Journal of Psychosomatic Research 174 (2023) 111493

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Psychological variables associated with resistance to treatment with serotonin and noradrenaline reuptake inhibitors in fibromyalgia

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ARTICLE INFO

Keywords:
Fibromyalgia
Temperament
Personality
Schizotypy
SNRI

ABSTRACT

Objective: The treatment of fibromyalgia (FM) often offers only partial pain relief. Among the most effective drugs for FM pain are serotonin and noradrenalin reuptake inhibitors (SNRI). Few studies investigated the affective temperaments and personality features in FM. Our objective was to explore the associations between the affective temperaments, personality traits, schizotypy and response to SNRI treatment in FM.
Methods: 60 FM patients: 30 responsive to SNRI (FM T[+]), 30 non-responsive to SNRI (FM T[−] and 30 healthy controls were recruited. Resistance to SNRI was defined as <30% pain reduction during at least 8-week treatment. Subjects were assessed by physician and filled self-report questionnaires: Temperament Scale of Memphis, Pisa and San Diego- autoquestionnaire, Ten Item Personality Inventory, Oxford-Liverpool Inventory of Feelings and Experiences and Fibromyalgia Impact Questionnaire (FIQ). ANOVA analysis and simple logistic regressions were used to examine the links between psychological variables and lack of response to SNRI.
Results: FM T[−] presented higher scores in total FIQ and in physical, work, well-being, pain, fatigue/sleep, stiffness domains than FM T[+]. FM T[−] showed higher levels of: irritable and anxious temperaments, neuroticism, schizotypy than FM T[+]. The levels of depressive, irritable and anxious temperaments, introversion, neuroticism and schizotypy were linked to lack of response to SNRI.
Conclusions: FM T[+] and FM T[−] differ in clinical presentation and psychological features. The levels of affective temperaments, personality and schizotypal traits are associated with lack response to SNRI in FM.

1. Introduction

The chronic widespread pain is the core symptom of the fibromyalgia (FM) syndrome, however the diagnostic criteria also include fatigue, insomnia, depression and cognitive dysfunction [1]. It is estimated that FM affects 2–4% of the general population [2] and that up to 80% of FM patients suffer from coexisting depression and/or anxiety [3] while bipolar spectrum symptoms are about twice as common in FM than in general population [4]. Current treatment recommendations suggested by European League Against Rheumatism encompass physical activity, physical therapies, psychotherapy and pharmacotherapy [5]. The most effective pharmacotherapies of FM include drugs used in the treatment of depression and anxiety: serotonin and noradrenalin reuptake inhibitors (SNRI) and the alpha-2 calcium channel blocker (pregabalin) [6]. Unfortunately, the majority of medications classified as effective in FM treatment provide only partial reduction of symptoms and little is known as to which factors have an impact on the occurrence of treatment response or lack of it. As we have observed in the preliminary phases of this study, FM patients responsive to SNRI treatment (FM T[+]) differ from those non-responsive to SNRI treatment (FM T[−]) in the severity of overall FM symptoms, anxiety, depression, cognitive dysfunction, disturbance of diurnal rhythms and insomnia [7,8] and in parameters of glucose metabolism [9,10].

At present, the temperament is defined as a biologically determined

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https://doi.org/10.1016/j.jpsychores.2023.111493
Received 5 April 2023; Received in revised form 7 September 2023; Accepted 7 September 2023
Available online 9 September 2023

core of the personality, that is largely stable throughout the course of life and regulates the primary level of activity, mood, energy and reactivity of a person. Akiskal et al. proposed a model of temperament important for affective disorders and offered a perspective on the temperamental type as a continuum ranging form subclinical features to severe psychiatric disorders [11,12]. Personality is commonly defined as a consistent pattern of emotions, thoughts and behaviors and its traits are the dimensions in which interindividual differences are described. Among the many models of personality traits, contemporarily the "Big Five" model described by Costa and McCrae is the most prevalently studied. It consists of 5 dimensions that is: neuroticism (vs. emotional stability), extraversion (vs. introversion), conscientiousness, openness to experience and agreeableness [13]. The schizotypy might also be ascribed on a spectrum ranging from mild symptoms below the clinical threshold on one end and the severe psychiatric psychopathology on the other. It is thought that temperamental, personality and schizotypal features might influence individuals functioning in both beneficial and disadvantageous ways [12–14]. Few studies have explored the role of temperamental and personality characteristics in FM. In a pilot study, Isik-Ulusoy [15] observed that as measured by TEMPS-A the FM patients showed higher depressive, anxious and cyclothymic traits compared to healthy participants and that the dimensions of affective temperament correlated with the severity of FM, depression and anxiety. Several reports are available in which the personality of FM patients was evaluated with the use of the Big Five Personality Model based inventory. Montoro Aguilar et al. [16] showed the associations between the central processing of painful stimuli and neuroticism as well as extraversion in FM. Bucourt et al. [17] found, that compared to those with rheumatoid arthritis, spondyloarthritis and Sjögren's syndrome, FM patients were characterized by higher levels of agreeableness, neuroticism and openness and that some personality traits (high neuroticism, low conscientiousness) were linked to higher levels of reported pain. Torres et al. [18] noted that two distinct clusters of FM could be distinguished with different personality trait profile: the one with higher neuroticism, lower extraversion, openness to experience, agreeableness and conscientiousness was characterized by a higher level of pretreatment pain, depression, anxiety, pain catastrophizing and more pronounced disfunctions in the family, social and economic areas as well as worse emotional state after 6 months of treatment. The work of Silva et al. [19] reported that compared to HC, FM patients showed higher neuroticism and one of conscientiousness subscales- commitment. Additionally, it was noted that lower levels of openness were linked to longer time to diagnosis of FM. Schizotypy is thought to represent a continuum of psychosis-proneness features that is observed in both the general population and psychotic patients. As suggested by Cladrige et al., schizotypy might be viewed as a personality domain [20]. To our knowledge, no data is available on the associations between affective temperament, personality and schizotypy in FM and the response to treatment with SNRI.

The aim of our work was to explore whether there is a link between the traits of affective temperament, personality, schizotypy and clinical presentation with the response to SNRI treatment in FM patients.

2. Methods

This work was designed as observational, cross-sectional study. Subjects were recruited between December 2020 and November 2022 from the Department of Rheumatology and Immunology and the Department of Psychiatry of the University Hospital in Cracow, Poland. The inclusion criteria for the patient groups were: 1) age 18–65, 2) diagnosis of fibromyalgia according to the 2016 American College of Rheumatology criteria confirmed by a rheumatologist [1], 3) history of treatment with SNRI (duloxetine 60-120 mg/d), venlafaxine (150-225 mg/d), milnacipran (100-200 mg/d). The exclusion criteria for the patient groups were: 1) any severe, acute, or chronic neurological, musculoskeletal, pain or other somatic disorders, 2) substance use disorder (other than smoking), 3) history or diagnosis of psychosis or bipolar disorder, 4) no history of SNRI treatment or history of taking suboptimal SNRI doses or history of taking an SNRI for <8 weeks. A physician collected the data on the illness duration, treatment duration, current pharmacotherapy. During the diagnostic and control visits the patients were regularly asked to evaluate the magnitude of pain relief experienced on the Numeric Rating Scale (score range 0–10 with 0 signifying no pain relief and 10 complete pain relief) and the results after at least 8 weeks of SNRI treatment were retrieved from the clinical records. The criteria of treatment response were based on the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) which define at least 30% pain relief as moderate and at least 50% pain relief as substantial clinical outcome. To distinguish subjects with clinically meaningful pain relief after SNRI treatment from those without it, treatment response was defined as ≥30% reduction of pain after treatment with SNRI (that is, no less than: 3 points for initial NRS scores 7–10; no less than: 2 points for initial NRS scores 4–6) [21]. Patients were than divided into two groups of either 1) responsive (FM [T+]) or 2) non-responsive (FM [T-]) to treatment with SNRI. Patients were examined by rheumatologist before enrollment and if needed evaluated further to rule out diseases other than FM. Both in the FM groups and in the HC group we included participants with appropriately treated and well controlled asthma, allergies, dermatoses, thyroid insufficiency, hyperlipidemia and hypertension.

The choice of particular SNRI depended on the decision of the attending physician who analyzed the clinical presentation and possible contraindications or interactions.

Moreover, a group of healthy controls (HC) was enrolled. The HC were recruited from family and acquaintances of the researchers within the same age criteria as the patient group. The exclusion criteria for this group were: 1) severe, acute, or chronic psychiatric disorders, 2) severe, acute, or chronic somatic disorders, 3) substance use disorder (other than smoking). All HC were interviewed by a physician and physical examination was performed to rule out any diseases.

Each participant completed self-report questionnaires to assess:

1) temperamental features the Temperament Scale of Memphis, Pisa and San Diego, self-administered version (TEMPS-A): TEMPS-A was constructed based on the concept of affective temperament traits proposed by Akiskal which include: depressive, cyclothymic, hyperthymic, irritable and anxious; we used the original 110-item TEMPS-A in a Polish version which showed good validity and reliability [12,22].
2) personality traits Ten-Item Personality Inventory (TIPI): TIPI is a short 10-item inventory to assess the "Big Five" personality dimensions; despite its briefness it has acceptable levels of convergence with the other longer "Big Five" scales, test-retest reliability, confluence with self and observer ratings as well as patterns of predicted external correlates [23]; we used its Polish version which presented good validity and reliability [24].
3) level of schizotypy the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): O-LIFE was created to measure the schizotypy in healthy individuals; we used the Polish version of the original 104 item version which showed good internal consistency, reliability and validity [14,25].

The severity of FM was assessed with the FIQ which evaluates 7 domains: physical functioning, well-being, work-related, pain, fatigue/sleep, stiffness, psychological symptoms in the week before the evaluation [26]. Additionally, to measure the severity of FM we used parameters included in the FM diagnostic criteria: the Widespread Pain Index (WPI), Symptom Severity Scale (SSI) and Fibromyalgia Severity (FS) which is the sum of WPI and SSI [1].

2.1. Study sample

Initially, 99 FM patients were recruited for this study, however 21 were not enrolled because further observation and diagnostics indicated that they suffered from serious comorbid diseases such as rheumatoid arthritis, lupus erythematosus, diabetes mellitus, alcohol dependence, bipolar disorder or others; 18 were not enrolled because they did not agree to participate in the study. Among the individuals not-enrolled due to serious somatic comorbidities 17 were non-responsive to SNRI and 4 were responsive to SNRI. Among the subjects not-enrolled because the did not agree to participate in the study, 10 were non-responsive to SNRI and 8 were responsive to SNRI.

All participants provided an informed written consent. The study was approved by the local Bioethical Committee (No. 1072.6120.172.2021).

2.2. Statistical analysis

The demographic data were compared between the groups with the use of Student *t*-test (quantitative variables) or Chi-squared (qualitative variables). Levene's test was used to examine the homogeneity of variances. In order to compare the levels of affective temperaments, personality traits and schizotypy in all studied groups and the severity of FM in the patient groups one-way ANOVA was performed. Welch or White corrections were applied in the cases of non-homogenous variances. Moreover, post-hoc tests (Tukey or Games-Howell) and effect size calculation (eta-squared or Hedges g) were conducted. In addition to post-hoc tests, effect sizes for each pairs of groups were calculated. The associations between the affective temperaments, personality traits, schizotypy and the lack of response to SNRI treatment were evaluated with a series of simple logistic regression analyses. Due to high correlations between psychological variables it was not possible to build a regression model with 2 or more independent variables. Statistical analyses were performed with the use of R software [27]. *t*-test, Chi-squared test, ANOVA, effect size and post-hoc comparisons were performed using rstatix package. For other analyses, functions from stats package were used. For the visualization of the results ggplot2 package was used.

3. Results

In sum 90 subjects participated in this study (30 FM T [+], 30 FM T [−] and 30 HC).

3.1. Demographic data

No significant differences were found among the groups in sex, age, height and comorbidities such as hyperlipidemia, hypertension and hypothyroidism, asthma, allergies, dermatoses. The mean weight and mean BMI were higher among the whole FM group compared with HC and among FM T [−] compared with HC however, no differences in mean weight or mean BMI were detected between HC vs. FM T [+]. There were no differences in the proportion of smoking subjects between HC vs. the whole FM group or HC and both FM T [+] and FM T [−] subgroups but the fraction of smoking participants was higher among FM T [−] vs. FM T [+] (Table 1). In the FM T [+] subgroup 27 patients were treated with duloxetine and 3 venlafaxine. In the FM T [−]

Table 1
Demographic data.

Variable	HC n = 30	FM *n* = 60	FM T [+] n = 30	FM T [−] *n* = 30	HC vs. FM *	All groups **	HC vs. FM T[+]	HC vs. FM T [−]	FM T [+] vs.FM T [−]
Age mean years ± SD	44.033 ± 12.75	45.117 ± 10.77	43.533 ± 10.81	46.7 ± 10.68	t(88) = −0.423 $p = 0.67$	F(2, 87) = 0.663 $p = 0.52$	$p = 0.98$	$p = 0.64$	$p = 0.53$
Height mean in cm ± SD	166.333 ± 6.16	167.2 ± 8.11	166.9 ± 7.65	167.5 ± 9.67	t(88) = −0.515 p = 0.6	F(2, 87) = 0.178 $p = 0.84$	$p = 0.96$	$p = 0.82$	$p = 0.95$
Weight mean in kg ± SD	67.45 ± 13.33	76.458 ± 18.08	72.033 ± 17.71	80.883 ± 17.61	t(88) = −2.42 $\mathbf{p = 0.017}$	F(2, 87) = 5.233 $\mathbf{p = 0.007}$	p = 0.53	$\mathbf{p = 0.006}$	p = 0.1
BMI kg/m2 ± mean	24.232 ± 3.72	27.234 ± 5.62	25.784 ± 5.87	28.683 ± 5.04	t(81) = −3.02 $\mathbf{p = 0.003}$	F(2, 87) = 6.233 $\mathbf{p = 0.003}$	$p = 0.45$	$\mathbf{p = 0.002}$	$p = 0.07$
Sex female/ male	26 / 4	51 / 9	25 / 5	26 / 4	χ^2 (90, 1) < 0.001 $p > 0.99$	χ^2 (90, 2) < 0.001 $p = 0.91$	p > 0.99	$p > 0.99$	p > 0.99
Hyper-lipidemia (yes)	4	2	1	1	χ^2 (90, 1) < 0.001 $p = 0.2$	χ^2 (90, 2) = 3.21 p = 0.2	$p = 0.35$	p > 0.99	$p > 0.99$
Hyper-tension (yes)	5	9	2	7	χ^2 (90, 1) = 1.81 $p = 0.18$	χ^2 (90, 2) = 3.42 $p = 0.18$	p = 0.67	$p = 0.51$	$p = 0.15$
Hypo-thyroidism (yes)	3	11	8	3	χ^2 (90, 1) < 0.001 $p = 0.47$	χ^2 (90, 2) = 4.23 p = 0.18	p = 0.18	p > 0.99	p = 0.18
Asthma (yes)	1	5	2	3	χ2 (90, 1) = 0.2 $p = 0.65$	χ2 (90, 2) = 1.1 $p = 0.58$	p > 0.99	$p = 0.61$	$p > 0.99$
Allergies (yes)	1	5	3	2	χ2 (90, 1) = 0.2 p = 0.65	χ2 (90, 2) = 1.1 p = 0.58	p = 0.61	p > 0.99	$p > 0.99$
Derma-toses (yes)	0	5	1	4	χ2 (90, 1) = 1.3 $p = 0.25$	χ2 (90, 1) = 5.51 $p = 0.06$	p > 0.99	$p = 0.12$	p = 0.35
Smoking (yes)	3	14	2	12	χ^2 (90, 1) < 0.001 $p = 0.21$	χ^2 (90, 2) = 13.2 $\mathbf{p = 0.002}$	p > 0.99	$p = 0.02$	$\mathbf{p = 0.006}$

FM- fibromyalgia patients as a whole group, FM T [+]- patients responsive to SNRI treatment, FM T [−]- patients resistant to SNRI treatment, HC- healthy controls, SD- standard deviation.
χ^2 test was used to compare the qualitative data. **t*-test was used to assess the differences in quantitative data, **- ANOVA was used to assess the differences in quantitative data.

subgroup 21 patients received duloxetine, 8 venlafaxine and 1 milnacipran. The proportions of patients taking duloxetine, venlafaxine or milnacipran were comparable between the FM T [+] and FM T [−] [$\chi 2$ (60, 2) = 3.86, $p = 0.104$].

3.2. Fibromyalgia clinical presentation

There were several significant differences among FM subgroups regarding the clinical presentation of FM. FM T [+] were characterized by shorter duration of illness ($p = 0.01$, Hedges' g = 0.68) and lower overall severity measured by the FIQ total score ($p < 0.001$, Hedges' g = 1.17), SSS (p < 0.001, Hedges' g = 1.00) and FS ($p = 0.006$, Hedges' g = 0.73) as well as lower impact of FM in the domains of physical functioning (p < 0.001, Hedges' g = 0.98), work (p < 0.001, Hedges' g = 1.12) and well-being ($p = 0.01$, Hedges' g = 0.67) compared to FM T [−]. The severity of pain ($p = 0.007$, Hedges' g = 0.71), fatigue, sleep disturbance ($p = 0.05$, Hedges' g = 0.51) and stiffness ($p = 0.03$, Hedges' g = 0.57) was higher in FM T [−] vs. FM T [+]. There were no differences between FM T [+] and FM T [−] in the time from symptoms onset of FM to diagnosis, severity of psychological symptoms as measured by FIQ items and number of painful areas assessed with WPI (Table 2).

3.3. Psychological variables.

3.3.1. Affective temperaments

Compared to HC, FM patients were characterized by higher levels of depressive ($p < 0.001$, Hedges' g = 1.12), cyclothymic ($p < 0.001$, Hedges' g = 1.20), irritable (p < 0.001, Hedges' g = 0.81) and anxious ($p < 0.001$, Hedges' g = 1.44) temperaments while no differences were noted among these groups in the level of hyperthymic temperament. Similarly, FM T [−] participants presented higher depressive ($p < 0.001$, Hedges' g = 1.34), cyclothymic ($p < 0.001$, Hedges' g = 1.66), irritable ($p < 0.001$, Hedges' g = 1.35) and anxious (p < 0.001, Hedges' g = 2.70) but not hyperthymic temperaments vs. HC. FM T [+] showed higher levels of depressive (p < 0.001, Hedges' g = 1.03) cyclothymic ($p = 0.001$, Hedges' g = 0.94) and anxious (p < 0.001, Hedges' g = 0.96) but not irritable or hyperthymic temperaments when compared to HC. FM subgroups comparisons indicated higher levels of irritable (p < 0.001, Hedges' g = 0.96) and anxious ($p < 0.001$, Hedges' g = 1.22) temperaments in FM T [−] vs. FM T [+]. No differences were observed in the levels of depressive, cyclothymic or hyperthymic temperaments between the FM T [+] vs. FM T [−] (Table 3).

3.3.2. Personality traits

The assessments of personality traits indicated that FM patients showed lower extraversion (higher introversion) ($p = 0.008$, Hedges' g = 0.54) and lower emotional stability (higher neuroticism) ($p < 0.001$, Hedges' g = 0.95) than HC. Likewise, lower levels of extraversion ($p = 0.004$, Hedges' g = 0.91) and emotional stability ($p < 0.001$, Hedges' g = 1.50) were observed in FM T [−] vs. HC. FM T [+] presented higher emotional stability than FM T [−] (p < 0.001, Hedges' g = 1.07). No differences were noted between the studied groups regarding the levels of agreeableness, conscientiousness and openness to experience (Table 3).

3.3.3. Schizotypy

FM patients as a whole group (p < 0.001, Hedges' g = 1.55) and the FM T [+] (p < 0.001, Hedges' g = 1.33) as well as the FM T [−] (p < 0.001, Hedges' g = 2.06) presented higher schizotypal traits as measured by all subscales of O-LIFE and its total score compared to HC. The comparison between FM T [+] and FM T [−] indicated that the level of cognitive disorganization ($p = 0.03$, Hedges' g = 0.61) and total score of O-LIFE ($p = 0.02$, Hedges' g = 0.63) were higher in FM T [−] vs. FM T [+] (Table 3).

The simple logistic regression analyses revealed that several psychological variables were linked to the lack of response to SNRI treatment in FM that is: 1) depressive ($p = 0.029$), irritable ($p = 0.002$) and anxious temperaments ($p < 0.001$), 2) lower extraversion (higher introversion) ($p = 0.04$) and lower emotional stability (higher neuroticism) (p < 0.001) and 3) higher cognitive disorganization ($p = 0.025$) as well as the total level of schizotypy ($p = 0.023$)(Table 4).

4. Discussion

Our study is one of the very few to assess the affective temperaments and personality traits and the first to examine schizotypy in FM patients and provide a comparison to HC. Furthermore, no previous studies have examined the relationships between these psychological variables and the lack of response to SNRI treatment. The majority of available research assesses FM patients as a homogenous group, however based on our clinical observation of significant differences between FM patients and our previous results [7,8,10] we decided to divide the FM group into subgroups of those who achieved the response to SNRI or those who did not. The obtained results corroborate our hypothesis that FM T [+] and FM T [−] subgroups are dissimilar in clinical presentation, with FM T [−] reporting higher severity of FM symptoms (pain, fatigue/sleep, stiffness) and its impact on functioning (physical, work-related and wellbeing) as assessed by FIQ, SSI and FS (Table 2). What is more, our results revealed several significant differences in the affective temperaments, personality traits and schizotypy between the FM [+] and FM T [−] subgroups. Similarly to Isik-Ulsoy [15], we observed higher levels of depressive, anxious and cyclothymic affective temperaments in the whole group of FM patients than in HC. In our study FM patients also showed higher levels of irritable temperament than HC. As previously

Table 2
Comparisons of FM characteristics between FM T [+] and FM T [−].

Variable	FM	FM T [+]	FM T[−]	T-Test	FM T [+] vs. FM T [−]	Hedges g
Duration of illness mean years ± SD	12.62 ± 10.69	9.1 ± 7.27	16.13 ± 12.42	t(46.76) = −2.77	**p = 0.01**	g = 0.68 medium
Time form onset to diagnosis mean years ± SD	7.29 ± 7.15	6.077 ± 6.88	8.5 ± 7.32	t(58) = −1.32	p = 0.19	g = 0.34 small
FIQ sum mean ± SD	50.5 ± 20.18	40.178 ± 19.59	60.82 ± 14.96	t(54.25) = −4.59	**p < 0.001**	g = 1.17 large
FIQ physical functioning mean ± SD	2.84 ± 2.43	1.757 ± 1.91	3.93 ± 2.43	t(58) = −3.85	**p < 0.001**	g = 0.98 large
FIQ wellbeing mean ± SD	6.16 ± 3.05	5.181 ± 3.19	7.15 ± 2.6	t(58) = −2.62	**p = 0.01**	g = 0.67 medium
FIQ work related mean ± SD	9.01 ± 5.1	6.473 ± 4.2	11.54 ± 4.68	t(58) = −4.41	**p < 0.001**	g = 1.12 large
FIQ pain mean ± SD	5.58 ± 2.09	4.867 ± 1.94	6.3 ± 2.02	t(58) = −2.80	**p = 0.007**	g = 0.71 medium
FIQ fatigue/ sleep mean ± SD	12.72 ± 5.76	11.267 ± 6.09	14.167 ± 5.12	t(58) = −1.99	**p = 0.05**	g = 0.51 medium
FIQ stiffness mean ± SD	5.67 ± 3.2	4.767 ± 3.51	6.567 ± 2.62	t(53.68) = −2.25	**p = 0.031**	g = 0.57 medium
FIQ psychological symptoms mean ± SD	8.63 ± 5.37	7.733 ± 4.87	9.533 ± 5.77	t(58) = −1.31	p = 0.45	g = 0.33 small
WPI mean ± SD	14.07 ± 4.32	13.2 ± 4.84	14.933 ± 3.6	t(58) = −1.57	p = 0.127	g = 0.40 small
SSS mean ± SD	8.083 ± 2.76	6.833 ± 2.55	9.333 ± 2.4	t(58) = −3.91	**p < 0.001**	g = 1.00 large
FS mean ± SD	22.133 ± 6.08	20 ± 6.23	24.267 ± 5.19	t(58) = −2.88	**p = 0.006**	g = 0.73 medium

FIQ- Fibromyalgia Impact Questionnaire, FM- fibromyalgia patients as a whole group, FM T [+]- patients responsive to SNRI treatment, FM T [−]- patients resistant to SNRI treatment, FS- Fibromyalgia Severity, g- Hedges g, HC- healthy controls, SD- standard deviation, SSS- Symptom Severity Scale, WPI- Widespread Pain Index. Hedges g is the measure of effect size. Effect size lower than 0.2 was counted as negligible. 0.2–0.5 as small. 0.5–0.8 as medium and for 0.8 as large.

Table 3
Comparisons of psychological variables between studied groups.

Variable	HC mean score ± SD	FM mean score ± SD	Test-T HC vs. FM*	FM T [+] mean score ± SD	FM T [−] mean score ± SD	ANOVA**	HC vs. FM T [+]	HC vs. FM T [−]	FM T [+] vs. FM T [−]
TEMPS-A depressive	0.383 ± 0.12	0.55 ± 0.16	t(88) = −5.03 **$p < 0.001$** g = 1.115	0.503 ± 0.11	0.597 ± 0.19	F(2, 87) = 15.825 **$p < 0.001$** η^2 = 0.275	**p < 0.001** g = 1.03	**p < 0.001** g = 1.34	$p = 0.06$ g = 0.59
TEMPS-A cyclothymic	0.227 ± 0.17	0.489 ± 0.24	t(88) = −6.01 **$p < 0.001$** g = 1.2	0.432 ± 0.25	0.547 ± 0.21	F(2, 87) = 17.446 **$p < 0.001$** η^2 = 0.286	**p = 0.001** g = 0.94	**p < 0.001** g = 1.66	p = 0.1 g = 0.49
TEMPS-A hyperthymic	0.368 ± 0.19	0.326 ± 0.2	t(88) = 0.952 $p = 0.34$ g = 0.21	0.338 ± 0.2	0.313 ± 0.21	F(2, 87) = 0.565 $p = 0.57$ $\eta^2 = 0.013$	$p = 0.83$ g = 0.15	$p = 0.54$ g = 0.27	$p = 0.88$ g = 0.12
TEMPS-A irritable	0.148 ± 0.15	0.301 ± 0.2	t(88) = −3.63 **p < 0.001** g = 0.81	0.212 ± 0.17	0.39 ± 0.2	F(2, 87) = 15.626 **p < 0.001** η^2 = 0.26	p = 0.34 g = 0.39	**p < 0.001** g = 1.35	**p < 0.001** g = 0.96
TEMPS-A anxious	0.271 ± 0.14	0.57 ± 0.23	t(88) = −7.4 **p < 0.001** g = 1.44	0.448 ± 0.23	0.692 ± 0.16	F(2, 87) = 41 **p < 0.001** η^2 = 0.485	**p < 0.001** g = 0.96	**p < 0.001** g = 2.70	**p < 0.001** g = 1.22
TIPI extraversion	5.733 ± 1.12	4.958 ± 1.52	t(74.5) = 2.72 **$p = 0.008$** g = 0.54	5.367 ± 1.54	4.55 ± 1.43	F(2, 87) = 5.822 **$p = 0.004$** η^2 = 0.12	p = 0.56 g = 0.27	**p = 0.004** g = 0.91	p = 0.06 g = 0.54
TIPI agreeableness	5.5 ± 1.03	5.417 ± 1.32	t(88) = 0.302 $p = 0.76$ g = 0.07	5.733 ± 0.99	5.1 ± 1.54	F(2, 87) = 1.757 $p = 0.179$ η^2 = 0.046	p = 0.64 g = 0.23	p = 0.47 g = 0.30	p = 0.15 g = 0.48
TIPI conscienciously-ness	5.717 ± 1.08	5.5 ± 1.53	t(88) = 0.693 $p = 0.49$ g = 0.15	5.65 ± 1.51	5.35 ± 1.55	F(2, 87) = 0.584 $p = 0.56$ η^2 = 0.013	p = 0.98 g = 0.05	p = 0.57 g = 0.27	$p = 0.69$ g = 0.19
TIPI emotional stability	4.7 ± 1.56	3.225 ± 1.51	t(88) = 4.32 df = 88 **$p < 0.001$** g = 0.95	3.95 ± 1.35	2.5 ± 1.33	F(2, 87) = 18.765 **p < 0.001** η^2 = 0.301	$p = 0.11$ g = 0.51	**$p < 0.001$** g = 1.50	**p < 0.001** g = 1.07
TIPI openness to experience	4.733 ± 0.91	4.95 ± 1.11	t(88) = −0.922 $p = 0.36$ g = 0.2	5.033 ± 0.85	4.867 ± 1.34	F(2, 87) = 0.609 $p = 0.55$ $\eta^2 = 0.014$	p = 0.51 g = 0.34	p = 0.88 g = 0.12	$p = 0.81$ g = 0.15
O-LIFFE unusual thoughts	2.77 ± 2.24	9.133 ± 6.39	t(88) = −6.91 **$p < 0.001$** g = 1.17	8.467 ± 7.16	9.8 ± 5.57	F(2, 87) = 25.74 **p < 0.001** η^2 = 0.25	**$p < 0.001$** g = 1.06	**p < 0.001** g = 1.64	p = 0.7 g = 0.21
O-LIFE cognitive disorganization	6.767 ± 4.2	13.583 ± 5.89	t(88) = −5.65 **$p < 0.001$** g = 1.25	11.833 ± 5.9	15.333 ± 5.42	F(2, 87) = 20.377 **p < 0.001** η^2 = 0.319	**p < 0.001** g = 0.98	**p < 0.001** g = 1.74	**p = 0.03** g = 0.61
O- LIFE introvertive anhedonia	6.267 ± 3	9.85 ± 4.75	t(83.1) = −4.35 **p < 0.001** g = 0.83	8.667 ± 3.83	11.033 ± 5.33	F(2, 87) = 9.847 **p < 0.001** η^2 = 0.18	**$p = 0.03$** g = 0.69	**p < 0.001** g = 1.09	$p = 0.13$ g = 0.50
O- LIFE compulsive nonconformity	5.4 ± 3.58	8.833 ± 4.46	t(70.6) = −3.94 **p < 0.001** g = 0.81	8 ± 4.59	9.667 ± 4.23	F(2, 87) = 8.035 **p < 0.001** η^2 = 0.156	**$p = 0.05$** g = 0.62	**p < 0.001** g = 1.07	$p = 0.27$ g = 0.37
O- LIFE sum	21.2 ± 9.01	41.4 ± 14.46	t(83.6) = −8.12 **p < 0.001** g = 1.55	36.967 ± 13.74	45.833 ± 14.01	F(2, 87) = 30.051 **p < 0.001** η^2 = 0.41	**p < 0.001** g = 1.33	**p < 0.001** g = 2.06	**p = 0.02** g = 0.63

FM- fibromyalgia patients as a whole group, FM T [+]- patients responsive to SNRI treatment, FM T [−]- patients resistant to SNRI treatment, HC- healthy controls, O-LIFE- Oxford-Liverpool Inventory of Feelings and Experiences, TEMPS-A- Temperament Scale of Memphis, Pisa and San Diego- autoquestionnaire, TIPI- Ten Item Personality Inventory.

* g- Hedges g is the measure of effect size. Effect size lower than 0.2 was counted as negligible. 0.2–0.5 as small. 0.5–0.8 as medium and for 0.8 as large.

** η^2 - (eta squared) is the measure of effect size. Effect size lower than 0.01 was counted as negligible, 0.01–0.06 as small, 0.06–0.14 as medium and higher than 0.14 as large.

mentioned, affective temperaments are ascribed on a spectrum ranging from levels observed in the general population to those noted in patients with psychiatric diagnoses [11,12]. It could be hypothesized that the higher levels of depressive, anxious and cyclothymic temperaments in FM vs. HC could be linked to the higher prevalence of depression, anxiety and bipolar disorders [3,4]. While Isik-Ulsoy [15] reported correlations between the depressive, anxious, cyclothymic and irritable dimensions of temperaments in FM with depression as well as anxious and cyclothymic temperaments and anxiety, the relationships between affective temperaments and occurrence of bipolar disorders in FM is yet

Table 4
Simple logistic regressions evaluating the associations between psychological variables and the FM subgroup (FM T [+]/ FM T [−]).

	Psychological variable	Intercept	Slope	p	AIC
Affective temperaments	depressive	−2.14	3.9	**0.03**	81.905
	cyclothymic	−1.07	2.19	0.06	84.469
	irritable	−1.64	5.65	**0.002**	73.83
	anxious	−3.54	6.15	**<0.001**	67.74
Personality traits	extraversion	1.86	−0.375	**0.04**	82.702
	emotional stability	2.555	−0.8	**<0.001**	71.648
Schizotypy	cognitive disorganization	−1.506	0.11	**0.03**	81.596
	total	−1.95	0.048	**0.02**	81.183

AIC - Akaike information criterion.

to be explored. Moreover, our results indicate that irritable and anxious temperaments are higher in FM T [−] vs. FM T [+], while the levels of irritable temperament do not differ between HC and FM T [+]. As reported by Silva et al. [19], our results indicated higher levels of neuroticism (lower emotional stability) in FM patients vs. HC, however we did not observe differences in conscientiousness between FM and HC which might be due to the use of a different, shorter tool assessing personality traits. Interestingly, there were no differences between the levels of neuroticism between HC and FM T [+], but FM T [−] presented higher neuroticism than both FM T [+] and HC. Additionally, FM T [−] patients had lower levels of extraversion compared to HC, while there were no differences in the level of extraversion between HC and FM as a whole group or HC vs. FM T [+]. Our work showed higher levels of all schizotypy subdomains as well as its overall level in FM vs. HC and FM T [+] or FM T [−] vs. HC. The levels of cognitive disorganization and overall level of schizotypy were higher in FM T [−] than those in FM T [+]. It was previously observed that high level of schizotypy, in particular the subdomain of cognitive disorganization, could be related to psychotic symptoms. Presumably, in the case of FM T [−] patients, who as we noted present higher schizotypy and cognitive disorganization, small doses of antipsychotic drugs could be beneficial [28]. The logistic regression analyses unraveled several psychological variables associated with the lack of response to SNRI treatment, that is higher levels of 1) affective temperaments: depressive, irritable and anxious, 2) personality traits: introversion, neuroticism, 3) schizotypy: cognitive disorganization and overall. Therefore, our results indicate that FM T [+] and FM T [−] differ not only in the domain of FM clinical presentation but also in the psychological dimensions (affective temperament, personality traits, schizotypy), and that compared to HC some of these psychological features are not more pronounced in all FM patients but only in those who do not achieve response to SNRI. We believe that future FM research could focus on distinguishing more homogenous subgroups of patients and assess each of them separately for more precise comparisons within the FM family. Furthermore, our results may help navigate clinical decisions. It was shown, that both neuroticism and introversion, as well as some aspects of schizotypy, which we found are linked to the lack of response to SNRI, may be altered in the course of psychotherapy or after psychological intervention [29,30]. Perhaps patients with high levels of neuroticism and introversion should be offered psychotherapy or other structured psychological interventions, especially if they do not achieve response to SNRI.

4.1. Limitations

Our work should be seen in the context of several limitations that is: the small number of participants, the fact that the subjects differed in several demographic aspects (weight, BMI), the cross-sectional construction of the study. It should be acknowledged, that HC were recruited from family and acquaintances of the researches which is not a random sample of the population. However, it's unlikely that this fact could significantly influence the primary results of this work, given that the primary analysis is not utilizing this control group. Also, in this study we did not include the assessment of the level of persistence to SNRI (other than regular control visit interviews), which might be related to the lack of effectiveness of SNRI. Previous studies have shown, that the persistence to SNRI as well as other pharmacotherapeutic agents in FM is low with only 9.3% of patients remaining adherent to treatment 1 year after the initial prescription [31]. On the other hand, FM pharmacotherapy is often prescribed in subtherapeutic doses which hampers the effectiveness of the treatment and might lead to non-adherence [32]. While in our study the appropriate dosing of the drugs was assured, the potential link between SNRI effectiveness and persistence requires more thorough investigation. Nonetheless, this work is pioneering in uncovering the associations between affective temperaments, personality traits, schizotypy, clinical presentation and the lack of response to SNRI treatment in FM and it lays ground for further, more robust research.

Our results indicate that FM T [−] show 1) higher scores of FM symptoms and FM impact, 2) higher levels of irritable and anxious temperaments, 3) lower emotional stability (higher neuroticism), 4) higher levels of cognitive disorganization and overall schizotypy compared to FM T [+]. The higher levels of depressive, irritable and anxious temperaments, introversion, neuroticism and schizotypy are associated with the lack of response to SNRI. We believe mental health care should be included in clinical care for FM patients in order to achieve the best treatment outcomes.

Funding

This work was funded by the statutory grant from the Jagiellonian University Medical College (no. N41/DBS/000535; to MS)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors are grateful for the contribution of all individuals who participated in this study.

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