=56)	RDS (3) (*n*=45)	ANOVA	T-test comparisons	Cohen's *d*

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MISCI (M, SD)	29.35 (8.24)	32.03 (7.10)	26.29 (8.43)	35.53 (8.50)	$F_{(2,162)}$= 17.35 p< .001	1 > 2**	.74
						1 < 3*	-.45
						2 < 3 **	-1.09

Note: MISCI= Multidimensional Inventory of Subjective Cognitive Impairment.

*p< .05; **p< .001.

Table 5. Change in the MISCI and FIQR after the MBSR intervention.

	MBSR (*n*=37)				**TAU (*n*=22)**					
	Pre	**Post**	***p***	***d***	**Pre**	**Post**	***p***	***d***	**r-m ANOVA**	**η_p^2**
MISCI	30.22 (7.13)	39.08 (9.09)	<.001	.98	27.95 (9.51)	29.32 (11.40)	n.s.	.20	$F_{(1,57)}$= 10.92; *p*=.002	.16
FIQR	61.81 (18.79)	48.10 (18.69)	<.001	.74	56.80 (22.87)	53.14 (21.85)	n.s.	.28	$F_{(1,54)}$= 4.70; *p*=.03	.08

Note: Changes in FIQR scores were also provided to facilitate clinical interpretation of the results. FIQR= Fibromyalgia Impact Questionnaire-Revised; FM= Fibromyalgia; MBSR= Mindfulness-Based Stress Reduction Program; MISCI= Multidimensional Inventory of Subjective Cognitive Impairment; TAU= Treatment-as-usual.

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Table 6. Hierarchical Regression Analysis of MISCI scores (*n*=96).

Predictor Variables	ΔR^2	*r*	*pr*	*β*	sr^2	t-value
Step 1	.05					
Years with FM		-.219*		-.09	.05	-.969
Step 2	.39					
Pain-FIQR		-.323**	-.028	-.06	.10	-.499
Fatigue-FIQR		-.447**	-.137	-.08	.20	-.700
Stiffness-FIQR		-.326**	-.077	-.08	.11	-.787
Unrefreshing sleep -FIQR		-.382**	-.117	-.09	.15	-.896
Depression-FIQR		-.469**	-.212*	-.21	.22	-1.999*
Anxiety-FIQR		-.417**	-.212*	-.21	.17	-2.133*
Tenderness to touch-FIQR		-.201*	.208	.17	.04	1.500
Balance problems-FIQR		-.440**	-.325*	-.28	.19	-2.409*
Environmental sensitivity-FIQR		-.354**	-.100	-.09	.12	-.919
Model with all predictors: R=.66, R^2=.44, F(10,78)=6.037, p<.0001						
Model only with 3 significant predictors:* R=.61, R^2=.38, F(3,92)=18.441, p<.0001						

Note: Zero-order (*r*) and partial correlations (*pr*) FIQR items-MISCI controlling for other FM symptoms were calculated. FIQR=Fibromyalgia Impact Questionnaire-Revised; FM=Fibromyalgia; MISCI= Multidimensional Inventory of Subjective Cognitive Impairment.

*p<.05; **p<.01.

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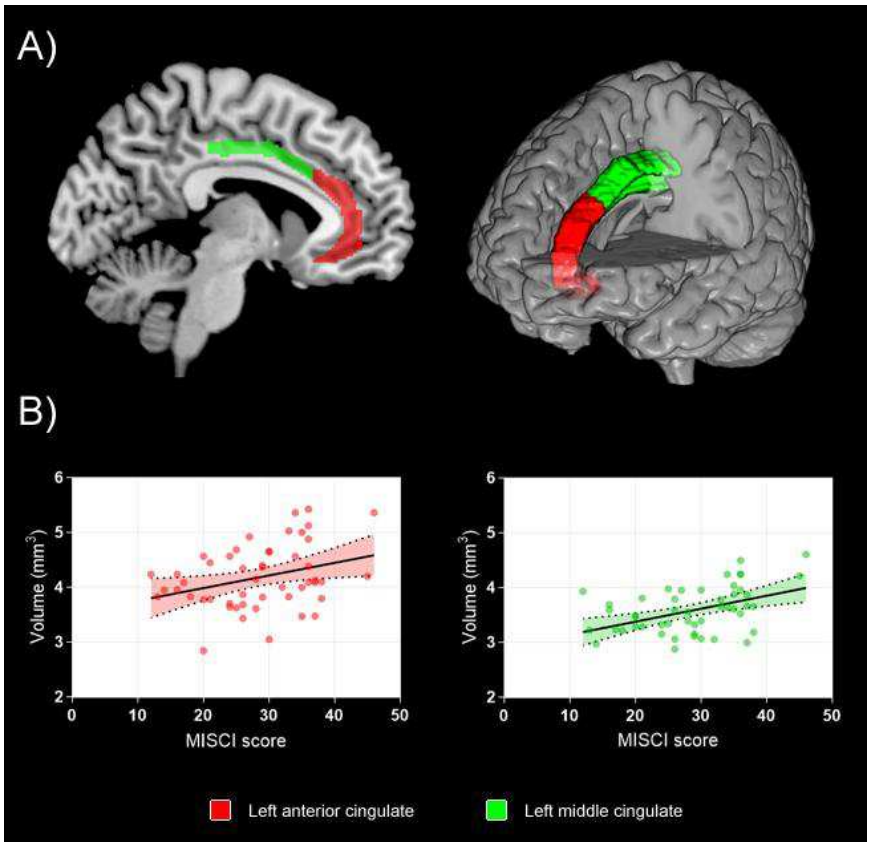

Figure 1. A) Sagittal (left) and 3D (right) views of the brain depicting the location of the left anterior cingulate (red) and the left middle cingulate (green) cortices. B) Scatter plots depicting the relationship between MISCI (Multidimensional Inventory of Subjective Cognitive Impairment) scores and left anterior cingulate (left) and left middle cingulate (right) volumes.

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