Adult Autism Subthreshold spectrum correlates to Post-traumatic Stress Disorder spectrum in patients with fibromyalgia

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ABSTRACT

Objective. *Fibromyalgia (FM) is an increasingly prevalent disorder that usually shows a chronic course and a disappointing therapeutic response in which psychiatric features seem to play a relevant role. Most recently, the relationship between FM and Post-traumatic Stress Disorder (PTSD) has gained interest since several studies demonstrated a higher rate of PTSD, both full blown and partial, and Post-traumatic Stress spectrum symptoms. While the relationship between higher burden of autistic symptoms and PTSD is reported in literature, the relationship between FM and autism spectrum symptoms is still unexplored. In this study we investigated both post-traumatic and autistic spectrum in a sample of FM patients with the aim of exploring the relationships between these dimensions.*

Methods. *One hundred and nineteen patients with FM, diagnosed according the American College of Rheumatology 2010 criteria, were consecutively enrolled at the Unit of Rheumatology, University of Pisa, Italy.*
Assessments included: the Trauma And Loss Spectrum-Self Report (TALS-SR), for the post-traumatic stress spectrum symptomatology, the Adult Autism Subthreshold spectrum (AdAS spectrum) for the assessment of subthreshold autism spectrum. The scores reported to AdAS (total and per domain) by the entire sample and subgroups with PTSD diagnosis, partial PTSD and no PTSD were compared in order to detect a relation between Autistic Traits (ATs) and post-traumatic spectrum in this clinical sample.

Results. *Our results show that FM patients with PTSD report an AdAS total score significantly higher than those reported by patients without PTSD. Moreover, through an examination of the correlation between AdAS spectrum and TALS-SR scores, significant correlations between the total score of the two instruments has emerged. The correlation resulted to be particularly significant between TALS-SR scores and non-verbal communication domain of the AdAS and between hyper-hypo reactivity to sensory input domain and several TALS-SR domains.*

Conclusion. *These results highlight the clinical relevance of autistic traits in FM patients with PTSD. In this regard, we may claim a potential role of abnormal processing of sensory input and deficits in non-verbal communication in explaining this association.*

Introduction

Fibromyalgia (FM) is a widespread and challenging disease characterised by multifaceted clinical phenotypes, in which pain is the defining feature (1-4). Accordingly, ICD-11 defines FM as a chronic primary pain syndrome (5), and the belonging of this pathology to a defined field of specialty is the matter of long-standing debates (6-9). As far as triggers are concerned, several potentially precipitating factors (such as physical and psychological stressors) have been called into question, albeit without unequivocal conclusions (10, 11). This notwithstanding, literature has progressively recognised the relevance of traumatic or major life stressful events in triggering FM manifestations in vulnerable subjects, and hence the existence of a relationship between FM and trauma-related disorders, in particular Post-traumatic Stress Disorder (PTSD) (12, 13).

PTSD is a highly prevalent psychiatric condition (14-17), whose onset follows direct or indirect exposure to one or

more traumatic events and is characterised by an heterogeneous clinical picture, tendency to a chronic course, poor response to treatments and relevant rate of somatic symptoms (18) and medical comorbidities (*i.e.* cardiovascular diseases, metabolic disorders, autoimmune diseases) (19, 20). Indeed, PTSD and trauma exposure history were related to the onset of various somatic diseases as well as chronic pain conditions (18, 21-24). In particular, several researches demonstrate that PTSD is a psychiatric disorder commonly occuring in FM patients, with comorbidity rates as high as 45.5% (25, 26), and that PTSD has a detrimental prognostic significance in this clinical population, even in subthreshold forms (27, 28). In addition, anamnestic evidence of a traumatic exposure is common in FM patients with a significant prepoderance of the so-called interpersonal and network events (28).

Interestingly, the finding of previous traumatic events and the high prevalence of PTSD are shared features between FM and patients with Autism Spectrum Disorder (ASD) or subthreshold autistic traits (ATs) (29). ASD, as defined by DSM-5, is a neurodevelopmental disorder whose key features are impairment in social interaction and communication and repetitive behaviors. Beyond the DSM diagnostic boundaries, previous studies have been demonstrating that ATs are dimensionally distributed in the general population, and that they are more pronounced among relatives of patients with ASD and patients suffering from other psychiatric conditions, such as PTSD (30, 31). In this framework, growing evidence has been demonstrating a strong link between Post-traumatic Stress spectrum symptoms and ASD, showing a high prevalence of Post-traumatic spectrum symptoms or PTSD in subjects with pronounced ATs (32-34).

However, the relationship between FM and adult autism spectrum is to date still unexplored, although this issue may be worth of attention in the light of some findings. Studies conducted on paediatric population suffering from Somatic Symptoms Disorder (SSD) revealed a correlation between somatic symptoms and higher ATs, suggesting that children with mild ATs may become somatisation-prone adults (35-38). Although the relation between FM and SSD is controversial, this finding is still of interest since SSD – whose main features are the presence of somatic symptoms and concerns about them - is at the same time a common differential diagnosis and a misdiagnosis of FM (39-41), as a well as a relatively common comorbidity in FM patients (39). In addition, people with ASD show a peculiar pattern of sensory responses, which is characterised by hypo- or hypersensitivity to sensory stimuli, including pain (42-45). This issue is of interest considering that the multisensory hypersensitivity has been investigated in several studies concerning the FM physiopathology (46-49) and an abnormal functioning of brain areas involved in processing of sensory and painful stimuli has been hypothesised as the underlying neural substrate of the so-called "pain centralisation" (50-55).

Despite the suggestive findings on the complex relationship between ATs, PTSD and pain or somatic symptoms, there is still a lack of data on this issue in FM patients. In this study we explored the presence of ATs and PTSS in a sample of FM subjects in order to examine the possible relationship between these psychopathological dimensions.

Material and methods

Study sample

A sample of 119 patients was enrolled in the Reumathology Unit of Azienda Ospedaliera Universitaria Pisana (A.O.U.P, Pisa, Italy). Eligible subjects included patients of age between 18 and 77 years diagnosed with FM according to the 2010 diagnostic criteria of the American College of Rheumatology (ACR) (56). A psychiatric assessment was performed for each patient by psychiatrists of the Psychiatric Unit of the A.O.U.P. Exclusion criteria included the lack of knowledge of the Italian language or other limits to verbal communication, poor capacity of collaboration or inability to provide informed consent, the documented mental retardation or IQ<70, history of neurologic disease, seizures, stroke, or head injury resulting in prolonged loss of consciousness and/or neurological sequelae in the previous three months.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Area Vasta Nord Ovest Toscana, Pisa, Italy.

Assessment

A trained clinician (CA) collected socio-demographic data of the sample, such as marital status, employment, educational level. Participants also fulfilled two self-reported instruments: the Adult Autism Subthreshold spectrum (AdAS Spectrum) in order to investigate autistic traits; the Trauma And Loss Spectrum Self-Report (TALS-SR) to examine Post-traumatic Stress spectrum symptoms.

The AdAS is a self-reported questionnaire constituted by 160 dichotomous items, developed in order to explore typical and atypical symptoms or personological traits which can be referred to the autistic spectrum. It should be emphasised that this psychometric instrument follows a dimensional approach and has no diagnostic purpose as to ASD diagnosis (57). The items are grouped in seven domains exploring respectively childhood and adolescence (I), verbal communication (II), non-verbal communication (III), empathy (IV), inflexibility and routinarity (V), restricted interests and ruminations (VI) and hypo-hyperreactivity to stimuli (VII). The AdAS Spectrum demonstrated excellent internal consistency for the total score as well as for five out of seven domains and found test-retest reliability (ICC= .976). Subjects with ASD reported significantly higher AdAS Spectrum total scores than both patients with feed and eating disorder and healthy controls (57).

The TALS-SR includes 116 dichotomous items exploring the lifetime experience of a range of loss and/or traumatic events and lifetime symptoms, behaviors and personal characteristics that might represent manifestations and/or risk factors for the development of a stress response syndrome. The items are grouped into nine domains, and do-

Table I. Socio-demographic characteristics of the study sample (119 patients).

Age (years)		mean ± SD 48.33 ± 11.63
		n (%)
Marital status	Single	35; 29.9%
	Married or partnered	52; 44.5%
	Separated/divorced	22;18.8%
	Widowed	8; 6.8%
Occupation	Student	2;3.3%
	Unemployed	6; 9.8%
	Housewife	15; 24.6%
	Employed	33; 73.8%
	Retired	5; 8.2%
Educational level	Primary School	3; 4.9%
	Secondary school	19; 31.1%
	High school diploma	31; 50.8%
	Univeristy degree	5;8.2%
	Post graduate degree	2; 3.3%
Development disorders	Language	3; 3%
	Movement	6; 5.9%

main scores are obtained by counting the number of positive answers. The nine domains explored by the TALS-SR are: loss events (I); grief reactions (II); potentially traumatic events (III); reactions to losses or upsetting events (IV); re-experiencing (V); avoidance and numbing (VI); maladaptive coping (VII); arousal (VIII); and personal characteristics/risk factors (IX). In its validation study, TALS-SR demonstrated excellent validity and reliability as to the PTSD diagnosis (58).

According to previous studies, the presence of PTSD was assessed by means of TALS-SR items endorsed corresponding to DSM-5 criteria for PTSD diagnosis (59, 60). Specifically, we utilised the following matching between symptom criteria and TALS-SR items:

Criterion B (B1=80; B2=77; B3=79; B4=78; B5=81).

Criterion C (C1=86; C2=87 and/or 88 and/or 89).

Criterion D (D1=90; D2=95; D3=85; D4=96; D5=91; D6=93; D7=92).

Criterion E (E1=108; E2=99 and/or 100 and/or 102 and/or 103 and/or 104; E3=106; E4=107; E5=105; E6=109).

Criteria proposed by previous studies were adopted to assess the presence of partial PTSD, that was the endorsement of two or three DSM-5 symptoms cluster. This procedure allowed us to divide the sample in three groups: subjects with PTSD, partial PTSD and without PTSD ones.

Statistical analysis

To describe clinical and demographical characteristics in our sample we calculated the mean and the standard deviation (SD) for the quantitative variables. Conversely, frequencies and percentages were used to describe categorical data.

The comparison of the AdAS Spectrum domains and total scores between different groups constitued by patients with PTSD, partial PTSD and without PTSD was performed by means of one-way variance analysis (ANOVA). The *post-hoc* multiple comparisons were carried out with the *t*-test of Bonferroni or with the Games-Howell test, respectively, if the variance was equal or not equal, according to the test of homogeneity of variances. The relationship between AdAS and TALS-SR score was examined through Pearson coefficient. The data were analysed using the Statistical Package for the Social Sciences (OSSO). All tests were two-tailed and a p value <.05 was considered statistically significant.

Results

The study sample was constituted by 106 females (89%), 13 males (10.9%), the mean age was 48.33±11.63 years. Socio-demographic characteristics are summarised in Table I. A total of 108 patients completed both the AdAS and TALS-SR lifetime questionnaires.

The TALS-SR analysis showed that 40 patients (33.6%) met a PTSD diagnosis, while 40 (33.6%) reported a partial PTSD one. It is notewhorty that the percentage of patients reporting at least a partial PTSD was as high as 67.2% (n=80) of the total sample (n=119).

Table II. Comparison between the AdAS total and domain score in the overall sample (108 patients) and by subgroup without PTSD (group **a**), with partial PTSD (group **b**) and with a PTSD diagnosis (group **c**).

AdAS Spectrum Domains	FM patients (n=108) mean ± SD	FM patients without PTSD (n=39) mean ± SD	FM patients with Partial PTSD (n=35) mean ± SD	FM patients with PTSD (n=34) mean ± SD	F(2,105), p	p<0.05
I. Childhood/adolescence	4.83 ± 3.4	3.10 ± 1.99	5.00 ± 3.50	6.64 ± 3.69	11.804, <0.001	c,b>a
II. Verbal Communication	4.36 ± 2.75	3.23 ± 2.25	4.45 ± 2.52	5.55 ± 3.02	7.294, 0.001	c>a
III. Non-Verbal Communication	6.12 ± 3.79	3.51 ± 2.71	8.35 ± 3.73	8.35 ± 3.73	22.022, <0.001	c>a
IV. Empathy	3.45 ± 2.64	3.25 ± 2.67	3.48 ± 2.36	3.64 ± 2.92	0.199, 0.820	-
V. Inflexibility and adherence to routine	10.74 ± 6.3	7.57 ± 4.37	11.91 ± 6.69	13.14 ± 6.45	9.154, <0.001	c>a
VI. Restricted interest and rumination	5.42 ± 4.05	3.28 ± 2.6	6.02 ± 4.05	7.26 ± 4.39	11.066, <0.001	c>a
VII. Hyper-and hyporeactivity to sensory input	5.42 ± 4.05	3.02 ± 2.19	4.65 ± 3.54	5.91 ± 3.44	8.033, 0.001	c,b>a
Total score	39.4 ± 19.92	27.00 ± 13.14	42.42 ± 18.79	50.52 ± 20.12	17,302 <0.001	c,b>a

Table III. Correlations between total score and single domains score of TALS-SR and AdAS spectrum total and domain scores in the study sample (n=108).

		TALS-SR									
		Loss events *r,p*	Reactions to loss *r,p*	Potentially traumatic events *r,p*	Reactions to to loss and trauma *r,p*	Re-experiencing *r,p*	Avoidance and numbing *r,p*	Maladaptive behaviours *r,p*	Arousal *r,p*	Risk factors *r,p*	Total *r,p*
AdAS	**I. Childohood and adolescence**	0.187 0.053	0.285* 0.003	0.392* 0.000	0.380* 0.000	0.374* 0.000	0.476** 0.000	0.416** 0.000	0.419** 0.000	0.272 0.004	0.465 0.000
	II. Verbal communication	0.118 0.225	0.312* 0.001	0.358* 0.000	0.406** 0.000	0.351* 0.000	0.402** 0.000	0.331* 0.009	0.426** 0.000	0.338* 0.000	0.451** 0.000
	III. Non-verbal communication	0.188 0.051	0.413** 0.000	0.560** 0.000	0.539** 0.000	0.577** 0.000	0.572** 0.000	0.530** 0.000	0.591** 0.000	0.436** 0.000	**0.643***** 0.000
	IV. Empathy	0.233* 0.015	0.055 0.575	0.204* 0.034	0.049 0.616	0.119 0.220	0.112 0.248	0.143 0.139	0.143 0.139	0.193 0.045	0.157 0.106
	V. Routinarity and inflexibility	0.103 0.289	0.427** 0.000	0.411** 0.000	0.459** 0.000	0.434** 0.000	0.452** 0.000	0.535** 0.000	0.535** 0.000	0.269* 0.005	0.536** 0.000
	VI. Restricted interests and ruminations	0.051 0.603	0.439** 0.000	0.400* 0.000	0.459** 0.000	0.450** 0.002	0.487** 0.000	0.471** 0.000	0.459** 0.000	0.329* 0.001	0.526** 0.000
	VII. Hypo/Hyperreactivity to stimuli	0.036 0.783	0.277 0.004	0.442** 0.000	0.400* 0.000	0.398* 0.000	0.396* 0.000	0.462** 0.000	0.437** 0.000	0.246* 0.010	0.466** 0.000
	Total	0.180 0.062	0.448** 0.000	0.535** 0.000	0.535** 0.000	0.533** 0.000	0.568** 0.000	0.509** 0.000	0.603*** 0.000	0.395* 0.000	0.639*** 0.000

*weak to moderate correlation; **moderate to strong correlation; ***strong correlation.

In the one way ANOVA, FM patients diagnosed with PTSD had a significant higher AdAS Spectrum total score with respect to without ones, besides a significant higher score in all AdAS domains, except for the *empathy* one (IV). Patients with partial PTSD, reported intermediary results with respect to the other two groups, showing a significant difference only in AdAS Spectrum domains *childhood/adolescence* (I), and *hypo-hyper reactivity to stimuli* (VIII), beside AdAS Spectrum total score if compared with FM patients without PTSD (Table II).

Finally, the Pearson correlations between the AdAS Spectrum and TALS domains enlighted the existence of a positive association between several domains of the two scales (Table III).

Discussion

To the best of our knowledge, this is the first study exporing the relationship between subthreshold adult autistic spectrum symptoms and PTSD or Post-traumatic Stress spectrum symptoms, in patients with FM. The evidence of a positive relation between the scores reported at the AdAS and the presence of PTSD in FM patients sheds further light on the clinical and pathophysiological interface between these clinical entities. On one hand, it is aknowledged that ASD and ATs are not only associated to a greater traumatic exposure (61) but also represent a vulnerable substrate for the development of posttraumatic stress symptoms in the aftermath of a trauma (26). On the other hand, several studies demonstrated the high prevalence of full-blown or subthreeshold PTSD among FM patients and the relevance of this comorbidity in adversely affecting the clinical picture of FM (27, 28, 62, 63). In this proposal, when examining these results, we may take into account the possible impact of a symptomatological overlap of FM and some PTSD symptoms. In particular, symptoms such as restlessness, sleeping and concentration problems and hyper-vigilance are commonly observed in both conditions (64, 65). This notwithstanding, in our view the symptomatological overlap between PTSD and FM does not weaken in itself the validity and clinical relevance of the two distinct diagnosis, provided that the corresponding diagnostic criteria are met. Hence, the PTSD prevalence rate in our sample, that is in line with literature (25, 26), may be considered as a further argument in favour of the high comorbidity rate between these two clinical conditions. It is also noteworthy that the analysis of the TALS-SR domain scores showed, consistently with literature (66-69), a high prevalence of previous traumatic experiences with a significant preponderance of interpersonal loss events and other relational trauma events. However, to date no study has examined the presence of autistic subthreshold symptoms and their relation with PTSD diagnosis in a clinical sample of FM patients.

Our result enlighted significantly higher AdAS Spectrum score in the group with PTSD in respect to the group constitued by patients who did not meet a PTSD diagnosis, with a significant

gap in all AdAS Spectrum domains except the VIth (empathy). The group diagnosed with partial PTSD was in an intermediate position, with significantly higher values in the overall AdAS Spectrum score in respect to the group of patients without PTSD. In addition, a comparison between the average AdAS Spectrum scores of this sample and that reported by the control group of AdAS Spectrum validation study (57) provide further insights: while no significant differences emerged between the entire sample of FM patients and control group, the PTSD group showed higher score in all AdAS domains.

These results suggest that ATs may play a role in shaping clinical manifestations of PTSD, thereby resulting in an increased vulnerability to development of somatic symptoms, such as pain symptoms or other functional disorder. On one hand, this hypothesis could be supported by literature evidence concerning the presence of neurodevelopmental disorder and higher ATs in paediatric patients with SDD, whose potential meaning has been indicated in the introduction (35-41). In this regard, a potential underpinning pathophysiological diathesis may consist in the documented alteration of sensory response to stimuli. Indeed, hyper-reactivity to sensory stimuli is one of the several ATs explored by the AdAS Spectrum questionnaire (*e.g.* items 150 and 153) and at the same time well-known clinical features of FM (10, 49). This overlapping feature, along with the results of the present study, may in our opinion encourage further researches aimed to examine this issue. Moreover, while the multisensory hypersensitivity and pain centralisation have been conceptualised as the aetiopathogenetic core features of FM (50, 51, 70, 71), other mechanisms (such as the disregulation of opioidergic system, a common finding both in ASD and in FM) may deserve attention. Indeed, some researches, though not leading to univocal results, suggest that the opioid system plays a key role not only in pain modulation, but also in social interactions and attachment behaviour (72); in addition, the response to opioidergic therapies in FM is usually disappointing (73, 74). On the other hand, the clinical burden of somatic symptoms in post-traumatic stress pathology has been increasingly recognised, with recent studies focusing on medical comorbidities and on the presence of multiple somatic complaints in PTSD patients such as chronic pain, headache and gastrointestinal disorder (75-79). In this regard, the underlying mechanisms are still debated, since the interplay between hypotalamic-pituitary-adrenal (HPA) axis alterations, proflogistic diathesis, and opioidergic system impairment outlines a complex physio-pathological scenario (80-85). In this framework, the correlation between AdAS Spectrum score and PTSD diagnosis and that between AdAS and TALS-SR domains in this cluster of patients - who suffer, by definition, of multidistrict pain – may suggest that subthreshold autistic symptoms confer a combined vulnerability to Post-traumatic Stress spectrum development and to somatisation in response to psychological and/or physical stressors. This hypothesis is strengthened by the resulting relationship between the score reported in domain VII of the AdAS, which explores hypo-hyperreactivity to stimuli.

In addition, two further findings are worth mentioning: a moderate association between the score reported in the verbal comunication domain and the total TALS-SR score and a strong association between the latter and the non-verbal communication domain score. This finding is in line with previous literature focusing on the association of alexithimia (*i.e.* multidimensional psychological construct that describes a difficulty in cognitive processing of emotional experience leading to impairment in communicating feelings and in emotional regulation) and pain severity in both FM and ASD patients (63, 86-90). In this regard, although the association between FM and alexithimia is consistently reported its aetiopathogenetic role is still controversial, recent studies suggesting that this association is mainly mediated by psychological distress (86).

These results should be interpreted in the framework of some limitations. First, FM patients are prone to over-report a wide range of symptoms, including symptoms which are not FM related (91). It has been hypothesised that over-reporting and central augmentation may either coexist in the same patient or either may prevail in different patients (91, 92). In this regard, however, it is worth noticing that in our sample only the subsample of FM patients with PTSD reported significantly higher AdAS Spectrum score, this suggesting that in this sample the high score was not attributable to FM *per se*. Other limitations are represented by the dishomogeneity of gender groups; the use of self-reported instruments, such as AdAS Spectrum and TALS-SR; the lifetime structure of TALS-SR assessment, which does not allow us to examine the temporal relationship between the onset of the conditions under investigation. Finally, our research did not gather data on medical and psychiatric comorbidities in the sample.

Conclusion

The results emerging from this study confirm on one hand the high comorbidity rate between PTSD and FM, and on the other hand the existence of a relevant relation between this association and the presence of higher autistic symptoms in this cluster of patients. In this framework, the analysis of the correlations between AdAS Spectrum and TALS-SR score leads to hypotesise a particular relevance of the hypo-hyper sensitivity to stimuli and of deficit in verbal and non-verbal comunication in explaining this finding. Further studies are warranted in order to confirm this correlation, to detangle its directionality and to examine underlying psychological and/or neurobiological mechanisms.

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