Revista de Psiquiatría y Salud Mental

Negative symptoms and sex differences in first episode schizophrenia: what's their role in the functional outcome? A longitudinal study

--Manuscript Draft--

Manuscript Number:	RPSM-D-22-00227R1
Article Type:	Original Article
Keywords:	First-episode of psychosis; schizophrenia; Negative symptoms; Sex; Functional outcome
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Abstract:	Introduction: Negative symptoms (NS) include asociality, avolition, anhedonia, alogia, and blunted affect and are linked to poor prognosis. It has been suggested that they reflect two different factors: diminished expression (EXP) (blunted affect and alogia) and amotivation/pleasure (MAP) (anhedonia, avolition, asociality). The aim of this article was to examine potential sex differences among first-episode schizophrenia (FES) patients and analyze sex-related predictors of two NS symptoms factors (EXP and MAP) and functional outcome.

	Material and Methods: Two hundred and twenty-three FES (71 females and 152 males) were included and evaluated at baseline, six-months and one-year. Repeated measures ANOVA was used to examine the effects of time and sex on NS and a multiple linear regression backward elimination was performed to predict NS factors (MAP-EXP) and functioning. Results: Females showed fewer NS (p=0.031; Cohen's d=-0.312), especially those related to EXP (p=0.024; Cohen's d=-0.326) rather than MAP (p=0.086), than males. In both male and female group, worse premorbid adjustment and higher depressive symptoms made a significant contribution to the presence of higher deficits in EXP at one-year follow-up, while positive and depressive symptoms predicted alterations in MAP. Finally, in females, lower deficits in MAP and better premorbid adjustment predicted better functioning at one-year follow-up (R2=0.494; p<0.001), while only higher deficits in MAP predicted worse functioning in males (R2=0.088; p=0.012). Conclusions: Slightly sex differences have been found in this study. Our results lead us to consider that early interventions of NS, especially those focusing on motivation and pleasure symptoms, could improve functional outcomes.
Suggested Reviewers:	Susana Ochoa sochoa@pssjd.org Experta en diferencias de sexo
	Alicia Valiente avaliente@imim.es Validó una escala de síntomas negativos
Opposed Reviewers:	
Response to Reviewers:	ANSWERS TO REVIEWERS We thank the referees for carefully reading our manuscript and for the helpful comments that will greatly improve it. We have tried to do our best to respond to the points raised. As indicated below, we have checked all the general and specific comments provided by the Referees and we have made the necessary changes in accordance with the suggestions that they have made. Reviewer nº1: Thank you for inviting me to review this manuscript. The study aims to explore two relevant factors to be considered in follow-up (one-year) functional outcome in first episode of schizophrenia (FES) patients: sex and negative symptoms. This is a relevant topic, explored in a representative group of 223 FES patient, and the results are very interesting. Response: Authors are grateful to the reviewer for his/her positive and encouraging comments. However, in reviewing the manuscript, major questions/concerns arose. Specifically: 1. I consider that the first sentence in the abstract, focused on the two factors which specific factor analyses have (Kirkpatrick et al., Kring et al., Strauss et al.) linked to negative symptoms (NS), introduces concepts so abruptly. In addition, at least the acronym and MAP (for amotivation and pleasure) can be better presented. Response: Thank you for your suggestion. Based on your comment, we have reformulated and rewritten the abstract. We have tried to explain it in more detail, taking into account the word limit. 2. The second aim has to be better posed: 2) To analyze sex-related clinical and "others" predictors of two main negatives symptoms factors (EXP and MAP) and functional outcome. Response: We have made the suggested change. 3. The sentence about "severity of symptoms" in page 4 is not correct for "remission criteria". Maybe adding "mild severity"?

	Response: We thank the reviewer for carefully reading this section and for this well seen suggestion. We have followed the remission criteria proposed by Andreasen (Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus, doi.org/10.1176/appi.ajp.162.3.441). “Specific items selected for consideration as criteria for remission in schizophrenia were chosen to map the three dimensions of psychopathology identified by factor analyses and the five criteria for schizophrenia specified in DSM-IV (see Table 2 for details). With regard to severity, the working group consensus defined a score of mild or less (Positive and Negative Syndrome Scale item scores of ≤3; BPRS item scores of ≤3, using the 1–7 range for each item; SAPS and SANS item scores of ≤2) simultaneously on all items as representative of an impairment level consistent with symptomatic remission of illness. Given the long-term course and intrinsic character of schizophrenia, the working group consensus defined a period of 6 months as a minimum time threshold during which the aforementioned symptom severity must be maintained to achieve remission. The same criteria has been used in other papers: “As PANSS scale provides ratings investigating not only symptom severity per se but also functional impairment, a score of “mild” or better (i.e. 3 points or less) at all eight “core” symptoms was considered sufficiently representative of a level of impairment consistent with symptomatic remission of the disorder [7].” (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852933/) However, we rephrased the sentence to make it more understandable and we have pointed out that this referral criterion was based on Andreasen's criteria. 4. In page 5, review again how the acronyms for EXP and MAP are presented. Response: Thanks for the suggestion, we have reviewed the acronyms in all manuscript. 5. Data analyses is the weakest section. There is a rule about not including more than 10 variables in a regression analyses, and they should be selected attending significance in groups comparisons not in correlations. I assume that these correlations are those presented in Supplementary Tables 1, but it includes 16 variables not 17. Please, review carefully the statistics approach and how this section is presented. Response: We thank the reviewer by his/her comment. In Supplementary Table 1, Negative Symptom Factor Score (NSF) was missing, and for that reason, there were 16 variables and not 17. However, based on your suggestion and on reviewer 2's comment [In the analysis exploring predictors of MAP and EXP, or functioning using multiple linear regression analysis, the authors conduct a sex-stratified analysis. In my view, if one aim of the study is to explore sex differences when exploring predictors of different outcomes, a better approach would be to conduct the analyses in the whole sample and to explore whether predictors differ between sexes with interaction terms including sex and each potential predictors. Only significant predictors might be included in the final equation, but a sex by predictor interaction term allows to test whether the association between the predictor and a particular outcome (e.g. MAP) differs between men and women. With a sex-stratified analysis this is not really true, and some significant findings in men or women might be influenced by differences in the statistical power (larger sample for men)], we have performed new analyses. 6. The percentage of women (31%) is particularly low and the lack of differences in the age of onset between FES women and men unusual. Could you explain why? Response: We agree this right observation. As mentioned by Ochoa et al., (2011), differences in age of onset are the most replicated finding in studies into gender differences in schizophrenia (Ochoa et al., 2006). However, a number of studies found no gender difference in the age of onset (Naqvi H et al., 2005). Some authors have suggested that differences in age of onset appear to depend on the presence or absence of family history, with no differences being found between men and women if they had a family history (Albus et al., 1994; Häfner et al., 1998). Furthermore, we do not have balanced samples size in our study. Thus, in this line, we have added it in the discussion section.

7. Considering that your statistical analyses approach as correct, the finding about DUP, that is similar for both female and male FES patients (183 and 199 days respectively), as a predictor for expressivity just in female is intriguing. I would appreciate an interpretation of this result. In general, the literature uses to report shorter DUP in women.

Response: Authors appreciate this comment and we agree that this finding was surprising. In the literature, a longer DUP has been associated with worse treatment response and poorer functional outcomes. However, its impact on negative symptom severity remains unclear. These inconclusive results could be explained due to the fact that some studies were with patients with early-stage disease and others with late/chronic stages of the disease. It may also be attributable to not having taken into account negative symptoms as a unidimensional construct rather than differentiated subdomains as motivational and/or expressivity dimensions. In addition, the small sample size in the women's group makes us to interpret and take these findings into consideration with caution.
Notwithstanding, as mentioned above, for the present reviewed manuscript, following the referees' suggestions, we have conducted new analyses and found that there is no interaction of sex and DUP.

8. Cognitive Reserve doesn't show significant differences between groups and you mention that it is a significant variable in linear regression models but I can't see this table so I can't see how regression analyses for functional outcome were conducted. Could you explain further?

Response: Thank you for your suggestion. As pointed previously, following reviewers' suggestions, we have repeated some of the analyses. We have also included a new Table (Table 4), with the results of the linear regression models for predictors of functioning at one-year follow-up in women and men.

9. Table 2 with time variables in colons and female/male in lines would be more easy to consult, particularly the lack of interaction time by group.

Response: We thank the referee for this suggestion. We have changed Table 2, with time variables in colons and female/male in lines.

10. I would appreciate some discussion about the correlation of CPZ on both EXP and MAP in female.

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11. The study has limitations by far more important than how CR has been measured.

Response: Thank you for your suggestion. We have added two important limitations: 1) high percentage of patients discontinued; 2) small sample size of women's group. In addition, we have mentioned that because of this, some aspects should have been considered with caution in order to extrapolate the present findings.

	Discussion section (page 10): “This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women’s group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different variables of interest.” 12. Figure 1 is very nice to be used in a poster or oral presentation but, in my opinion, not to be included in a scientific manuscript. I find much more important to include the table for predictors of functioning that you mention in 3.4 as Supplementary Table 2 but it is not included. Furthermore, Figure 1 does not consider functioning, the main outcome of your study attending the title. Response: Thank you for the suggestion. We agree with this point. Following this comment, we have removed the figure and included as Table 4 the linear regression models for predictors of functioning at one-year follow-up in women and men. 13. The paper is well written but the abstract should be carefully revised/rewritten. Response: Thank you. Based on your suggestion, we have reformulated and rewritten the abstract. The paper needs major revisions in order to be truly relevant to the debate and to warrant to be published. Reviewer nº2: This manuscript examines potential sex differences among first-episode schizophrenia (FES) patients and analyses predictors of negative dimensions and functioning at one-year follow-up for each sex. The manuscript is well written. Although the authors found sex differences in several predictors, I have some concerns about the statistical approach, particularly the sex-stratified analysis using multiple linear regression for exploring predictors but not exploring potential sex interactions (see my first comment below). I include several comments in order to improve the quality of the manuscript: Response: We are grateful to the referee for the time spent in reviewing this manuscript and for the appreciated comments suggested. 1. In the analysis exploring predictors of MAP and EXP, or functioning using multiple linear regression analysis, the authors conduct a sex-stratified analysis. In my view, if one aim of the study is to explore sex differences when exploring predictors of different

outcomes, a better approach would be to conduct the analyses in the whole sample and to explore whether predictors differ between sexes with interaction terms including sex and each potential predictors. Only significant predictors might be included in the final equation, but a sex by predictor interaction term allows to test whether the association between the predictor and a particular outcome (e.g. MAP) differs between men and women. With a sex-stratified analysis this is not really true, and some significant findings in men or women might be influenced by differences in the statistical power (larger sample for men).

Response: Many thanks for your suggestion. Based on your comment we have turned the analyses around. Data analysis, results and discussion sections were modified according to these new analyses.

2. Page 4, line 28-29. FEP is introduced for the first time with an abbreviation. Please include the full description for first episode psychosis for the first time.

Response: Thank you. We have spelled out the abbreviation, and we have checked all the acronyms through the manuscript

3. Page 7, lines 30-33. The authors state that "the time x sex interaction effect indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta p2=0.118$), NSF ($p<0.001$, $\eta p2=0.140$), EXP ($p<0.001$, $\eta p2=0.117$) and MAP ($p<0.001$, $\eta p2=0.118$),…" However, when looking at Table 2, the time x sex interaction is not significant. Please revise if the sentence is ok. If I understood well, the significant interaction term is between sex and each psychometric scale (PANSS, NSF, EXP, MAP). This interaction means that these scales differ between sexes (as already shown in univariate analysis). As the interaction term time x sex is non-significant, the pattern over time (changes in psychometric scale) is similar in men and women.

Response: We are in full agreement and we thank the reviewer for this comment. Although we indicated at the end of the paragraph that "no significant interaction of time and sex was found", we agree with the reviewer that the sentence is not clear. For this reason, we have reworded it as follows: “Of the 71 females assessed at baseline, 51 were assessed at 6 months and 45 at one-year follow-up. 152 males were assessed at baseline, 101 at 6 months and 75 at one-year follow-up. The repeated measures ANOVA results for the main effect of our within-groups factor (time) and the time x sex interaction effect indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta p2=0.118$), NSF ($p<0.001$, $\eta p2=0.140$), EXP ($p<0.001$, $\eta p2=0.117$) and MAP ($p<0.001$, $\eta p2=0.118$), with follow-up scores being significantly lower than baseline (see Table 2). However, no significant interaction of time and sex was found. Thus, there were significant time effects on all variables, indicating an improvement for both sexes, with no difference between them.”

4. In the supplementary material, correlation analyses (Tables SM 1 and SM 2) include 45 women and 75 men. However, in the baseline sample Ns were 71 women and 152 men. Please revise if numbers are correct. If the numbers are correct and the smaller numbers of supplementary tables are explained by drop-outs, the authors should specify the number of patients that have been lost at follow-up and comment it on the Discussion section (it would mean a high proportion of dropouts, about 50% of men and 40% of women). This needs to be also discussed as a limitation about the representativeness of the findings of the study.

Response: We agree with the reviewer. Based on your suggestion, we have performed analyses in order to identify differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. We have elaborated a little further on this:
-Supplementary Table 1
-Results (3.1. Sociodemographic, clinical and functional characteristics of the sample

	and sex differences): Those patients who were assessed at follow-up (n=120) were indistinguishable from those who were not (n=103) in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF (p=0.045, Cohen's d=0.275; 95% CI=[0.025, - 2.064]), but not when they were measured by the PANSS positive subscale (p= 0.108). For more details, see Supplementary Table 1. - Discussion: This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women's group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different var

March 17th, 2023

Prof. Eduard Vieta
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08036 Barcelona, Catalonia (Spain)

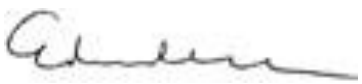
Dear Prof. Crespo-Facorro,

Thank you very much for the opportunity to resubmit the manuscript '**Negative symptoms and sex differences in first episode schizophrenia: what's their role in the functional outcome? A longitudinal study**'. Please, see attached this new version, including additional data, new information, text edition and the answers to all the questions raised by the reviewers.

Here follows our response, point by point, to all the comments and concerns addressed. We are very grateful to the reviewers for their positive criticisms and comments. In our opinion, all these changes have significantly increased the quality of the resulting manuscript. We hope that this version is now acceptable for publication in the Journal.

Sincerely,

Eduard



Prof Eduard Vieta, M.D., Ph.D.

ANSWERS TO REVIEWERS

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Reviewer nº1:

Thank you for inviting me to review this manuscript. The study aims to explore two relevant factors to be considered in follow-up (one-year) functional outcome in first episode of schizophrenia (FES) patients: sex and negative symptoms. This is a relevant topic, explored in a representative group of 223 FES patient, and the results are very interesting.

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However, in reviewing the manuscript, major questions/concerns arose. Specifically:

1. I consider that the first sentence in the abstract, focused on the two factors which specific factor analyses have (Kirkpatrick et al., Kring et al., Strauss et al.) linked to negative symptoms (NS), introduces concepts so abruptly. In addition, at least the acronym and MAP (for amotivation and pleasure) can be better presented.

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3. The sentence about "severity of symptoms" in page 4 is not correct for "remission criteria". Maybe adding "mild severity"?

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the long-term course and intrinsic character of schizophrenia, the working group consensus defined a period of 6 months as a minimum time threshold during which the aforementioned symptom severity must be maintained to achieve remission.

TABLE 2. Proposed Items for Remission Criteria With Cross-Scale Correspondence and Relationship to Historical Constructs of Psychopathology Dimensions and DSM-IV Criteria for Schizophrenia[a]

		Proposed Remission Criteria Items					
		Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) Items		Positive and Negative Syndrome Scale Items		Brief Psychiatric Rating Scale (BPRS) Items	
Dimension of Psychopathology	DSM-IV Criterion	Criterion	Global Rating Item Number	Criterion	Item Number	Criterion[b]	Item Number
Psychoticism (reality distortion)	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
						Suspiciousness	11
				Unusual thought content	G9	Unusual thought content	15
	Hallucinations	Hallucinations (SAPS)	7	Hallucinatory behavior	P3	Hallucinatory behavior	12
Disorganization	Disorganized speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganized or catatonic behavior	Bizarre behavior (SAPS)	25	Mannerisms/ posturing	G5	Mannerisms/ posturing	7
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening (SANS)	7	Blunted affect	N1	Blunted affect	16
		Avolition-apathy (SANS)	17	Social withdrawal	N4	No clearly related symptom	
		Anhedonia-asociality (SANS)	22				
		Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

[a] For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number.
[b] Use of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission.

The same criteria has been used in other papers: “As PANSS scale provides ratings investigating not only symptom severity per se but also functional impairment, a score of “mild” or better (i.e. 3 points or less) at all eight “core” symptoms was considered sufficiently representative of a level of impairment consistent with symptomatic remission of the disorder [7].”

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3852933/)

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Response: Thank you for your suggestion. We have added two important limitations: 1) high percentage of patients discontinued; 2) small sample size of women's group. In addition, we have mentioned that because of this, some aspects should have been considered with caution in order to extrapolate the present findings.

Discussion section (page 10): "This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to

constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women's group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different variables of interest."

12. Figure 1 is very nice to be used in a poster or oral presentation but, in my opinion, not to be included in a scientific manuscript. I find much more important to include the table for predictors of functioning that you mention in 3.4 as Supplementary Table 2 but it is not included. Furthermore, Figure 1 does not consider functioning, the main outcome of your study attending the title.

Response: Thank you for the suggestion. We agree with this point. Following this comment, we have removed the figure and included as Table 4 the linear regression models for predictors of functioning at one-year follow-up in women and men.

13. The paper is well written but the abstract should be carefully revised/rewritten.
Response: Thank you. Based on your suggestion, we have reformulated and rewritten the abstract.

The paper needs major revisions in order to be truly relevant to the debate and to warrant to be published.

Reviewer nº2: This manuscript examines potential sex differences among first-episode schizophrenia (FES) patients and analyses predictors of negative dimensions and functioning at one-year follow-up for each sex. The manuscript is well written. Although the authors found sex differences in several predictors, I have some concerns about the statistical approach, particularly the sex-stratified analysis using multiple linear regression for exploring predictors but not exploring potential sex interactions (see my first comment below). I include several comments in order to improve the quality of the manuscript:

Response: We are grateful to the referee for the time spent in reviewing this manuscript and for the appreciated comments suggested.

1. In the analysis exploring predictors of MAP and EXP, or functioning using multiple linear regression analysis, the authors conduct a sex-stratified analysis. In my view, if one aim of the study is to explore sex differences when exploring predictors of different outcomes, a better approach would be to conduct the analyses in the whole sample and to explore whether predictors differ between sexes with interaction terms including sex and each potential predictors. Only significant predictors might be included in the final equation, but a sex by predictor interaction term allows to test whether the association between the predictor and a particular outcome (e.g. MAP) differs between men and women. With a sex-stratified analysis this is not really true, and some significant findings in men or women might be influenced by differences in the statistical power (larger sample for men).

Response: Many thanks for your suggestion. Based on your comment we have turned the analyses around. Data analysis, results and discussion sections were modified according to these new analyses.

2. Page 4, line 28-29. FEP is introduced for the first time with an abbreviation. Please include the full description for first episode psychosis for the first time.

Response: Thank you. We have spelled out the abbreviation, and we have checked all the acronyms through the manuscript

3. Page 7, lines 30-33. The authors state that "the time x sex interaction effect indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta p2=0.118$), NSF ($p<0.001$, $\eta p2=0.140$), EXP ($p<0.001$, $\eta p2=0.117$) and MAP ($p<0.001$, $\eta p2=0.118$),…" However, when looking at Table 2, the time x sex interaction is not significant. Please revise if the sentence is ok. If I understood well, the significant interaction term is between sex and each psychometric scale (PANSS, NSF, EXP, MAP). This interaction means that these scales differ between sexes (as already shown in univariate analysis). As the interaction term time x sex is non-significant, the pattern over time (changes in psychometric scale) is similar in men and women.

Response: We are in full agreement and we thank the reviewer for this comment. Although we indicated at the end of the paragraph that "no significant interaction of time and sex was found", we agree with the reviewer that the sentence is not clear. For this reason, we have reworded it

as follows: "Of the 71 females assessed at baseline, 51 were assessed at 6 months and 45 at one-year follow-up. 152 males were assessed at baseline, 101 at 6 months and 75 at one-year follow-up. The repeated measures ANOVA results ~~for the main effect of our within-groups factor (time) and the time x sex interaction effect~~ indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta_p^2=0.118$), NSF ($p<0.001$, $\eta_p^2=0.140$), EXP ($p<0.001$, $\eta_p^2=0.117$) and MAP ($p<0.001$, $\eta_p^2=0.118$), with follow-up scores being significantly lower than baseline (see **Table 2**). However, no significant interaction of time and sex was found. Thus, there were significant time effects on all variables, indicating an improvement for both sexes, with no difference between them."

4. In the supplementary material, correlation analyses (Tables SM 1 and SM 2) include 45 women and 75 men. However, in the baseline sample Ns were 71 women and 152 men. Please revise if numbers are correct. If the numbers are correct and the smaller numbers of supplementary tables are explained by drop-outs, the authors should specify the number of patients that have been lost at follow-up and comment it on the Discussion section (it would mean a high proportion of dropouts, about 50% of men and 40% of women). This needs to be also discussed as a limitation about the representativeness of the findings of the study.

Response: We agree with the reviewer. Based on your suggestion, we have performed analyses in order to identify differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. We have elaborated a little further on this:

- **Supplementary Table 1**
- **Results** (3.1. Sociodemographic, clinical and functional characteristics of the sample and sex differences): Those patients who were assessed at follow-up (n=120) were indistinguishable from those who were not (n=103) in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF (p=0.045, Cohen's d=0.275; 95% CI=[0.025, - 2.064]), but not when they were measured by the PANSS positive subscale (p= 0.108). For more details, see **Supplementary Table 1**.
- **Discussion:** This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women's group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we

analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different variables of interest.

Title page (authors names, affiliations and corresponding author)

Negative symptoms and sex differences in first episode schizophrenia: what's their role in the functional outcome? A longitudinal study

Short running title: Negative symptoms and sex in first episode schizophrenia

Síntomas negativos y diferencias de sexo en el primer episodio de esquizofrenia: ¿cuál es su papel en el resultado funcional? Un estudio longitudinal

Título corto: Síntomas negativos y sexo en el primer episodio de esquizofrenia

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Word count: Abstract 249, Main document (references not included) 3961

Conflicts of interest

M. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of has received honoraria from talks and/or consultancy of Adamed, Angelini, Casen-Recordati, Ferrer, Janssen-Cilag, Lundbeck, Neuraxpharm, Otsuka, Pfizer and Sanofi, and grants from Spanish Ministry of Health, Instituto de Salud Carlos III (PI20/01066).

R. Rodriguez-Jimenez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/ BMD-2422 AGES; S2017/BMD-3740), Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini.

A. Ibáñez has received research support from or served as speaker or advisor for Janssen-Cilag, Lundbeck and Otsuka.

E. Vieta has received research support from or served as consultant, adviser or speaker for AB-Biotics, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Suibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

J.A. Ramos-Qurioga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió, Raffo in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli- Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

M. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of AB-Biotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

C. De-la-Camara received financial support to attend scientific meetings from Janssen, Almirall, Lilly, Lundbeck, Rovi, Esteve, Novartis, Astrazeneca, Pfizer and Casen Recordati

J. Saiz-Ruiz has been as speaker for and on the advisory boards of Adamed, Lundbeck, Servier, Medtronic, Casen Recordati, Neurofarmagen, Otsuka, Indivior, Lilly, Schwabe, Janssen and Pfizer, outside the submitted work.

A. Tortorella received research support and travel grants from Lundbeck and Angelini (unrelated to the present work)

G. Menculini received travel grants from Angelini and Janssen.

The rest of authors report no biomedical financial interests or potential conflicts of interest.

Author contributions

MB obtained funding for the study. GM, SA, EV, NV and MB designed the study, drafted the article, and critically revised the manuscript for intellectual content. All authors have participated in the recruitment. All authors have read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding authors.

Funding

This study received economic support from the Spanish Ministry of Economic Affairs and Competitiveness, the Carlos III Health Care Institute (Grant Number PI08/0208; PI11/00325; PI14/00612), the European Regional Development Fund, the European Union, "Una manera de hacer Europa/ A Way of Shaping Europe", and CIBERSAM; Departament de Salut de la Generalitat de Catalunya, en la convocatoria corresponent a l'any 2017 de concessió de subvencions del Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020, modalitat Projectes de recerca orientats a l'atenció primària, amb el codi d'expedient SLT006/17/00345.

Acknowledgements

We are extremely grateful to all participants.

This study is part of a coordinated-multicentre Project, funded by the Ministerio de Economía y Competitividad (PI08/0208; PI11/00325; PI14/00612), Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional. Unión Europea. Una manera de hacer Europa, Centro de Investigación Biomédica en Red de salud Mental, CIBERSAM, by the CERCA Programme / Generalitat de Catalunya AND Secretaria d'Universitats i Recerca del Departament d'Economia I Coneixement (2021 SGR 01120). Departament de Salut de la Generalitat de Catalunya, en la convocatòria corresponent a l'any 2017 de concessió de subvencions del Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020, modalitat Projectes de recerca orientats a l'atenció primària, amb el codi d'expedient SLT006/17/00345. MB is also grateful for the support of the Institut de Neurociències, Universitat de Barcelona.

S. Amoretti has been supported by Sara Borrell doctoral programme (CD20/00177) and M-AES mobility fellowship (MV22/00002), from the Instituto de Salud Carlos III (ISCIII), and co-funded by European Social Fund "Investing in your future".

The study has been supported by a BITRECS project conceded to N. Verdolini. BITRECS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754550 and from "La Caixa" Foundation.

R. Rodriguez-Jimenez thanks the support of the Instituto de Salud Carlos III (PI19/00766; Fondo de Investigaciones Sanitarias/FEDER) and of Madrid Regional Government (S2017/BMD-3740).

A. Ibáñez thanks the support by the Madrid Regional Government (R&D Activities in Biomedicine and European Union Structural Funds (S2017/BMD3740: AGES-CM 2-CM) and the support by CIBERSAM.

E. Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI18/00805; PI21/00787) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2021 SGR 1358) and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

We also would like to thank the authors of the 2EPs group who participated in the development of this manuscript, namely, Maria Florencia Forte [2,3], Maria Serra [3,4], Anna Alonso-Solís [4,11], Eva Grasa [4,11], Edurne García Corres [4,8], Jessica Fernandez Sevillano [4,8], Alba Toll [4,9], Laura Martínez-Sadurní [9], Aggie Nuñez-Doyle [4,10], Luis Sanchez-Pastor [4,10], Edith Pomarol-Clotet [4,12], Amalia Guerrero-Pedraza [4,12,18], Anna Butjosa, [4,14,19], Marta Pardo [4,14,19], Jose M. López-Ilundain [5,6], María Ribeiro [5,6], Jerónimo Saiz-Ruiz [13], Leticia León-Quismondo [13], María José Escarti [20], Fernando Contreras [4, 21], Concepción De-la-Cámara [4,22], Arantzazu Zabala Rabadán [4,23], M Paz Portilla [24].

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Title: Negative symptoms and sex differences in first episode schizophrenia: what's their role in the functional outcome? A longitudinal study

Abstract

Introduction: Negative symptoms (NS) include asociality, avolition, anhedonia, alogia, and blunted affect and are linked to poor prognosis. It has been suggested that they ~~and~~ reflect two different factors: diminished expression (EXP) (blunted affect and alogia) and amotivation/pleasure (MAP) (anhedonia, avolition, asociality). The aim of this article was to examine potential sex differences among first-episode schizophrenia (FES) patients and analyze sex-related predictors of two main NS factors (EXP and MAP) and functional outcome~~predictors of negative dimensions and functioning at one-year follow-up for each sex~~.

Material and Methods: Two hundred and twenty-three FES (71 females and 152 males) ~~in clinical remission~~ were included and evaluated at baseline, six-months and one-year. Repeated measures ANOVA was used to examine the effects of time and sex on NS and a multiple linear regression backward elimination was performed to predict NS factors (MAP-EXP) and functioning.

Results: Females showed fewer NS (p=0.031; Cohen's d=-0.312~~; 95% CI=[-0.595, -0.029]~~), especially those related to ~~expressiveness~~ EXP (p=0.024; Cohen's d=-0.326~~; 95% CI=[-0.610, -0.043]~~) rather than ~~amotivation~~ MAP (p=0.086), than males. In both male and female group, worse premorbid adjustment and higher depressive symptoms made a significant contribution to the presence of higher deficits in EXP at one-year follow-up, while positive and depressive symptoms predicted alterations in MAP. ~~In females, duration of untreated psychosis, baseline negative and positive symptoms and functioning significantly contributed to the presence of higher deficits in EXP at one-year (R^2=0.783, p<0.001), while premorbid adjustment was the only predictor for deficits in MAP (R^2=0.270, p<0.001). In males, baseline NS predicted higher deficits in EXP at one-year (R^2=0.369, p<0.001), and premorbid adjustment, negative and depressive symptoms predicted greater MAP (R^2=0.479, p<0.001).~~ Finally, in females, lower deficits in MAP and better premorbid adjustment predicted better functioning at one-year follow-up (R^2=0.494; p<0.001), while only higher deficits in MAP predicted worse functioning in males (R^2=0.088; p=0.012).~~in females, lower alterations in EXP and higher cognitive reserve predicted better functioning at one-year, while higher depressive symptoms predicted worse functioning in males.~~

Conclusions: Slightly ~~Notable~~ sex differences have been found in this study. ~~Thus,~~Our results lead us to consider that early interventions of NS, especially those focusing on motivation and pleasure symptoms, could improve functional outcomes. ~~differential needs between men and women and sex-specific personalized therapeutic strategies focused on NS should be considered in early intervention services.~~

Key words

First-episode of psychosis; Schizophrenia; Negative symptoms; Sex; Functional outcome

Título: Síntomas negativos y diferencias de sexo el primer episodio de esquizofrenia: ¿cuál es su papel en el resultado funcional? Un estudio longitudinal

Resumen

Introducción: Los síntomas negativos (SN) incluyen la asocialidad, la avolición, la anhedonia, la alogia y el afecto embotado y están relacionados con un mal pronóstico. Se ha sugerido que ~~y~~ reflejan dos factores: la disminución de la expresión (EXP) (afecto embotado y alogia) y la amotivación/placer (MAP) (anhedonia, avolición, asocialidad). El objetivo de este artículo fue examinar las posibles diferencias de sexo entre los pacientes con un primer episodio de esquizofrenia (FES) y analizar los predictores relacionados con el sexo de ~~de~~ las dimensiones negativas (EXP y MAP) y ~~d~~el funcionamiento al año de seguimiento ~~para cada sexo~~.

Material y métodos: Se incluyeron 223 FES (71 mujeres y 152 hombres) ~~en remisión clínica y~~ que fueron ~~se~~ evaluad~~r~~os~~n~~ al inicio, a los seis meses y al año. Se utilizó un ANOVA de medidas repetidas para examinar los efectos del tiempo y el sexo sobre el SN y se realizó una regresión lineal múltiple (eliminación hacia atrás) para predecir los factores MAP-EXP y el funcionamiento.

Resultados: Las mujeres mostraron menos SN que los hombres (p=0.~~,~~031; d de Cohen=-0~~,~~.312~~; IC 95%=[-0,595, -0,029~~]), especialmente las relacionadas con la ~~expresividad~~ EXP (p=0.~~,~~024; d de Cohen=-0.~~,~~326~~; IC 95%=[-0,610, -0,043~~]) más que con la ~~amotivación~~ MAP (p=0,086). En ambos sexos un peor ajuste premórbido y una mayor sintomatología depresiva contribuyeron significativamente a la presencia de mayores déficits en la EXP al año de seguimiento, mientras que los síntomas positivos y depresivos predijeron alteraciones en la MAP. Finalmente, en las mujeres, menores déficits en MAP y un mejor ajuste premórbido predijeron un mejor funcionamiento al año de seguimiento (R^2=0.494; p<0.001), mientras que en los varones únicamente los déficits en MAP predijeron un peor funcionamiento (R^2=0.088; p=0.012).~~En las mujeres, la duración de la psicosis no tratada, los síntomas negativos y positivos basales y el funcionamiento contribuyeron significativamente a la presencia de mayores déficits en la EXP al año (R2=0,783, p<0,001), mientras que el ajuste premórbido fue el único predictor de los déficits en la MAP (R2=0,270, p<0,001). En los varones, el SN basal predijo mayores déficits en la EXP al año (R2=0,369, p<0,001), y el ajuste premórbido, los síntomas negativos y depresivos predijeron una mayor MAP (R2=0,479, p<0,001). Finalmente, en las mujeres, las menores alteraciones en la EXP y la mayor reserva cognitiva predijeron un mejor funcionamiento al año, mientras que los mayores síntomas depresivos predijeron un peor funcionamiento en los varones.~~

Conclusiones: En este estudio se han encontrado ~~notables~~ ligeras diferencias de sexo. Nuestros resultados nos llevan a considerar que las intervenciones tempranas de los SN, especialmente las centradas en los síntomas de motivación y placer, podrían mejorar los resultados funcionales.~~Por lo tanto, en los servicios de intervención temprana deberían considerarse las necesidades diferenciales entre hombres y mujeres y estrategias terapéuticas personalizadas centradas en el SN específicas para cada sexo.~~

Palabras clave

Primer episodio de psicosis; Esquizofrenia; Síntomas negativos; Sexo; Funcionalidad

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1. Introduction

Schizophrenia is a complex and heterogeneous disorder with sex differences in clinical, functional and cognitive manifestations. Nevertheless, the nature of the relationship between sex-specific and clinical manifestations, cognitive impairment and functional outcome still remains unclear (1). The usual course of schizophrenia is marked by psychotic episodes with positive (delusions, hallucinations) and negative symptoms (apathy, social withdrawal, avolition) as well as cognitive impairment, which may result in the individual suffering a functional disability (2). The accomplishment of symptomatic and functional remission is one of the major objectives in early-stage interventions, as it is after presenting a first-episode of schizophrenia (FES) (3). Although the majority of FES patients may show an improvement in their symptomatology after antipsychotic treatment, many continue to have long-term impairments in functioning (4). It has been well demonstrated that interventions at early stages of the illness –that is, at the onset of FES– can improve subsequent outcomes. Thus, individuals with a first-episode of psychosis constitute a key group for studying the risk factors linked to the development of schizophrenia and other related disorders and its progression in terms of clinical outcome in later stages. Therefore, the early identification of clinical, functional and sociodemographic features may be important in identifying subsets of patients with similar characteristics, facilitating personalized treatment approaches from the early stages of the disease.

Negative symptoms have long been considered a core and independent dimension, distinct from other aspects of the illness (e.g., positive, cognitive and motor symptoms) (5). This symptomatology is also highly predictive of poor psychosocial functional outcomes (6) and largely contributes to the burden that the disorder poses on affected people, their relatives and society (7), suggesting it should be a key treatment target. Unfortunately, both pharmacological and psychosocial interventions for negative symptoms have demonstrated limited effectiveness. To address this critical unmet therapeutic need, the National Institute of Mental Health (NIMH) sponsored a consensus development conference to delineate research priorities for the field and stimulate treatment development (8). One of the main conclusions of this meeting was the nature of this symptomatology; instead of categorizing it into a single category, it was suggested that the negative symptoms construct is multidimensional, comprising 5 discrete domains (anhedonia, avolition, asociality, blunted affect, alogia) with at least two correlated factors creating a hierarchical structure consisting of two higher-order dimensions: diminished expression (EXP) and amotivation and pleasure (MAP), that have more basic subordinate domains (~~MAP = anhedonia, avolition, asociality;~~ EXP = blunted affect, alogia; MAP = anhedonia, avolition, asociality). Both factors may represent separable treatment targets with distinct etiologies (9-10). In this way, identifying specific dimensions that underline negative symptoms in early stages of schizophrenia could improve the understanding and the treatment of such invalidating symptomatology and its potential impact on the psychosocial functional outcome as well as progression of the illness (6).

Related to sex-outcome differences in FES patients, studies have found mixed results (11). In schizophrenia and related disorders, sex differences have been observed in several clinical features; it has been well demonstrated that the outcome of schizophrenia is poorer in male than in female patients (11-12). Compared to women, men tend to show a higher incidence of the disorder, an earlier age of onset, poorer premorbid adjustment, worse psychosocial

functioning and a more severe course of the disease (12). Specifically, although not all the studies found differences, most of them found that regarding negative symptomatology, men have shown higher propensity to present these symptoms, especially in social withdrawal and blunted or incongruent affects than female patients, who presented more affective symptoms (13), and in alogia and avolition-apathy (14).

The aims of the present study were 1) To explore sex differences among first-episode schizophrenia patients through one year follow-up focusing on different outcome measures as clinical, with a special focus on negative symptom dimensions, and psychosocial functioning, and 2) To analyze clinical predictors of negative dimensions and functional outcome, that is, motivation, pleasure, and expression~~expressivity~~.

2. Material and Methods

2.1. Sample

The sample of this study has been recruited though the "2EPs Project". It is a multicenter, coordinated, naturalistic, and longitudinal follow-up study of three years' duration. "2EPs" included Spanish patients who met diagnosis of schizophrenia or schizophreniform disorder with a first psychotic episode with less than five years of evolution. All the information about the methodology of the "2EPs Project" can be found elsewhere (15) .

The inclusion criteria were: 1) aged between 16 to 40 years at the first evaluation; 2) met diagnostic criteria according to DSM-IV for schizophrenia or schizophreniform disorder; 3) ability to speak Spanish correctly; 4) signed informed consent; 5) have presented a first episode psychosis (FEP) in the last 5 years and are currently in remission according to Andreasen's criteria (3). According to this criteria, ~~Remission~~ remission is achieved when the patient's Positive and Negative Symptom Scale (PANSS) score is 3 or less ("mild" or better) in 8 items ~~(mild severity, as representative of an impairment level consistent with symptomatic remission of illness)~~. There is also a minimum period of six months in which the symptoms severity must be maintained ~~Severity symptoms must be maintained for a minimum of 6 months~~ and the patient must not have relapsed after the episode. The exclusion criteria were: 1) having experienced a brain trauma with loss of consciousness; 2) an Intelligence Quotient (IQ) lower than 70 and with significant difficulties or malfunctioning with adaptive processes; and 3) somatic pathology with mental affectation.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethics committees of all participating centers approved the current study. Each subject agreed to participate and signed the informed consent before their inclusion.

2.2. Assessments

At baseline, patients performed a complete evaluation that included: structured interviews, clinical scales and premorbid adjustment scales. Clinical and functional scales were also administered every three months for three years. In case of relapse, a visit was performed and the subject's participation in the study was terminated. For the current study, baseline, 6 months and one-year follow-up data was used (because a high percentage of subjects were lost to follow-up).

Sociodemographic, clinical and substance use assessment

Sex, age and age at the onset of the illness were collected along with the duration of the untreated psychosis (DUP). DUP was calculated as the number of days between the first manifestations of psychotic symptoms and the initiation of adequate treatment for psychosis. Parental socioeconomic status (SES) was determined using Hollingshead's Two-Factor Index of Social Position (16). The diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) (SCID-I and II) (17) or the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (18) according to DSM-IV criteria. The participants at baseline were asked to report personal and family history of psychiatric disorders, namely affective and psychotic disorders. A psychopathological assessment was carried out with the Spanish versions of the following scales: maniac and depressive symptom severities were assessed using the Young Mania Rating Scale (YMRS) (19) and the Montgomery-Asberg Depression Rating Scale (MADRS) (20), respectively; and positive, negative, and general symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (21). On each scale, the items were summed to obtain a total score. Higher scores indicate greater severity.

Although the PANSS is one of the most widely used measures of negative symptom severity, it has been well-demonstrated that it has several limitations; for instance, it was not designed to evaluate negative symptoms exclusively. Thus, we have also used the PANSS-Marder Factor Scores (22) as it has more restrictive criteria to assess positive and negative symptomatology. The sum of the following items of the PANSS were used to calculate the Positive Symptom Factor (PSF): delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), stereotyped thinking (N7), somatic concerns (G1), unusual thought content (G9) and lack of judgment and insight (G12); and for the Negative Symptom Factor (NSF): blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity and conversation flow (N6), motor retardation (G7) and active social avoidance (G16). This structure has proved to be beneficial to obtain more specific information (23).

As previously commented, the literature revealed the existence of two factors: EXP (Diminished expression) and MAP (~~Motivation~~ amotivation and pleasure) ~~and EXP (Expressivity/Diminished expression)~~(9, 24). Following a previous work which used the PANSS (24), EXP factor was calculated as the sum of the following items of the PANSS: blunted affect (N1), poor rapport (N3), lack of spontaneity and conversation flow (N6) and motor retardation (G7), and MAP factor with emotional withdrawal (N2), passive/apathetic social withdrawal (N4) and active social avoidance (G16)(24).

Antipsychotic mean doses were collected and converted to chlorpromazine equivalents (CPZ) based on international consensus (25). Drug abuse was assessed using the adaptation of the multidimensional assessment tool European Addiction Severity Index (EuropAsi)(26).

Functional assessment

The overall functional outcome was assessed by the Functioning Assessment Short Test (FAST) (27) and the Global Assessment of Functioning Scale (GAF)(28). Higher scores of FAST indicate greater disability, while higher scores on GAF correspond to better functioning.

Premorbid adjustment and cognitive reserve

Premorbid adjustment, namely levels of functioning before the onset of psychosis, was assessed with The Premorbid Adjustment Scale (PAS)(29). The scale considers different life stages: childhood, early adolescence, late adolescence, and adulthood. Only childhood and early adolescence life periods have been taken into account since they were the two time periods for which the answers of all the participants were available. Higher scores indicate worse premorbid adjustment.

To assess cognitive reserve (CR) the three most commonly proposed proxy indicators of CR have been used (30): 1. The estimated premorbid IQ was calculated with the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III)(31). 2. Education was assessed taking into account the degree of schooling attained and passed by the subject; 3. Lifetime participation in leisure, social and physical activities was assessed with the PAS scale (scholastic performance) and the FAST scale, which allows us to assess specific life-domains such as interpersonal relationships and leisure time. When patients were assessed, they had already experienced a FES. For that reason, we could only estimate premorbid variables. To summarize the information of the three main proxies of CR, a Principal Components Analysis (PCA) was performed to create a "Composite CR score" for each subject. Higher scores correspond to better performance.

2.3. Data Analysis

Demographic, clinical and functional sex differences were examined using unpaired t-tests and chi-square. A repeated measures ANOVA was used to examine the effects of time and sex on negative symptoms. To explore which variables could predict MAP, ~~and~~ EXP or functioning at one-year follow-up three steps were undertaken: (1) Candidate exploratory variables were selected carefully taking into account their possible role in the prediction of negative symptom severity (focusing on total scores and on MAP and EXP factors separately) and functioning (GAF) at one-year follow-up. The potential predictors ~~variables~~ were: age, DUP, age at psychosis onset, socioeconomic status, personal and family psychiatric history, total scores of the PAS, cognitive reserve, Marder PANSS positive ~~and negative~~ factor score (PSF~~ and NSF~~), depressive symptoms (MADRS), psychosocial functioning (FAST), antipsychotic medication treatment, and alcohol, cannabis and/or tobacco consumption at baseline and lifetime cannabis use (all these variables from the baseline visit); (2) General Linear Model (GLM) Univariate Analysis ~~A correlation analysis~~ was performed to explore whether predictors differ between sexes (interaction term between sex and each potential predictors)~~to determine, from the 17 variables mentioned above, those factors that were associated with MAP and EXP for each group (female and males)~~; and (3) To explore which of these factors could predict general negative symptom severity and functioning at follow-up, significant predictors ~~the factors that were significantly correlated with MAP and/or EXP separately (p<0.05)~~ were included in a multiple linear regression model with backward elimination. ~~The same analysis was carried out to explore which variables could predict functioning at one-year follow-up.~~

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v25). All statistical tests were carried out two-tailed, with an alpha level of significance set at $p \leq 0.05$.

3. Results

3.1. Sociodemographic, clinical and functional characteristics of the sample and sex differences

Of the 223 FEP patients participating in the study, 31.8% (n=71) were females and 68.2% (n=152) were males. Mean age of onset was 26.77±6.15 years for female and 25.55±5.96 for male (p=0.160). The mean DUP time was 196.95 days (28 weeks approximately), without differences between females and males. Baseline sex differences in sociodemographic, clinical and functional characteristics are shown in **Table 1**. More males reported tobacco (p=0.014) and cannabis (p=0.003) use than females. Females showed a significantly lower severity of general and total symptoms according to the PANSS (p=0.049 and p=0.039), better premorbid adjustment (p=0.003) and greater functionality measured by the FAST scale (p=0.002), but not by the GAF (p=0.322). Women also showed fewer general negative symptoms than men, as measured by NSF (p=0.031, Cohen's d=-0.312; 95% CI=[-0.595, -0.029]), while there was only a tendency to signification in negative symptoms measured by the PANSS negative subscale (p=0.058). Finally, regarding dimensions specific to negative symptoms, females showed significantly less expressivity impairment (such as blunted affect or alogia) than males (p=0.024; Cohen's d=-0.326; 95% CI=[-0.610, -0.043]), without differences in motivation and pleasure disablement (e.g. anhedonia, avolition or asociality) (p=0.086). There were no differences between sex groups in terms of age, SES, age of onset, alcohol use, positive, manic and depressive symptoms, cognitive reserve and chlorpromazine equivalents.

[Please insert table 1 here]

Those patients who were assessed at follow-up (n=120) were indistinguishable from those who were not (n=103) in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF (p=0.045, Cohen's d=0.275; 95% CI=[0.025, -2.064]), but not when they were~~are~~ measured by the PANSS positive subscale (p= 0.108). For more details, see **Supplementary Table 1**.

3.2. Sex differences in negative symptoms course

Of the 71 females assessed at baseline, 51 were assessed at 6 months and 45 at one-year follow-up. 152 males were assessed at baseline, 101 at 6 months and 75 at one-year follow-up. The repeated measures ANOVA results ~~for the main effect of our within-groups factor (time) and the time x sex interaction effect~~ indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta_p^2=0.118$), NSF ($p<0.001$, $\eta_p^2=0.140$), EXP ($p<0.001$, $\eta_p^2=0.117$) and MAP ($p<0.001$, $\eta_p^2=0.118$), with follow-up scores being significantly lower than baseline (see **Table 2**). However, no significant interaction of time and sex was found. Thus, there were significant time effects on all variables, indicating an improvement for both sexes, with no difference between them.

[Please insert table 2 here]

3.3. Predictors of amotivation and pleasure (MAP) and diminished expression ~~expressivity~~ (EXP) at one-year follow-up differentiating between females and males

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The baseline ~~factors~~ predictors ~~associated with~~of EXP at one-year follow-up with an interaction by sex ~~in females~~ were: ~~age, DUP, age at onset,~~ family ~~and personal~~ psychiatric history, PAS, ~~CR,~~ PSF, ~~NSF,~~ MADRS, ~~,~~ FAST and alcohol consumption ~~and CPZ. For males they were: PAS, PSF, NSF, MADRS, FAST and alcohol consumption at baseline~~ (see **Supplementary Table ~~1~~ 2** for more details). The ~~factors associated with~~predictors of MAP ~~in females~~ were ~~PAS,~~ PSF, ~~NSF,~~ MADRS, FAST, ~~and CPZ, and in males they were PAS, CR, PSF, NSF MADRS, FAST and~~ tobacco use and alcohol consumption.

Predictors of EXP and MAP in females and males are shown in **Table 3.** Regarding females, premorbid adjustment (t=2.679, p=0.011), ~~DUP (t=4.837, p<0.001), NSF (t=4.270, p<0.001), FAST (t=3.800, p=0.001)~~ and ~~PSF~~ depressive symptoms (t=2.926~~450~~, p=0.0~~0621~~) ~~-~~at baseline made a significant contribution to the presence of higher deficits in expressivity at one-year follow-up (F=~~32~~17.499~~473~~, R^2=0.593~~783~~, p<0.001). Positive (t=2.426, p=0.020) and depressive (t=2.205, p=0.033) symptoms ~~PAS predicted(t=3.749, p<0.001) was the only predictor for~~ deficits in ~~motivation and pleasure~~ motivation and pleasure at one-year follow-up (F=~~14~~9.056~~054~~, R^2=0.~~270~~317, p=~~<~~0.001). In males, worse premorbid adjustment (t= 3.498, p=0.001), and higher depressive symptoms (t=3.113, p=0.003)~~NSF~~ at baseline ~~(t=4.418, p<0.001) was the only predictor~~predicted higher deficits in expression ~~for higher deficits in expressivity~~ at one-year follow-up (F=~~19~~13.544~~576~~, R^2=0.~~288~~369, p<0.001). Finally, positive (t=2.254, p=0.027) and depressive (t=4.218, p<0.001) symptoms and alcohol consumption ~~PAS (t=2.006, p=0.049), NSF (t=2.664, p=0.010) and MADRS~~ (t= ~~-~~2.363~~2.903~~, p=0.~~005~~021) at baseline predicted greater amotivation ~~greater amotivation~~ at one-year follow-up (F=~~18~~15.438~~384~~, R^2=0.398~~479~~, p<0.001).

[Please insert table 3 here]

3.4. Predictors of functioning

The predictors of ~~F~~functioning at follow-up (GAF) that differed between the sexes with interaction terms were ~~was associated with age, age of onset, SES,~~ premorbid adjustment (F=2.066, p=0.010, η_p^2=0.820) and ~~, cognitive reserve, Marder PANSS positive and negative factor score (PSF and NSF), MAP, EXP, MADRS and FAST at baseline in females and with NSF,~~ MAP (F= 2.443, p=0.003, η_p^2=0.303)~~, EXP and MADRS in males~~ (see **Supplementary Table ~~2~~ 3** for more details). The regression model (see **Table 4**) showed that lower ~~EXP~~ MAP (t=~~-~~3.941~~4.236~~, p<0.001) and ~~higher~~ better premorbid adjustment ~~CR~~ (t=~~-~~2.165~~2.554~~, p=0.0~~3~~17) predicted better functioning in females at one-year follow-up (F=19~~3~~.054~~785~~, R^2=0.494~~605~~, p<0.001). Regarding males, the strongest predictor has proven to be the amotivation~~depressive symptomatology~~; higher ~~depressive symptoms~~ deficits in motivation and pleasure ~~-~~(t=~~-~~2.577~~-3.819~~, p=~~<~~0.~~0~~012) predicted worse functioning (F=~~14~~6.639~~587~~, R^2=0.088~~167~~, p=0.012~~<0.001~~).

[Please insert table 4 here]

4. Discussion

Four findings emerged from the present study. Firstly, females showed lesser negative symptoms, especially those related to expressiveness rather than amotivation, a better

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premorbid adjustment and better psychosocial functioning than males. Secondly, there were clinically relevant improvements in negative symptoms in both groups through the first year after inclusion. Thirdly, in both male and~~the~~ female group, worse premorbid adjustment (PAS) and higher depressive symptoms ~~longer DUP, higher negative and positive symptoms and poor psychosocial functioning at baseline~~ made a significant contribution to the presence of higher deficits in expression ~~expressivity~~ at one-year follow-up, while positive and depressive symptoms predicted ~~worse premorbid adjustment (PAS) was the only predictor for~~ alterations in motivation and pleasure. In males, alcohol consumption also predicted deficits in motivation and pleasure at one-year follow-up~~negative symptomatology was the only predictor for higher deficits in expressivity at one-year follow-up, and premorbid adjustment, negative and depressive symptoms, for deficits in motivation~~. Finally, in females, lower deficits in motivation and pleasure ~~alterations in expressivity~~ and ~~higher~~ better premorbid adjustment ~~cognitive reserve~~ predicted better functioning at one-year follow-up, while only higher deficits in motivation and pleasure ~~depressive symptoms~~ predicted worse functioning in males.

Our results suggest that males showed more general negative symptoms than women measured by NSF but there was only a tendency to signification when measured by the PANSS subscale. Although PANSS is a widely used instrument for measuring symptomatology in patients with schizophrenia, it seems that Marder's factor (NSF) has several aspects of improved content validity in comparison to the original negative PANSS subscale (6, 22). Factor analytic studies in PANSS found that two items (difficulty in abstract thinking (N5) and stereotyped thinking (N7)) should no longer be considered part of the negative symptom domain (32-33). In addition, females showed less expressivity impairment than males (such as flat affect), without differences in motivation and pleasure severity (i.e., anhedonia, avolition or asociality) between both groups. These results are in accordance with previous literature (34). ~~Finally, a~~Moreover, as expected, in the present study females showed a better premorbid adjustment and greater functionality, which is also in accordance with previous studies (12, 14). Finally, although sex differences in age of onset is a replicated finding in the literature (35-36), in our study no significant differences were found in this regard. There are other studies that found no gender differences in age of onset (37). It has been hypothesised that differences in age of onset could depend on the presence or absence of family history (12,38). In addition, it should be noted that this study does not have balanced samples.

The obtained results suggest that regardless of sex, patients showed a reduction in the severity of negative symptomatology at one-year follow-up. According to our results, a meta-analysis revealed that negative symptoms decrease in almost all patients (~~35~~39). Moreover, a previous study of our group found a reduction in the negative symptomatology one year after a FEP and that this change remained stable at two years (6). Thus, it seems that negative symptoms tend to be stable and persistent in the long-term, but can fluctuate in severity (~~36~~40) and can even improve in the early stages.

As negative symptoms are not a homogeneous construct, when comparing the predictors of MAP and EXP between males and females, we found that, regardless of sex, premorbid adjustment seems to be a good predictor of EXP, which is in accordance with previous research that has shown a strong association between premorbid adjustment and the course of negative symptoms (6, ~~37~~41). Moreover, in males, ~~negative~~ positive and depressive symptoms were

predictors of greater amotivation (~~38~~42). Regarding the predictors ~~of more diminished expressivity at one-year follow-up~~, in both groups ~~females, DUP,~~ premorbid adjustment ~~negative~~ and depressive ~~positive~~ symptoms ~~and psychosocial functioning~~ at baseline made a significant contribution to the presence of higher deficits in the area of expressiveness, while positive and depressive symptoms predicted alterations in motivation and pleasure~~, while in males, the general negative symptom severity at baseline was the only predictor~~.

Thus, these results could suggest that implementing early and personalized interventions at the onset of the illness, that is, after a first-episode, tailored to individual needs and paying special attention to the clinical~~,~~ and functional features that have been related to severe outcomes may help in their prognosis ~~(see **Figure 1**)~~. However, further studies are required to confirm these findings. Briefly, early interventions will differ in terms of the target, independently of sex ~~and the special needs that each group (females and males) presents at one year after the first episode~~. Our results suggests that in those patients with worse premorbid adjustment and depressive symptoms, interventions should be oriented toward improving self-reflectivity, linguistic cohesion, and cognitive symptoms (43). Meanw~~, w~~hile, in those patients with positive and depressive symptoms, ~~s~~interventions ~~interventions an intervention~~ oriented ~~toward~~, to increase cognitive control of positive emotions ~~positive emotions programme for schizophrenia can be suggested~~, as the Positive Emotions Programme for Schizophrenia (PEPS), could be suggested (44). The latter it~~t~~ is a programme designed to improve pleasure and motivation in schizophrenia patients by targeting emotion regulation and cognitive skills relevant to apathy and anhedonia (44). In general, without taking sex or MAP/EXP into account, poor premorbid adjustment ~~and negative symptoms emerging~~ in the early illness stage predict negative symptom severity at follow-up (6). Thus, assessing premorbid adjustment and early interventions focused on treating negative symptoms is of paramount importance (38). ~~Regarding males~~Moreover, our study suggests that ~~,~~ depressive symptoms should also be considered. ~~In comparison, there are other additional factors to take into account in females such as DUP, positive symptoms and psychosocial functioning. Thus, in this group, positive emotion programs and psychosocial remediation interventions could be implemented. In cases in which there is also an alteration in the expressivity dimension, emotion recognition programs could be established too.~~

~~Although a longer DUP was associated with worse treatment response, their impact on negative symptom severity remains unclear. While a meta-analysis showed that shorter DUP is associated with lower negative symptom severity (39), studies revealed no significant interaction (40). These differences and inconclusive results could be explained due to the fact that some studies were with patients with early-stage disease and others with late/chronic stages of the disease. It may also be attributable to not having taken into account sex or taking into account negative symptoms as a unidimensional construct rather than differentiated subdomains.~~

Finally, regarding psychosocial outcome prediction, in accordance with the literature, lower negative symptoms (6) and premorbid adjustment ~~and higher CR (30)~~ predicted better functioning at one-year follow-up ~~in females while higher depressive symptoms predicted worse functioning in males~~. It is well-known that negative symptoms account for a large part of long-term disability and poor functional outcomes. However, the study of the impact of negative symptom factors, taken as a multimodal construct, on functional outcome is of special interest. Our results showed that MAP could predict psychosocial functioning, but EXP could not,

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suggesting that symptoms such as anhedonia, avolition and asociality should be prioritized in assessment and focused on when developing early interventions targeting psychosocial functioning in FEP. ~~Regarding the link found between depression symptoms and a worse functioning in males, a potential explanation is that depressive symptoms may also underlie secondary negative symptoms, such as a reduced emotional expression, diminished amount of speech, social withdrawal, anhedonia and/or lack of motivation. In this case, specific psychological interventions focusing on social skills training and pharmacological treatment with second generation antipsychotics should be preferred to first generation medications (7).~~

This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women's group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. ~~Secondly~~Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different variables of interest.

In conclusion, clinical phenotypes in FES and its predictors can vary slightly by sex. However, our study suggest that there are no differential needs between men and women nor sex-specific personalized therapeutic strategies focused on NS. Our results lead us to consider that early interventions of negative symptoms, especially those focusing on motivation and pleasure symptoms, could improve functional outcomes. Due to the fact that the negative dimension constitutes one of the most impairing aspects of schizophrenia, and since treatments for this symptomatology have had limited success to date, it might be worthy of further investigation. A greater understanding of its impact on the functional outcome will help to change this situation, giving way to the design of longitudinal studies that focus on negative symptoms from a multidimensional approach. ~~In conclusion, clinical phenotypes in FES and its predictors can vary by sex. Thus, differential needs between men and women and sex-specific personalized therapeutic strategies focused on NS should be considered in early intervention services. Our results lead us to consider that early interventions of negative symptoms could decrease the~~

~~severity of negative symptomatology in the long term, improving functional outcomes; especially if psychological and pharmacological interventions focus and are designed taking into account the two dimensions that comprise the main negative symptom construct, that is, motivation and pleasure and expressivity dimensions. Due to the fact that the negative dimension constitutes one of the most impairing aspects of schizophrenia, and since treatments for this symptomatology have had limited success to date, it might be worthy of further investigation. A greater understanding of its impact on the functional outcome will help to change this situation, giving way to the design of longitudinal studies that focus on negative symptoms from a multidimensional approach.~~

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Table with Tracked Changes

Table 1. Sex differences in sociodemographic, clinical and functional characteristics at baseline

	Female (n=71)	Male (n=152)	t / χ^2	Sig.	Cohen's d or Cramer's V	95% CI
Age	26.77±6.15	25.55±5.96	1.411	0.160	0.203	[-0.080—, 0.485]
Socioeconomic status (%)			3.639	0.602	0.128	
High	6 (8.5)	8 (5.3)				
Medium-High	4 (5.6)	8 (5.3)				
Medium	7 (9.9)	13 (8.6)				
Medium-Low	22 (31)	45 (29.6)				
Low	31 (43.7)	78 (51.3)				
Missing value	1 (1.4)	0 (0)				
Tobacco: Yes, N (%)	29 (41)	87 (58)	5.444	**0.014**		OR=1.969 [1.110, 3.491]
Cannabis: Yes, N (%)	5 (7)	33 (22)	7.679	**0.003**		OR=3.755 [1.398, 10.085]
Alcohol: Yes, N (%)	32 (45)	70 (46)	0.032	0.487		OR=1.053 [0.598, 1.856]
DUP (days)	183.23±396.29	199.58±367.54	-0.292	0.771	-0.043	[-0.325—, 0.238]
Age of onset	25.58±6.00	24.10±5.63	1.708	0.089	0.257	[-0.025—, 0.540]
Cognitive reserve	61.96±7.05	60.32±9.73	1.204	0.231	0.183	[-0.099—, 0.465]
PAS	40.03±18.30	49.22±22.06	-2.993	**0.003**	-0.439	[-0.724—, -0.154]
PANSS positive	9.03±2.90	9.55±2.94	-1.246	0.214	-0.178	[-0.460—, 0.105]
PANSS negative	12.69±5.16	14.07±5.00	-1.905	0.058	-0.273	[-0.556—, 0.010]
PANSS general	22.99±6.26	24.96±7.23	-1.980	**0.049**	-0.284	[-0.567—, -0.001]
PANSS total	44.70±12.64	48.59±13.15	-2.079	**0.039**	-0.300	[-0.583—, -0.016]
PSF	11.08±3.77	12.03±3.80	-1.742	0.083	-0.251	[-0.533—, 0.032]
NSF	12.58±5.36	14.24±5.31	-2.177	**0.031**	-0.312	[-0.595—, -0.029]
EXP	7.03±3.12	8.05±3.13	-2.279	**0.024**	-0.326	[-0.610—, -0.043]
MAP	5.55±2.54	6.19±2.61	-1.725	0.086	-0.247	[-0.530—, 0.035]
YMRS score	0.72±1.99	1.20±2.14	-1.615	0.108	-0.229	[-0.512—, 0.053]
MADRS score	5.52±5.33	6.93±6.46	-1.598	0.111	-0.230	[-0.513—, 0.052]
Chlorpromazine equivalents	228.73±238.15	302.96±291.74	-1.872	0.063	-0.269	[-0.552—, 0.014]
GAF	71.04±12.59	69.05±14.35	0.992	0.322	0.144	[-0.138—, 0.426]
FAST	19.01±13.20	26.05±18.30	-2.850	**0.002**	-0.418	[-0.702—, -0.133]

Abbreviations: DUP= Duration of Untreated Psychosis; PAS= Premorbid Adjustment Scale; PANSS= Positive and Negative Symptom Scale; PSF= Positive Symptoms Factor of the PANSS; NSF= Negative Symptoms Factor of the PANSS; EXP= Diminished expression; MAP= Amotivation and pleasure; YMRS= Young Mania Rating Scale; MADRS= Montgomery-Asberg Depression Rating Scale; GAF= Global Assessment of Functioning; FAST=Functioning Assessment Short Test. Significant differences (p<0.05) marked in bold.

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Table 2. Sex differences in negative symptoms course

		Female	Male	t	Cohen's d	95% CI	Sig.	Within-Subjects Effects	Between-Subjects Effect
PANSS	Baseline	12.69±5.16	14.07±5.00	-1.905	-0.273	-0.556 - 0.010	0.058	Time (F=9.707, p<**0.001**), PANSS*Sex (F=0.336, p=0.715)	F=3.966, p=**0.049**
	6 months	11.20±4.40	13.10±4.73	-2.398	-0.411	-0.751 - -0.071	**0.018**		
	1 year	10.64±4.29	12.42±4.88	-2.020	-0.381	-0.753 - -0.009	**0.046**		
NSF	Baseline	12.58±5.36	14.24±5.31	-2.177	-0.312	-0.595 - -0.029	**0.031**	Time (F=11.743, p<**0.001**), NSF*Sex (F0.062, p=0.940)	F=4.367, p=**0.039**
	6 months	11.10±4.54	13.12±4.91	-2.457	-0.422	-0.762 - -0.082	**0.015**		
	1 year	10.69±4.52	12.55±5.15	-2.011	-0.378	-0.749 - -0.006	**0.047**		
EXP	Baseline	7.03±3.12	8.05±3.13	-2.279	-0.326	-0.610 - -0.043	**0.024**	Time (F=7.973, p<**0.001**), EXP*Sex (F=0.213, p=0.808)	F=4.208, p=**0.043**
	6 months	6.45±2.80	7.49±3.07	-2.031	-0.349	-0.688 - -0.010	**0.044**		
	1 year	6.02±2.71	7.05±3.07	-1.861	-0.350	-0.721 - 0.021	0.065		
MAP	Baseline	5.55±2.54	6.19±2.61	-1.725	-0.247	-0.530 - 0.035	0.086	Time (F=10.045, p<**0.001**), MAP*Sex (F=0.787, p=0.456)	F=3.736, p=0.056
	6 months	4.65±2.12	5.63±2.16	-2.660	-0.457	-0.797 - -0.116	**0.009**		

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	1 year	4.67±2.20	5.50±2.37	-1.921	-0.360	-0.731 - 0.012	0.057		

Negative symptoms	Negative PANSS			Negative Symptoms Factor of the PANSS (NSF)			Diminished expression (EXP)			Amotivation and pleasure (MAP)		
Time	Baseline	6 months	1 year	Baseline	6 months	1 year	Baseline	6 months	1 year	Baseline	6 months	1 year
Female	12.69±5.16	11.20±4.40	10.64±4.29	12.58±5.36	11.10±4.54	10.69±4.52	7.03±3.12	6.45±2.80	6.02±2.71	5.55±2.54	4.65±2.12	4.67±2.20
Male	14.07±5.00	13.10±4.73	12.42±4.88	14.24±5.31	13.12±4.91	12.55±5.15	8.05±3.13	7.49±3.07	7.05±3.07	6.19±2.61	5.63±2.16	5.50±2.37
t	-1.905	-2.398	-2.020	-2.177	-2.457	-2.011	-2.279	-2.031	-1.861	-1.725	-2.660	-1.921
Cohen's d	-0.273	-0.411	-0.381	-0.312	-0.422	-0.378	-0.326	-0.349	-0.350	-0.247	-0.457	-0.360
95% CI	[-0.556, 0.010]	[-0.751, -0.071]	[-0.753, -0.009]	[-0.595, -0.029]	[-0.762, -0.082]	[-0.749, -0.006]	[-0.610, -0.043]	[-0.688, -0.010]	[-0.721, 0.021]	[-0.530, 0.035]	[-0.797, -0.116]	[-0.731, 0.012]
Sig.	0.058	**0.018**	**0.046**	**0.031**	**0.015**	**0.047**	**0.024**	**0.044**	0.065	0.086	**0.009**	0.057
Within-Subjects Effects	Time (F=9.707, p<**0.001**), PANSS*Sex (F=0.336, p=0.715)			Time (F=11.743, p<**0.001**), NSF*Sex (F0.062, p=0.940)			Time (F=7.973, p<**0.001**), EXP*Sex (F=0.213, p=0.808)			Time (F=10.045, p<**0.001**), MAP*Sex (F=0.787, p=0.456)		
Between-Subjects Effect	F=3.966, p=**0.049**			F=4.367, p=**0.039**			F=4.208, p=**0.043**			F=3.736, p=0.056		

Abbreviations: PANSS= Positive and Negative Symptom Scale~~; NSF= Negative Symptoms Factor of the PANSS; EXP= Diminished expression; MAP= Amotivation and pleasure;~~.

Significant differences (p<0.05) marked in bold.

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Table 3. Linear regression models for predictors of Motivation and Pleasure and ~~Expressivity/~~Diminished expression at one-year follow-up in females and males

		~~Model~~	~~Beta~~	~~t~~	~~Sig.~~	~~R~~	~~R^2~~	~~Adjusted R^2~~	~~SEE~~	~~F~~	~~Sig.~~	~~Cohen's f^2~~
~~Females~~	~~Expressivity~~	~~DUP~~	~~0.436~~	~~4.837~~	~~**<0.001**~~	~~0.885~~	~~0.783~~	~~0.759~~	~~1.452~~	~~32.473~~	~~**<0.001**~~	~~3.610~~
		~~NSF~~	~~0.437~~	~~4.270~~	~~**<0.001**~~							
		~~FAST~~	~~0.390~~	~~3.800~~	~~**0.001**~~							
		~~PSF~~	~~0.229~~	~~2.450~~	~~**0.021**~~							
	~~Motivation and Pleasure~~	~~PAS~~	~~0.520~~	~~3.749~~	~~**0.001**~~	~~0.520~~	~~0.270~~	~~0.251~~	~~1.890~~	~~14.054~~	~~**0.001**~~	~~0.370~~
~~Males~~	~~Expressivity~~	~~PAS~~	~~0.200~~	~~1.811~~	~~0.075~~	~~0.607~~	~~0.369~~	~~0.350~~	~~2.431~~	~~19.576~~	~~**<0.001**~~	
		~~NSF~~	~~0.487~~	~~4.418~~	~~**<0.001**~~							
	~~Motivation and Pleasure~~	~~PAS~~	~~0.219~~	~~2.006~~	~~**0.049**~~	~~0.692~~	~~0.479~~	~~0.453~~	~~1.687~~	~~18.384~~	~~**<0.001**~~	~~0.920~~
		~~NSF~~	~~0.320~~	~~2.664~~	~~**0.010**~~							
		~~MADRS~~	~~0.319~~	~~2.903~~	~~**0.005**~~							

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		Model	Beta	t	Sig.	R	R^2	Adjusted R^2	SEE	F	Sig.	Cohen's f^2
Females	Amotivation and Pleasure	(Constant)		1.091	0.282	0.563	0.317	0.282	1.807	9.056	**0.001**	0.464
		PSF	0.352	2.426	**0.020**							
		MADRS	0.320	2.205	**0.033**							
	Diminished expression	(Constant)		0.544	0.590	0.770	0.593	0.559	1.819	17.499	**<0.001**	1.457
		PAS	0.345	2.679	**0.011**							
		PSF	0.205	1.720	0.094							
		MADRS	0.400	2.926	**0.006**							
Males	Amotivation and Pleasure	(Constant)		4.027	<0.001	0.631	0.398	0.372	1.883	15.438	**<0.001**	0.661
		PSF	0.221	2.254	**0.027**							
		MADRS	0.418	4.218	**<0.001**							
		Alcohol	-0.228	-2.363	**0.021**							
	Diminished expression	(Constant)		4.341	<0.001	0.537	0.288	0.267	2.582	13.544	**<0.001**	0.404
		PAS	0.367	3.498	**0.001**							
		MADRS	0.327	3.113	**0.003**							

Abbreviations: SEE= standard errors of the estimates; ~~DUP= Duration of Untreated Psychosis;~~ PAS=Premorbid Adjustment Scale; PSF= Positive Symptoms Factor of the Positive and Negative Symptom Scale; ~~NSF= Negative Symptoms Factor of the Positive and Negative Symptom Scale;~~ MADRS= Montgomery-Asberg Depression Rating Scale. Significant differences ($p<0.05$) marked in bold.

Table 4. Linear regression models for predictors of functioning at one-year follow-up in females and males

	Model	Beta	t	Sig.	R	R^2	Adjusted R^2	SEE	F	Sig.	Cohen's f^2
Females	(Constant)		27.147	<0.001	0.703	0.494	0.468	8.910	19.054	**<0.001**	0.976
	MAP	-0.517	-3.941	**<0.001**							
	PAS	-0.284	-2.165	**0.037**							
Males	(Constant)		18.039	<0.001	0.296	0.088	0.075	15.171	6.639	**0.012**	0.096
	MAP	-0.296	-2.577	**0.012**							

Abbreviations: SEE= standard errors of the estimates; MAP= Amotivation and pleasure; PAS=Premorbid Adjustment Scale; MADRS= Montgomery-Asberg Depression Rating Scale. Significant differences (p<0.05) marked in bold.

Supplementary material with Tracked Changes

Title: Negative symptoms and sex differences in first episode schizophrenia: what's their role in the functional outcome? A longitudinal study

Abstract

Introduction: Negative symptoms (NS) include asociality, avolition, anhedonia, alogia, and blunted affect and are linked to poor prognosis. It has been suggested that they reflect two different factors: diminished expression (EXP) (blunted affect and alogia) and amotivation/pleasure (MAP) (anhedonia, avolition, asociality). The aim of this article was to examine potential sex differences among first-episode schizophrenia (FES) patients and analyze sex-related predictors of two NS symptoms factors (EXP and MAP) and functional outcome.

Material and Methods: Two hundred and twenty-three FES (71 females and 152 males) were included and evaluated at baseline, six-months and one-year. Repeated measures ANOVA was used to examine the effects of time and sex on NS and a multiple linear regression backward elimination was performed to predict NS factors (MAP-EXP) and functioning.

Results: Females showed fewer NS (p=0.031; Cohen's d=-0.312), especially those related to EXP (p=0.024; Cohen's d=-0.326) rather than MAP (p=0.086), than males. In both male and female group, worse premorbid adjustment and higher depressive symptoms made a significant contribution to the presence of higher deficits in EXP at one-year follow-up, while positive and depressive symptoms predicted alterations in MAP. Finally, in females, lower deficits in MAP and better premorbid adjustment predicted better functioning at one-year follow-up (R^2=0.494; p<0.001), while only higher deficits in MAP predicted worse functioning in males (R^2=0.088; p=0.012).

Conclusions: Slightly sex differences have been found in this study. Our results lead us to consider that early interventions of NS, especially those focusing on motivation and pleasure symptoms, could improve functional outcomes.

Key words

First-episode of psychosis; Schizophrenia; Negative symptoms; Sex; Functional outcome

Título: Síntomas negativos y diferencias de sexo el primer episodio de esquizofrenia: ¿cuál es su papel en el resultado funcional? Un estudio longitudinal

Resumen

Introducción: Los síntomas negativos (SN) incluyen la asocialidad, la avolición, la anhedonia, la alogia y el afecto embotado y están relacionados con un mal pronóstico. Se ha sugerido que reflejan dos factores: la disminución de la expresión (EXP) (afecto embotado y alogia) y la amotivación/placer (MAP) (anhedonia, avolición, asocialidad). El objetivo de este artículo fue examinar las posibles diferencias de sexo entre los pacientes con un primer episodio de esquizofrenia (FES) y analizar los predictores relacionados con el sexo de las dimensiones negativas (EXP y MAP) y el funcionamiento al año de seguimiento.

Material y métodos: Se incluyeron 223 FES (71 mujeres y 152 hombres) que fueron evaluados al inicio, a los seis meses y al año. Se utilizó un ANOVA de medidas repetidas para examinar los efectos del tiempo y el sexo sobre el SN y se realizó una regresión lineal múltiple (eliminación hacia atrás) para predecir los factores MAP-EXP y el funcionamiento.

Resultados: Las mujeres mostraron menos SN que los hombres (p=0.031; d de Cohen=-0.312]), especialmente las relacionadas con la EXP (p=0.024; d de Cohen=-0.326) más que con la MAP (p=0,086). En ambos sexos un peor ajuste premórbido y una mayor sintomatología depresiva contribuyeron significativamente a la presencia de mayores déficits en la EXP al año de seguimiento, mientras que los síntomas positivos y depresivos predijeron alteraciones en la MAP. Finalmente, en las mujeres, menores déficits en MAP y un mejor ajuste premórbido predijeron un mejor funcionamiento al año de seguimiento (R^2=0.494; p<0.001), mientras que en los varones únicamente los déficits en MAP predijeron un peor funcionamiento (R^2=0.088; p=0.012).

Conclusiones: En este estudio se han encontrado ligeras diferencias de sexo. Nuestros resultados nos llevan a considerar que las intervenciones tempranas de los SN, especialmente las centradas en los síntomas de motivación y placer, podrían mejorar los resultados funcionales.

Palabras clave

Primer episodio de psicosis; Esquizofrenia; Síntomas negativos; Sexo; Funcionalidad

1. Introduction

Schizophrenia is a complex and heterogeneous disorder with sex differences in clinical, functional and cognitive manifestations. Nevertheless, the nature of the relationship between sex-specific and clinical manifestations, cognitive impairment and functional outcome still remains unclear (1). The usual course of schizophrenia is marked by psychotic episodes with positive (delusions, hallucinations) and negative symptoms (apathy, social withdrawal, avolition) as well as cognitive impairment, which may result in the individual suffering a functional disability (2). The accomplishment of symptomatic and functional remission is one of the major objectives in early-stage interventions, as it is after presenting a first-episode of schizophrenia (FES) (3). Although the majority of FES patients may show an improvement in their symptomatology after antipsychotic treatment, many continue to have long-term impairments in functioning (4). It has been well demonstrated that interventions at early stages of the illness –that is, at the onset of FES– can improve subsequent outcomes. Thus, individuals with a first-episode of psychosis constitute a key group for studying the risk factors linked to the development of schizophrenia and other related disorders and its progression in terms of clinical outcome in later stages. Therefore, the early identification of clinical, functional and sociodemographic features may be important in identifying subsets of patients with similar characteristics, facilitating personalized treatment approaches from the early stages of the disease.

Negative symptoms have long been considered a core and independent dimension, distinct from other aspects of the illness (e.g., positive, cognitive and motor symptoms) (5). This symptomatology is also highly predictive of poor psychosocial functional outcomes (6) and largely contributes to the burden that the disorder poses on affected people, their relatives and society (7), suggesting it should be a key treatment target. Unfortunately, both pharmacological and psychosocial interventions for negative symptoms have demonstrated limited effectiveness. To address this critical unmet therapeutic need, the National Institute of Mental Health (NIMH) sponsored a consensus development conference to delineate research priorities for the field and stimulate treatment development (8). One of the main conclusions of this meeting was the nature of this symptomatology; instead of categorizing it into a single category, it was suggested that the negative symptoms construct is multidimensional, comprising 5 discrete domains (anhedonia, avolition, asociality, blunted affect, alogia) with at least two correlated factors creating a hierarchical structure consisting of two higher-order dimensions: diminished expression (EXP) and amotivation and pleasure (MAP), that have more basic subordinate domains (EXP = blunted affect, alogia; MAP = anhedonia, avolition, asociality). Both factors may represent separable treatment targets with distinct etiologies (9-10). In this way, identifying specific dimensions that underline negative symptoms in early stages of schizophrenia could improve the understanding and the treatment of such invalidating symptomatology and its potential impact on the psychosocial functional outcome as well as progression of the illness (6).

Related to sex-outcome differences in FES patients, studies have found mixed results (11). In schizophrenia and related disorders, sex differences have been observed in several clinical features; it has been well demonstrated that the outcome of schizophrenia is poorer in male than in female patients (11-12). Compared to women, men tend to show a higher incidence of the disorder, an earlier age of onset, poorer premorbid adjustment, worse psychosocial

functioning and a more severe course of the disease (12). Specifically, although not all the studies found differences, most of them found that regarding negative symptomatology, men have shown higher propensity to present these symptoms, especially in social withdrawal and blunted or incongruent affects than female patients, who presented more affective symptoms (13), and in alogia and avolition-apathy (14).

The aims of the present study were 1) To explore sex differences among first-episode schizophrenia patients through one year follow-up focusing on different outcome measures as clinical, with a special focus on negative symptom dimensions, and psychosocial functioning, and 2) To analyze clinical predictors of negative dimensions and functional outcome, that is, motivation, pleasure, and expression.

2. Material and Methods

2.1. Sample

The sample of this study has been recruited though the "2EPs Project". It is a multicenter, coordinated, naturalistic, and longitudinal follow-up study of three years' duration. "2EPs" included Spanish patients who met diagnosis of schizophrenia or schizophreniform disorder with a first psychotic episode with less than five years of evolution. All the information about the methodology of the "2EPs Project" can be found elsewhere (15) .

The inclusion criteria were: 1) aged between 16 to 40 years at the first evaluation; 2) met diagnostic criteria according to DSM-IV for schizophrenia or schizophreniform disorder; 3) ability to speak Spanish correctly; 4) signed informed consent; 5) have presented a first episode psychosis (FEP) in the last 5 years and are currently in remission according to Andreasen's criteria (3). According to this criteria, remission is achieved when the patient's Positive and Negative Symptom Scale (PANSS) score is 3 or less ("mild" or better) in 8 items, as representative of an impairment level consistent with symptomatic remission of illness. There is also a minimum period of six months in which the symptoms severity must be maintained and the patient must not have relapsed after the episode. The exclusion criteria were: 1) having experienced a brain trauma with loss of consciousness; 2) an Intelligence Quotient (IQ) lower than 70 and with significant difficulties or malfunctioning with adaptive processes; and 3) somatic pathology with mental affectation.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethics committees of all participating centers approved the current study. Each subject agreed to participate and signed the informed consent before their inclusion.

2.2. Assessments

At baseline, patients performed a complete evaluation that included: structured interviews, clinical scales and premorbid adjustment scales. Clinical and functional scales were also administered every three months for three years. In case of relapse, a visit was performed and the subject's participation in the study was terminated. For the current study, baseline, 6 months and one-year follow-up data was used (because a high percentage of subjects were lost to follow-up).

Sociodemographic, clinical and substance use assessment

Sex, age and age at the onset of the illness were collected along with the duration of the untreated psychosis (DUP). DUP was calculated as the number of days between the first manifestations of psychotic symptoms and the initiation of adequate treatment for psychosis. Parental socioeconomic status (SES) was determined using Hollingshead's Two-Factor Index of Social Position (16). The diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) (SCID-I and II) (17) or the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (18) according to DSM-IV criteria. The participants at baseline were asked to report personal and family history of psychiatric disorders, namely affective and psychotic disorders. A psychopathological assessment was carried out with the Spanish versions of the following scales: maniac and depressive symptom severities were assessed using the Young Mania Rating Scale (YMRS) (19) and the Montgomery-Asberg Depression Rating Scale (MADRS) (20), respectively; and positive, negative, and general symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (21). On each scale, the items were summed to obtain a total score. Higher scores indicate greater severity.

Although the PANSS is one of the most widely used measures of negative symptom severity, it has been well-demonstrated that it has several limitations; for instance, it was not designed to evaluate negative symptoms exclusively. Thus, we have also used the PANSS-Marder Factor Scores (22) as it has more restrictive criteria to assess positive and negative symptomatology. The sum of the following items of the PANSS were used to calculate the Positive Symptom Factor (PSF): delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), stereotyped thinking (N7), somatic concerns (G1), unusual thought content (G9) and lack of judgment and insight (G12); and for the Negative Symptom Factor (NSF): blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity and conversation flow (N6), motor retardation (G7) and active social avoidance (G16). This structure has proved to be beneficial to obtain more specific information (23).

As previously commented, the literature revealed the existence of two factors: EXP (Diminished expression) and MAP (amotivation and pleasure) (9, 24). Following a previous work which used the PANSS (24), EXP factor was calculated as the sum of the following items of the PANSS: blunted affect (N1), poor rapport (N3), lack of spontaneity and conversation flow (N6) and motor retardation (G7), and MAP factor with emotional withdrawal (N2), passive/apathetic social withdrawal (N4) and active social avoidance (G16)(24).

Antipsychotic mean doses were collected and converted to chlorpromazine equivalents (CPZ) based on international consensus (25). Drug abuse was assessed using the adaptation of the multidimensional assessment tool European Addiction Severity Index (EuropAsi)(26).

Functional assessment

The overall functional outcome was assessed by the Functioning Assessment Short Test (FAST) (27) and the Global Assessment of Functioning Scale (GAF)(28). Higher scores of FAST indicate greater disability, while higher scores on GAF correspond to better functioning.

Premorbid adjustment and cognitive reserve

Premorbid adjustment, namely levels of functioning before the onset of psychosis, was assessed with The Premorbid Adjustment Scale (PAS)(29). The scale considers different life stages: childhood, early adolescence, late adolescence, and adulthood. Only childhood and early adolescence life periods have been taken into account since they were the two time periods for which the answers of all the participants were available. Higher scores indicate worse premorbid adjustment.

To assess cognitive reserve (CR) the three most commonly proposed proxy indicators of CR have been used (30): 1. The estimated premorbid IQ was calculated with the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III)(31). 2. Education was assessed taking into account the degree of schooling attained and passed by the subject; 3. Lifetime participation in leisure, social and physical activities was assessed with the PAS scale (scholastic performance) and the FAST scale, which allows us to assess specific life-domains such as interpersonal relationships and leisure time. When patients were assessed, they had already experienced a FES. For that reason, we could only estimate premorbid variables. To summarize the information of the three main proxies of CR, a Principal Components Analysis (PCA) was performed to create a "Composite CR score" for each subject. Higher scores correspond to better performance.

2.3. Data Analysis

Demographic, clinical and functional sex differences were examined using unpaired t-tests and chi-square. A repeated measures ANOVA was used to examine the effects of time and sex on negative symptoms. To explore which variables could predict MAP, EXP or functioning at one-year follow-up three steps were undertaken: (1) Candidate exploratory variables were selected carefully taking into account their possible role in the prediction of negative symptom severity (focusing on total scores and on MAP and EXP factors separately) and functioning (GAF) at one-year follow-up. The potential predictors were: age, DUP, age at psychosis onset, socioeconomic status, personal and family psychiatric history, total scores of the PAS, cognitive reserve, Marder PANSS positive factor score (PSF), depressive symptoms (MADRS), psychosocial functioning (FAST), antipsychotic medication treatment, and alcohol, cannabis and/or tobacco consumption at baseline and lifetime cannabis use (all these variables from the baseline visit); (2) General Linear Model (GLM) Univariate Analysis was performed to explore whether predictors differ between sexes (interaction term between sex and each potential predictors); and (3) To explore which of these factors could predict general negative symptom severity and functioning at follow-up, significant predictors were included in a multiple linear regression model with backward elimination.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v25). All statistical tests were carried out two-tailed, with an alpha level of significance set at $p \leq 0.05$.

3. Results

3.1. Sociodemographic, clinical and functional characteristics of the sample and sex differences

Of the 223 FEP patients participating in the study, 31.8% (n=71) were females and 68.2% (n=152) were males. Mean age of onset was 26.77±6.15 years for female and 25.55±5.96 for male

(p=0.160). The mean DUP time was 196.95 days (28 weeks approximately), without differences between females and males. Baseline sex differences in sociodemographic, clinical and functional characteristics are shown in **Table 1**. More males reported tobacco (p=0.014) and cannabis (p=0.003) use than females. Females showed a significantly lower severity of general and total symptoms according to the PANSS (p=0.049 and p=0.039), better premorbid adjustment (p=0.003) and greater functionality measured by the FAST scale (p=0.002), but not by the GAF (p=0.322). Women also showed fewer general negative symptoms than men, as measured by NSF (p=0.031, Cohen's d=-0.312; 95% CI=[-0.595, -0.029]), while there was only a tendency to signification in negative symptoms measured by the PANSS negative subscale (p=0.058). Finally, regarding dimensions specific to negative symptoms, females showed significantly less expressivity impairment (such as blunted affect or alogia) than males (p=0.024; Cohen's d=-0.326; 95% CI=[-0.610, -0.043]), without differences in motivation and pleasure disablement (e.g. anhedonia, avolition or asociality) (p=0.086). There were no differences between sex groups in terms of age, SES, age of onset, alcohol use, positive, manic and depressive symptoms, cognitive reserve and chlorpromazine equivalents.

[Please insert table 1 here]

Those patients who were assessed at follow-up (n=120) were indistinguishable from those who were not (n=103) in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF (p=0.045, Cohen's d=0.275; 95% CI=[0.025, -2.064]), but not when they were measured by the PANSS positive subscale (p= 0.108). For more details, see **Supplementary Table 1**.

3.2. Sex differences in negative symptoms course

Of the 71 females assessed at baseline, 51 were assessed at 6 months and 45 at one-year follow-up. 152 males were assessed at baseline, 101 at 6 months and 75 at one-year follow-up. The repeated measures ANOVA results indicate that the mean scores for negative symptoms were significantly different across time points for PANSS ($p<0.001$, $\eta_p^2=0.118$), NSF ($p<0.001$, $\eta_p^2=0.140$), EXP ($p<0.001$, $\eta_p^2=0.117$) and MAP ($p<0.001$, $\eta_p^2=0.118$), with follow-up scores being significantly lower than baseline (see **Table 2**). However, no significant interaction of time and sex was found. Thus, there were significant time effects on all variables, indicating an improvement for both sexes, with no difference between them.

[Please insert table 2 here]

3.3. Predictors of amotivation and pleasure (MAP) and diminished expression (EXP) at one-year follow-up differentiating between females and males

The baseline predictors of EXP at one-year follow-up with an interaction by sex were: family psychiatric history, PAS, PSF, MADRS, FAST and alcohol consumption (see **Supplementary Table 2** for more details). The predictors of MAP were PSF, MADRS, FAST, tobacco use and alcohol consumption.

Predictors of EXP and MAP in females and males are shown in **Table 3.** Regarding females, premorbid adjustment (t=2.679, p=0.011), and depressive symptoms (t=2.926, p=0.006) at baseline made a significant contribution to the presence of higher deficits in expressivity at one-year follow-up (F=17.499, $R^2=0.593$, $p<0.001$). Positive (t=2.426, p=0.020) and depressive

(t=2.205, p=0.033) symptoms predicted deficits in motivation and pleasure at one-year follow-up (F=9.056, R^2=0.317, p=0.001). In males, worse premorbid adjustment (t= 3.498, p=0.001), and higher depressive symptoms (t=3.113, p=0.003) at baseline predicted higher deficits in expression at one-year follow-up (F=13.544, R^2=0.288, p<0.001). Finally, positive (t=2.254, p=0.027) and depressive (t=4.218, p<0.001) symptoms and alcohol consumption (t= -2.363, p=0.021) at baseline predicted greater amotivation at one-year follow-up (F=15.438, R^2=0.398, p<0.001).

[Please insert table 3 here]

3.4. Predictors of functioning

The predictors of functioning at follow-up (GAF) that differed between the sexes with interaction terms were premorbid adjustment (F=2.066, p=0.010, η_p^2=0.820) and MAP (F= 2.443, p=0.003, η_p^2=0.303)(see **Supplementary Table 3** for more details). The regression model (see **Table 4**) showed that lower MAP (t=-3.941, p<0.001) and better premorbid adjustment (t=-2.165, p=0.037) predicted better functioning in females at one-year follow-up (F=19.054, R^2=0.494, p<0.001). Regarding males, the strongest predictor has proven to be the amotivation; higher deficits in motivation and pleasure (t=-2.577, p=0.012) predicted worse functioning (F=6.639, R^2=0.088, p=0.012).

[Please insert table 4 here]

4. Discussion

Four findings emerged from the present study. Firstly, females showed lesser negative symptoms, especially those related to expressiveness rather than amotivation, a better premorbid adjustment and better psychosocial functioning than males. Secondly, there were clinically relevant improvements in negative symptoms in both groups through the first year after inclusion. Thirdly, in both male and female group, worse premorbid adjustment (PAS) and higher depressive symptoms made a significant contribution to the presence of higher deficits in expression at one-year follow-up, while positive and depressive symptoms predicted alterations in motivation and pleasure. In males, alcohol consumption also predicted deficits in motivation and pleasure at one-year follow-up. Finally, in females, lower deficits in motivation and pleasure and better premorbid adjustment predicted better functioning at one-year follow-up, while only higher deficits in motivation and pleasure predicted worse functioning in males.

Our results suggest that males showed more general negative symptoms than women measured by NSF but there was only a tendency to signification when measured by the PANSS subscale. Although PANSS is a widely used instrument for measuring symptomatology in patients with schizophrenia, it seems that Marder's factor (NSF) has several aspects of improved content validity in comparison to the original negative PANSS subscale (6, 22). Factor analytic studies in PANSS found that two items (difficulty in abstract thinking (N5) and stereotyped thinking (N7)) should no longer be considered part of the negative symptom domain (32-33). In addition, females showed less expressivity impairment than males (such as flat affect), without differences in motivation and pleasure severity (i.e., anhedonia, avolition or

asociality) between both groups. These results are in accordance with previous literature (34). Moreover, as expected, in the present study females showed a better premorbid adjustment and greater functionality, which is also in accordance with previous studies (12, 14). Finally, although sex differences in age of onset is a replicated finding in the literature (35-36), in our study no significant differences were found in this regard. There are other studies that found no gender differences in age of onset (37). It has been hypothesised that differences in age of onset could depend on the presence or absence of family history (12,38). In addition, it should be noted that this study does not have balanced samples.

The obtained results suggest that regardless of sex, patients showed a reduction in the severity of negative symptomatology at one-year follow-up. According to our results, a meta-analysis revealed that negative symptoms decrease in almost all patients (39). Moreover, a previous study of our group found a reduction in the negative symptomatology one year after a FEP and that this change remained stable at two years (6). Thus, it seems that negative symptoms tend to be stable and persistent in the long-term, but can fluctuate in severity (40) and can even improve in the early stages.

As negative symptoms are not a homogeneous construct, when comparing the predictors of MAP and EXP between males and females, we found that, regardless of sex, premorbid adjustment seems to be a good predictor of EXP, which is in accordance with previous research that has shown a strong association between premorbid adjustment and the course of negative symptoms (6, 41). Moreover, in males, positive and depressive symptoms were predictors of greater amotivation (42). Regarding the predictors, in both groups premorbid adjustment and depressive symptoms at baseline made a significant contribution to the presence of higher deficits in the area of expressiveness, while positive and depressive symptoms predicted alterations in motivation and pleasure. Thus, these results could suggest that implementing early and personalized interventions at the onset of the illness, that is, after a first-episode, tailored to individual needs and paying special attention to the clinical and functional features that have been related to severe outcomes may help in their prognosis. However, further studies are required to confirm these findings. Briefly, early interventions will differ in terms of the target, independently of sex. Our results suggests that in those patients with worse premorbid adjustment and depressive symptoms, interventions should be oriented toward improving self-reflectivity, linguistic cohesion, and cognitive symptoms (43). Meanwhile, in those patients with positive and depressive symptoms, interventions oriented to increase cognitive control of positive emotions, as the Positive Emotions Programme for Schizophrenia (PEPS), could be suggested (44). The latter it is a programme designed to improve pleasure and motivation in schizophrenia patients by targeting emotion regulation and cognitive skills relevant to apathy and anhedonia (44). In general, without taking sex or MAP/EXP into account, poor premorbid adjustment in the early illness stage predict negative symptom severity at follow-up (6). Thus, assessing premorbid adjustment and early interventions focused on treating negative symptoms is of paramount importance (38). Moreover, our study suggests that depressive symptoms should also be considered.

Finally, regarding psychosocial outcome prediction, in accordance with the literature, lower negative symptoms (6) and premorbid adjustment predicted better functioning at one-year follow-up. It is well-known that negative symptoms account for a large part of long-term

disability and poor functional outcomes. However, the study of the impact of negative symptom factors, taken as a multimodal construct, on functional outcome is of special interest. Our results showed that MAP could predict psychosocial functioning, but EXP could not, suggesting that symptoms such as anhedonia, avolition and asociality should be prioritized in assessment and focused on when developing early interventions targeting psychosocial functioning in FEP.

This study has certain limitations which must be taken into account. Firstly, no specific scale was used to assess negative symptomatology, due to constraints associated with the PANSS scale. Although it is one of the most widely used measures of negative symptom severity, we acknowledge that it has several limitations. Firstly, the PANSS scale was not designed to evaluate negative symptoms exclusively. Rather, it is a comprehensive scale for the assessment of psychopathology. Secondly, the PANSS can measure the two-correlated factor, but it was not designed for this purpose either. Thirdly, it does not evaluate the anhedonia symptom. Future studies making use of newer and improved negative symptom scales may be more appropriate for the evaluation of negative symptoms, such as anhedonia and avolition, because they capture both manifestations of the symptom, internal motivation and real world behavior. Also, due to a high percentage of patients discontinued the study before the follow-up visit (particularly due to they refused the re-evaluation), this resulted in a small sample size of women's group. Because of this, some aspects should have been considered with caution in order to extrapolate the present findings. Nevertheless, we analysed the differences between patients who were assessed at follow-up and those who were only assessed at baseline and we found that they did not differ in terms of sex, sociodemographic, clinical and functional characteristics, except for positive symptoms measured by PSF. Finally, a limitation present in all CR studies undertaken on a psychiatric population is that as there is not yet a valid instrument to measure CR, criteria established and replicated in previous studies were followed. Finally, another potential limitation of the study is the short follow-up period and the small and unbalanced sample size. However, it is a naturalistic and multicentric study with a representative sample of FES patients in a stable clinical phase recruited from the whole Spanish territory. Furthermore, the sample is very well characterized because it includes different variables of interest.

In conclusion, clinical phenotypes in FES and its predictors can vary slightly by sex. However, our study suggest that there are no differential needs between men and women nor sex-specific personalized therapeutic strategies focused on NS. Our results lead us to consider that early interventions of negative symptoms, especially those focusing on motivation and pleasure symptoms, could improve functional outcomes. Due to the fact that the negative dimension constitutes one of the most impairing aspects of schizophrenia, and since treatments for this symptomatology have had limited success to date, it might be worthy of further investigation. A greater understanding of its impact on the functional outcome will help to change this situation, giving way to the design of longitudinal studies that focus on negative symptoms from a multidimensional approach.

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Table

Table 1. Sex differences in sociodemographic, clinical and functional characteristics at baseline

	Female (n=71)	Male (n=152)	t / χ^2	Sig.	Cohen's d or Cramer's V	95% CI
Age	26.77±6.15	25.55±5.96	1.411	0.160	0.203	[-0.080, 0.485]
Socioeconomic status (%)			3.639	0.602	0.128	
High	6 (8.5)	8 (5.3)				
Medium-High	4 (5.6)	8 (5.3)				
Medium	7 (9.9)	13 (8.6)				
Medium-Low	22 (31)	45 (29.6)				
Low	31 (43.7)	78 (51.3)				
Missing value	1 (1.4)	0 (0)				
Tobacco: Yes, N (%)	29 (41)	87 (58)	5.444	**0.014**		OR=1.969 [1.110, 3.491]
Cannabis: Yes, N (%)	5 (7)	33 (22)	7.679	**0.003**		OR=3.755 [1.398, 10.085]
Alcohol: Yes, N (%)	32 (45)	70 (46)	0.032	0.487		OR=1.053 [0.598, 1.856]
DUP (days)	183.23±396.29	199.58±367.54	-0.292	0.771	-0.043	[-0.325, 0.238]
Age of onset	25.58±6.00	24.10±5.63	1.708	0.089	0.257	[-0.025, 0.540]
Cognitive reserve	61.96±7.05	60.32±9.73	1.204	0.231	0.183	[-0.099, 0.465]
PAS	40.03±18.30	49.22±22.06	-2.993	**0.003**	-0.439	[-0.724, -0.154]
PANSS positive	9.03±2.90	9.55±2.94	-1.246	0.214	-0.178	[-0.460, 0.105]
PANSS negative	12.69±5.16	14.07±5.00	-1.905	0.058	-0.273	[-0.556, 0.010]
PANSS general	22.99±6.26	24.96±7.23	-1.980	**0.049**	-0.284	[-0.567, -0.001]
PANSS total	44.70±12.64	48.59±13.15	-2.079	**0.039**	-0.300	[-0.583, -0.016]
PSF	11.08±3.77	12.03±3.80	-1.742	0.083	-0.251	[-0.533, 0.032]
NSF	12.58±5.36	14.24±5.31	-2.177	**0.031**	-0.312	[-0.595, -0.029]
EXP	7.03±3.12	8.05±3.13	-2.279	**0.024**	-0.326	[-0.610, -0.043]
MAP	5.55±2.54	6.19±2.61	-1.725	0.086	-0.247	[-0.530, 0.035]
YMRS score	0.72±1.99	1.20±2.14	-1.615	0.108	-0.229	[-0.512, 0.053]
MADRS score	5.52±5.33	6.93±6.46	-1.598	0.111	-0.230	[-0.513, 0.052]
Chlorpromazine equivalents	228.73±238.15	302.96±291.74	-1.872	0.063	-0.269	[-0.552, 0.014]
GAF	71.04±12.59	69.05±14.35	0.992	0.322	0.144	[-0.138, 0.426]
FAST	19.01±13.20	26.05±18.30	-2.850	**0.002**	-0.418	[-0.702, -0.133]

Abbreviations: DUP= Duration of Untreated Psychosis; PAS= Premorbid Adjustment Scale; PANSS= Positive and Negative Symptom Scale; PSF= Positive Symptoms Factor of the PANSS; NSF= Negative Symptoms Factor of the PANSS; EXP= Diminished expression; MAP= Amotivation and pleasure; YMRS= Young Mania Rating Scale; MADRS= Montgomery-Asberg Depression Rating Scale; GAF= Global Assessment of Functioning; FAST=Functioning Assessment Short Test. Significant differences ($p<0.05$) marked in bold.

Table 2. Sex differences in negative symptoms course

Negative symptoms	**Negative PANSS**			**Negative Symptoms Factor of the PANSS (NSF)**			**Diminished expression (EXP)**			**Amotivation and pleasure (MAP)**		
Time	**Baseline**	**6 months**	**1 year**	**Baseline**	**6 months**	**1 year**	**Baseline**	**6 months**	**1 year**	**Baseline**	**6 months**	**1 year**
Female	12.69±5.16	11.20±4.40	10.64±4.29	12.58±5.36	11.10±4.54	10.69±4.52	7.03±3.12	6.45±2.80	6.02±2.71	5.55±2.54	4.65±2.12	4.67±2.20
Male	14.07±5.00	13.10±4.73	12.42±4.88	14.24±5.31	13.12±4.91	12.55±5.15	8.05±3.13	7.49±3.07	7.05±3.07	6.19±2.61	5.63±2.16	5.50±2.37
t	-1.905	-2.398	-2.020	-2.177	-2.457	-2.011	-2.279	-2.031	-1.861	-1.725	-2.660	-1.921
Cohen's d	-0.273	-0.411	-0.381	-0.312	-0.422	-0.378	-0.326	-0.349	-0.350	-0.247	-0.457	-0.360
95% CI	[-0.556, 0.010]	[-0.751, -0.071]	[-0.753, -0.009]	[-0.595, -0.029]	[-0.762, -0.082]	[-0.749, -0.006]	[-0.610, -0.043]	[-0.688, -0.010]	[-0.721, 0.021]	[-0.530, 0.035]	[-0.797, -0.116]	[-0.731, 0.012]
Sig.	0.058	**0.018**	**0.046**	**0.031**	**0.015**	**0.047**	**0.024**	**0.044**	0.065	0.086	**0.009**	0.057
Within-Subjects Effects	Time (F=9.707, p<**0.001**), PANSS*Sex (F=0.336, p=0.715)			Time (F=11.743, p<**0.001**), NSF*Sex (F0.062, p=0.940)			Time (F=7.973, p<**0.001**), EXP*Sex (F=0.213, p=0.808)			Time (F=10.045, p<**0.001**), MAP*Sex (F=0.787, p=0.456)		
Between-Subjects Effect	F=3.966, p=**0.049**			F=4.367, p=**0.039**			F=4.208, p=**0.043**			F=3.736, p=0.056		

Abbreviations: PANSS= Positive and Negative Symptom Scale. Significant differences (p<0.05) marked in bold.

Table 3. Linear regression models for predictors of Motivation and Pleasure and Diminished expression at one-year follow-up in females and males

		Model	Beta	t	Sig.	R	R^2	Adjusted R^2	SEE	F	Sig.	Cohen's f^2
Females	Amotivation and Pleasure	(Constant)		1.091	0.282	0.563	0.317	0.282	1.807	9.056	**0.001**	0.464
		PSF	0.352	2.426	**0.020**							
		MADRS	0.320	2.205	**0.033**							
	Diminished expression	(Constant)		0.544	0.590	0.770	0.593	0.559	1.819	17.499	**<0.001**	1.457
		PAS	0.345	2.679	**0.011**							
		PSF	0.205	1.720	0.094							
		MADRS	0.400	2.926	**0.006**							
Males	Amotivation and Pleasure	(Constant)		4.027	<0.001	0.631	0.398	0.372	1.883	15.438	**<0.001**	0.661
		PSF	0.221	2.254	**0.027**							
		MADRS	0.418	4.218	**<0.001**							
		Alcohol	-0.228	-2.363	**0.021**							
	Diminished expression	(Constant)		4.341	<0.001	0.537	0.288	0.267	2.582	13.544	**<0.001**	0.404
		PAS	0.367	3.498	**0.001**							
		MADRS	0.327	3.113	**0.003**							

Abbreviations: SEE= standard errors of the estimates; PAS=Premorbid Adjustment Scale; PSF= Positive Symptoms Factor of the Positive and Negative Symptom Scale; MADRS= Montgomery-Asberg Depression Rating Scale. Significant differences ($p<0.05$) marked in bold.

Table 4. Linear regression models for predictors of functioning at one-year follow-up in females and males

	Model	Beta	t	Sig.	R	R^2	Adjusted R^2	SEE	F	Sig.	Cohen's f^2
Females	(Constant)		27.147	<0.001	0.703	0.494	0.468	8.910	19.054	**<0.001**	0.976
	MAP	-0.517	-3.941	**<0.001**							
	PAS	-0.284	-2.165	**0.037**							
Males	(Constant)		18.039	<0.001	0.296	0.088	0.075	15.171	6.639	**0.012**	0.096
	MAP	-0.296	-2.577	**0.012**							

Abbreviations: SEE= standard errors of the estimates; MAP= Amotivation and pleasure; PAS=Premorbid Adjustment Scale; MADRS= Montgomery-Asberg Depression Rating Scale. Significant differences ($p<0.05$) marked in bold.

Ética de la publicación

1. **¿Su trabajo ha comportado experimentación en animales?:**
   No
2. **¿En su trabajo intervienen pacientes o sujetos humanos?:**
   Sí

   Si la respuesta es afirmativa, por favor, mencione el comité ético que aprobó la investigación:

   This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethics committees of all participating centers approved the current study. Each subject agreed to participate and signed the informed consent before their inclusion.

   Si la respuesta es afirmativa, por favor, confirme que los autores han cumplido las normas éticas relevantes para la publicación. :
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