Exploring the relationship between suicidality and persistent negative symptoms following a first episode of psychosis

Running title: suicidality and persistent negative symptoms

Joseph Ghanem, BA[a,b]

Massimiliano Orri, PhD[a,c]

Laura Moro, BA[a,e]

Katie M. Lavigne, PhD[a,c,f]

Delphine Raucher-Chéné, MD, PhD[a,c]

Ashok Malla, MBBS; FRCPC[a,c,d]

Ridha Joober, MD, PhD[a,c,d],

Martin Lepage, PhD[a,b,c,d].

[a]Douglas Mental Health University Institute, McGill University, Montreal, Canada

[b]Department of Psychology, McGill University, Montreal, Canada

[c]Department of Psychiatry, McGill University, Montreal, Canada

[d]Prevention and Early Intervention Program for Psychosis, Douglas Mental Health University Institute, Montreal, Canada.

[e]Department of Psychology, Université de Montreal, Montreal, Canada

[f] McGill Centre for Integrative Neuroscience, Montreal Neurological Institute, McGill University, Montreal, Canada

Corresponding author:

Martin Lepage, PhD

Douglas Mental Health University Institute

Frank B Common Pavilion, F1143, 6875 LaSalle Blvd., Verdun, Quebec, H4H 1R3, CANADA

Tel.: (514) 761-6131 ext. 4393

Fax: (514) 888-4064

Email address: martin.lepage@mcgill.ca

Abstract word count: 229

Text body word count: 3185

Word count (text body, figure legends, and acknowledgments): 3496

Abstract

Background and Hypothesis

Suicide is a leading cause of death in first-episode psychosis (FEP), with an elevated risk during the first year following illness onset. The association between negative symptoms and suicidality remains contentious. Some studies suggest that negative symptoms may be associated with lower suicidality, while others fail to find an association between the two. No previous studies have specifically investigated suicidality in Persistent Negative Symptoms (PNS) and its associated subgroups.

Study Design

In a large cohort of FEP patients (N=515) from an early intervention service, we investigated suicidality in those with PNS, secondary PNS (i.e., sPNS; PNS with clinical-level positive, depressive, or extrapyramidal symptoms), and non-PNS (all other patients) over 24 months. Patients were categorized into PNS groups based on symptoms from month 6 to month 12, and suicidality was evaluated using the Brief Psychiatric Rating Scale (BPRS).

Study Results

Covarying for age and sex, we found that sPNS had higher suicidality relative to PNS and non-PNS throughout the 24-month period, but PNS and non-PNS did not differ. These differences were maintained after adjusting for depressive symptoms.

Conclusion

We observed that PNS did not significantly differ from non-PNS. However, we identified sPNS as a group with elevated suicidality above and beyond depression, suggesting that sPNS would benefit from targeted intervention and that PNS categorization identifies a subgroup for whom negative symptoms are not associated with lower suicidality.

Keywords: suicide; first episode psychosis; idiopathic negative symptoms; secondary negative symptoms

1. Introduction

Suicide is a leading cause of death in people with psychotic disorders, contributing significantly to the well-noted 20-year reduction in life expectancy[1-3]. The highest rates of suicide in FEP occur during the first year following illness onset and treatment initiation[4, 5], with depressive symptoms, a history of suicidal behavior, male sex, substance use, psychotic symptom severity, family history of suicide, living alone, and previous hospitalizations emerging as risk factors[1, 6-8]. Despite an understanding of risk factors for suicidality, preventing suicide in individuals with psychosis remains challenging. Therefore, identifying FEP subgroups at high risk for suicide is needed for proper assessment and targeted intervention.

Among previously studied risk factors in FEP and schizophrenia, negative symptoms (e.g., avolition, anhedonia) show an interesting association with suicidality. For instance, some suggest an inverse relationship between negative symptom severity and suicidality[4, 6, 7, 9, 10]. Grover and colleagues[9] observed a significant decrease in suicidal ideation and attempt for each additional negative symptom endorsed, whereas Huang et al.[10] found negative symptoms to be associated with lower rates of death by suicide. Potential explanations for this finding are a reduced motivation to plan for suicide, lower emotional expressivity, and a reduced desire for social interaction[9, 10]. However, while many studies pointed toward this seemingly protective role, other FEP studies found no association between suicidality and negative symptoms[11, 12]. In addition, anhedonia has shown a significant association to negative symptoms[13] and a positive relationship with suicidal ideation in FEP, both at baseline and 2 years later[14]. Interestingly, this association was maintained after adjusting for depressive symptoms.

The relationship between negative symptoms and suicidality thus remains inconclusive. One explanation may be that broader negative symptom subgroups have been overlooked in relationship to suicidality in previous studies. Therefore, a potentially novel way of evaluating this association is to classify negative symptoms into etiologically driven subgroups. Our current knowledge is limited to research on deficit schizophrenia – a syndrome characterized by a minimum of two primary negative symptoms that

persist for 12 months[15, 16] – that observed lower suicidality relative to nondeficit schizophrenia[17]. Similarly, only one study investigating general clinical correlates of Persistent Negative Symptoms (PNS) observed a lower rate of suicide attempts in PNS compared to those without PNS (non-PNS) but in an early-onset psychosis cohort[18].

PNS is characterized by an enduring pattern of negative symptoms that are idiopathic (i.e., primary), persistent for a minimum of 6 months, clinically significant, and independent of secondary symptoms such as positive, depressive, or extrapyramidal symptoms[19]. These secondary symptoms confound the classification of PNS and can help define secondary persistent negative symptoms (sPNS) — a subgroup obscured in previous FEP studies by being lumped with non-PNS or other negative symptom subgroups[20, 21]. sPNS can therefore emerge because of other symptoms (i.e., positive, extrapyramidal) or as part of a depressive syndrome. Consistent with their putatively differing etiologies, sPNS can remit following treatment that improves secondary symptoms, while PNS does not respond to typical pharmacological treatments[22]. Since Buchanan's[19] initial conceptualization, patients with PNS have been shown to display greater verbal and working memory deficits[23], poorer insight[24], worse psychosocial functioning[25], and longer duration of untreated psychosis (DUP)[18] compared to non-PNS.

Because of the elevated suicidality observed early in the course of illness and beginning of treatment, properly identifying subgroups most at risk is crucial for assessment, intervention, and treatment. Thus, using a systematic and comprehensive longitudinal assessment protocol in a large cohort of FEP patients who received early intervention services, we categorized individuals into PNS, sPNS, and non-PNS from month 6 to month 12 after treatment initiation and examined suicidality during the 2 years of treatment in these three different subgroups. Consistent with the literature on the association between elevated negative symptoms and lower suicidality, we hypothesized that (1) PNS patients would have lower suicidality than sPNS and non-PNS patients. Moreover, because of the secondary nature of the negative symptoms in sPNS, we hypothesized that (2) sPNS patients would have higher suicidality

compared to PNS and non-PNS patients. In an exploratory approach, we later controlled for depression to evaluate whether the elevated suicidality in sPNS is independent of depressive symptoms.

2. Methods

2.1 Participants and Setting

Patients admitted to the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal) between 2003 and 2018 and for whom sufficient data was available for PNS classification were included in the study (N=515). Located at the Douglas Mental Health University Institute and established in 2003 within a catchment area of 300,000 individuals in southwest Montreal[26], PEPP is the only early intervention program in this area. As part of their routine evaluation, patients were systematically assessed at different time points throughout their two years at PEPP. Trained research assistants administered comprehensive evaluations at baseline, month 2, month 3, month 6, month 9, month 12, month 18, and month 24. Inclusion criteria for admission to PEPP are experiencing a first episode of psychosis, being aged 14 to 35, having less than 30 days of antipsychotic exposure, and being French- or English-speaking. Exclusion criteria are an IQ below 70, psychosis that is solely substance-induced, organic brain damage, or a primary neurodevelopmental disorder.

All participants were informed of the purpose of the study and provided written consent for their participation. They could withdraw at any time from involvement in research without treatment-related repercussions. Protocols were approved by the Douglas Mental Health University Institute's Research Ethics Board.

2.2 Measures

Positive and negative symptoms were evaluated using the Scale for the Assessment of Positive Symptoms (SAPS)[27] and the Scale for the Assessment of Negative Symptoms (SANS)[28], respectively. Depression was measured with the Calgary Depression Scale for Schizophrenia (CDSS)[29] and the Brief Psychiatric Rating

Scale (BPRS)[30]. DUP was evaluated using the Circumstances of Onset and Relapse Schedule (CORS)[31], and diagnosis at admission was established with the Structured Clinical Interview for the DSM-IV-TR (SCID)[32] and updated at month 12. IQ was measured with the Weschler Abbreviated Scale of Intelligence (WASI)[33] and years of education were recorded. The dose of antipsychotic medication was recorded and converted to its chlorpromazine equivalent (CPZ)[34] at each timepoint. Measures of psychopathology (i.e., SAPS, SANS, CDSS, BPRS) were repeated at every time point.

2.2.1 Suicidality

Suicidality was assessed using the BPRS suicidality item, rated on a 7-point Likert scale. A rating of 1 (not present) indicates the absence of suicidality, and a rating of 2 (very mild) indicates "occasional feelings of being tired of living" with no evident suicidal ideation. A rating of 3 (mild) is defined as "occasional suicidal thoughts without intent or plan" and denotes some level of suicidality. A rating of 4 (moderate) is characterized by frequent thoughts of suicide with no intent or plan. A rating of 5 (moderately severe) may indicate the presence of a plan or a low-lethality attempt. Ratings of 6 (severe) or 7 (extremely severe) indicate the clear presence of intent and a plan or a suicide attempt with lethal means. Similar to Iyer et al.[35], the full range of BPRS suicidality scores was used in the analyses as the outcome. To Include depression as a covariate, we averaged BPRS depression scores during the first year using ratings from baseline, month 3, month 6, month 9, and month 12.

2.3 Classifying Persistent Negative Symptoms

Consistent with our earlier work[23, 24, 36-41], patients were classified as having PNS if they presented with a global rating of moderate or higher (3 or more out of 5) on one or more negative symptom dimensions of the SANS, but a global rating of mild or lower (2 or less out of 5) on positive symptom dimensions evaluated on the SAPS. They additionally required a global score of 4 or lower on the CDSS (out of 27) and

no or mild extrapyramidal symptoms as measured by the Extrapyramidal Symptom Rating Scale (ESRS)[42]. Patients scoring moderate or higher on one or more negative symptom dimensions of the SANS but presenting clinically significant positive, depressive, or extrapyramidal symptoms were classified as sPNS. Importantly, for both PNS and sPNS, the symptoms characterizing their group had to persist for 6 months, specifically from month 6 to month 12, after admission to PEPP. The rest of the patients were classified as non-PNS.

2.4 Statistical Analyses

As appropriate, the sociodemographic and clinical characteristics of PNS groups were compared using Kruskal-Wallis, chi-square tests, or one-way ANOVAs, and pairwise comparisons were Bonferroni adjusted. To compare suicidality between PNS groups and over the 24-month period, a linear mixed-effects model was conducted with PNS group membership and time as fixed effects, as well as their interaction, covarying for age and sex. Subsequently, a BPRS depression score averaged over the first year was added as an additional covariate to control for the influence of depressive symptoms on suicidality. Missing data was handled by the model using restricted maximum likelihood. Post-hoc comparison tests were Bonferroni corrected and considered significant at the .05/3= .017 significance level. SPSS version 29 was used for descriptive statistics, and R version 4.2.2 was used for the linear mixed-effects model.

3. Results

3.1 Clinical and Demographic Characteristics

The demographic and clinical characteristics of the sample are presented in **Table 1**. The sample of 515 consisted of PNS (n=135), sPNS (n=98), and non-PNS (n=282) patients. The sPNS patients were classified based on positive symptoms (n=54), depressive symptoms (n=21), extrapyramidal symptoms (n=7), positive and depressive symptoms (n=13), and positive and extrapyramidal symptoms (n=3). The sample

was 68% male (n=350) and 32% female (n=165), the average age of onset of psychosis was 22.74 years (SD=4.81), and diagnoses of non-affective psychosis were most prevalent (n= 366, 71.1%).

PNS had an earlier age of onset (p=.02), a higher proportion of males (p<.05), lower IQ (p=.002), and fewer years of education relative to non-PNS (p< .001). sPNS had higher DUP (p<.001) and higher proportion of non-affective psychoses (p<.05) relative to non-PNS. Consistent with PNS classification, sPNS had significantly higher positive and depressive symptoms than PNS and non-PNS at month 12 (p <.001 for both) and received significantly higher doses of antipsychotics than PNS (p=.01) and non-PNS (p<.001).

3.2 Association between PNS and suicidality

The results of the linear mixed-effects model are presented in **Table 2.** Controlling for age and sex, PNS groups significantly differed in suicidality (F (2, 1292.87) =20.98, p<.001). Pairwise comparisons revealed that sPNS patients had higher suicidality relative to PNS patients (b= .64, SE=.10, p<.001) and non-PNS patients (b=.51, SE=.09, p<.001). However, there was no significant difference between PNS and non-PNS patients (b=.13, SE=.08, p=.11). There was also a significant decrease in suicidality overtime (F (1,2620.98) =161.26, p<.001), and a significant interaction between group and time (F (2, 2621.95) =3.34, p=.0354), indicating that suicidality decreased faster in sPNS relative to PNS and non-PNS (see **Figure 1**). After controlling for depression, PNS groups remained significantly different on suicidality (F (2, 1061.69), p=.0015). Specifically, the differences between sPNS and PNS (b=.42, SE=.12, p<.001), and sPNS and non-PNS (b=.30, SE=.11, p=.004) were maintained.

4. Discussion

In a large cohort of FEP patients who received early intervention services, we examined, for the first time, suicidality in PNS, sPNS, and non-PNS during 2 years of early intervention. We did not observe a significant

difference between PNS and non-PNS. However, despite prominent negative symptoms, sPNS presented with higher suicidality relative to PNS and non-PNS. These differences remained significant after adjusting for depression, suggesting that depression was not the sole factor contributing to the elevated suicidality observed in sPNS. Our findings highlight sPNS as a potential target for intervention following psychosis onset and treatment initiation.

4.1 sPNS: High-Risk Group and Target for Intervention

We found that patients with sPNS have higher suicidality relative to those with PNS and non-PNS. Importantly, these differences were maintained after controlling for depressive symptoms, suggesting that differences in suicidality are not entirely driven by depression. Nonetheless, it is important to note that depressive symptoms likely contribute to the elevated suicidality observed in sPNS. Indeed, the role of depression and hopelessness in suicidality is well-established, both in psychotic[43] and non-psychotic disorders[44].

Beyond depression, one explanation could be that the elevated suicidality observed in sPNS is driven by positive symptoms. Because of group classification, sPNS patients had greater positive symptom severity than PNS and non-PNS, and previous research has established hallucinations[4, 10, 45] and delusions[1, 9, 10] as risk factors for suicidality. Some have specified that the directive nature of command auditory hallucinations may drive the relationship between hallucinations and suicidality[10, 46], and others have suggested that delusions of guilt and suspiciousness contribute to this increased risk[1, 9].

In our sample, sPNS was a more severe subgroup of FEP patients with an elevated symptom burden who were prescribed significantly higher doses of antipsychotic medication compared to PNS and non-PNS. Therefore, sPNS represents a subgroup with a greater illness burden and a more severe presentation, and this constellation of symptoms may contribute to the elevated suicidality we observed. In addition, previous work from our group indicated that PNS and sPNS had lower insight than non-PNS[24].

Good insight is associated with better treatment adherence, cognitive functioning, and lower symptom severity, but also directly linked to increases in suicidality[47], highlighting the paradoxical nature of insight: better insight increases awareness about one's mental illness, fostering depression. However, insight has demonstrated a controversial relationship to suicidality in FEP samples. Bornheimer et al.[48] found that poorer insight protected against ideation, whereas Lopez-Morinigo and colleagues[11] found no evidence that insight was associated with suicidality but that depression and past suicidal behavior confounded this relationship.

Globally, because sPNS is characterized by depressive, positive, and extrapyramidal symptoms, proper follow-up, careful monitoring, and interventions for these symptoms are needed. Improving these secondary symptoms would alleviate the negative symptoms arising from them and improve outcomes for this subgroup. One potential intervention could be Metacognitive Training (MCT). A recent meta-analysis of MCT for psychosis revealed improvements in hallucinations, delusions, negative symptoms, and functioning sustained a year later[49]. Overall, psychosocial interventions effectively reduce suicidality in psychosis, specifically suicidal ideation and death by suicide[50]. Patients with sPNS and elevated suicidality would thus benefit from these interventions.

4.2 The lower suicidality in PNS and non-PNS

While we identified that suicidality in PNS was quite low, our findings are inconsistent with the literature on deficit schizophrenia[17] and on the association between high negative symptoms and low suicidality[4, 6, 7, 9, 10], since PNS and non-PNS did not significantly differ. They are also inconsistent with Karakus et al.[18] who observed a significantly lower number of suicide attempts in PNS relative to non-PNS. This inconsistency may be due to sample and measurement differences. Indeed, Karakus et al. [18] evaluated suicidality in an early-onset psychosis cohort, and used the Positive and Negative Symptom Scale (PANSS)[51] to classify PNS and sPNS rather than the SANS. Overall, our findings suggest that negative

symptoms are not necessarily associated with lower suicidality and that PNS classification parses out a subgroup for whom suicidality is elevated despite prominent negative symptoms. Had we combined sPNS with non-PNS into one subgroup, as some have done[20], we may have observed significantly lower suicidality in PNS. Furthermore, the nonsignificant difference between PNS and non-PNS raises the possibility that the absence of depressive and positive symptoms explains the low suicidality in PNS rather than the presence of negative symptoms. Nonetheless, despite this nonsignificant difference, the low suicidality in PNS and non-PNS may be for different underlying reasons.

It is possible that the lower risk observed in PNS results from more pronounced cognitive impairments associated with a reduced capacity to plan for suicide or engage in suicidal ideation. Negative symptoms are associated with greater cognitive impairment[52], and better working memory has been associated with greater suicidal ideation in first-episode schizophrenia patients[53]. In the same sample, our group demonstrated that PNS had more pronounced verbal and working memory deficits than sPNS and non-PNS[23] and reduced hippocampal and perirhinal cortex volume[38] — both regions implicated in memory. However, controversy remains, as a recent review of neuropsychological function and suicidal behaviors in FEP found that greater neurocognitive and social-cognitive impairments were associated with an elevated risk of suicidal behavior, except for working memory[54].

It can also be conjectured that the reduced need for social contact and the preference for solitude observed in those with high negative symptoms contribute to the lower suicidality observed in PNS[55]. The three-step theory of suicide (3ST)[56] and the interpersonal theory of suicide (IPTS)[57] — two of the most prominent theories of suicidality — posit that the absence of social connectedness and thwarted belongingness may precipitate suicide. Those with elevated negative symptoms may not desire social connection to the same extent as those with a different symptom profile which may serve as a protective factor.

In our sample, the low suicidality observed in non-PNS is not surprising. Patients with non-PNS had significantly lower positive and depressive symptoms than sPNS and received significantly lower doses of antipsychotic medication relative to PNS and sPNS one year after treatment initiation. Therefore, non-PNS may represent a subgroup with a significantly lower symptom burden that appears more responsive to treatment during the first year of early intervention. Importantly, non-PNS represents the majority of patients, suggesting that most FEP patients in our sample are not persistently symptomatic one year after the start of treatment.

4.3 Limitations and Future Directions

In the present study, the way we measured suicidality, using the BPRS, did not allow for a clear-cut distinction between individuals with suicidal ideation and those who attempted suicide. Future studies should consider using more structured assessments such as the Columbia-Suicide Severity Rating Scale (C-SSRS)[58]. The choice of a global suicidality score stems from the large proportion of patients with no or low suicidality and with low rates of suicide attempts. Nonetheless, Karakus et al.[18] observed a low frequency of suicide attempts in PNS, in line with the overall low suicidality observed in PNS in our study. Furthermore, sPNS were classified with the co-occurrence of secondary symptoms, which prevents us from inferring causality with the current symptom scales we used (i.e., whether negative symptoms are indeed caused by depressive symptoms or if they are comorbid with each other). Similarly, our longitudinal design is limited to the first 2 years of early intervention which does not allow for the evaluation of group differences in suicidality following the completion of early intervention or discharge from PEPP. It is possible that continuing with early intervention or treatment may attenuate these group differences. Additionally, our findings are limited to a sample of patients who received early intervention and may not be generalizable to individuals with a FEP who did not receive prompt treatment. Future work should follow the trajectories of suicidality in PNS for more extended follow-up periods.

5. Conclusion

We identified different associations between suicidality and subgroups of negative symptoms in FEP patients classified into PNS, sPNS, and non-PNS during 2 years of early intervention. PNS presented with lower suicidality relative to sPNS but did not significantly differ from non-PNS. By contrast, sPNS exhibited higher suicidality relative to PNS and non-PNS, and controlling for depressive symptoms maintained these differences. Our findings suggest that negative symptoms are not necessarily associated with lower suicidality and that PNS classification identifies sPNS as a group with elevated suicidality that would benefit from targeted intervention early in the course of illness.

6. Acknowledgments

This study was funded by the Canadian Institutes of Health Research (CIHR) (grant number: 68961). Salary awards include Fonds de la Recherche en Santé du Québec (M.O, M.L. and R.J.) and James McGill Chair (M.L.). These funding sources did not contribute to study design, data collection, statistical analysis, writing, or interpretation of the findings. We thank all participants for their participation, and the PEPP-Montreal staff for recruitment and data collection. M.L. reports grants from Otsuka Lundbeck Alliance and personal fees from Otsuka Canada, Lundbeck Canada, and MedAvante-Prophase, as well as grants and personal fees from Janssen. A.M. reports no funding from industry in more than three years. K.M.L. reports grants and speaking fees from Otsuka and Lundbeck. R. J. reports grants, speaker honoraria, and honoraria from AstraZeneca, Janssen, Otsuka, Lundbeck, Pfizer Canada, BMS, Shire, and Sunovion, and royalties from Henry Stewart Talks. These interests had no relation to the present study. Other co-authors have no conflicts of interest to declare.

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7. Tables and Figures

Table 1. Demographic and Clinical Characteristics by PNS Group and Timepoint.

	PNS (n=135)		**sPNS** (n=98)		**Non-PNS** (n=282)		**Statistic**
	Mean/%	**SD**	**Mean/%**	**SD**	**Mean/%**	**SD**	
Age of Onset	21.90$_b$	4.22	22.40	4.90	23.25$_a$[281]	4.98	F=3.90*
DUP (weeks)	49.76$_b$ [128]	83.20	69.63$_b$ [95]	119.91	45.82$_a$ [254]	119.06	H=18.87*
Years of Education	11.01$_b$ [128]	2.61	11.51 [94]	2.88	12.27$_a$ [268]	2.91	F=9.19*
IQ	93.17$_b$ [117]	15.47	96.63 [87]	16.89	99.13$_a$ [218]	13.63	F=6.14*
Sex							χ2=15.82*
Male	80%$_a$ [108]		71.4% [70]		61%$_b$ [172]		
Female	20%$_a$ [27]		28.6% [28]		39%$_b$ [110]		
Diagnosis							χ2=20.47*
Non-Affective	77.8%$_a$ [105]		84.7%$_a$ [83]		63.1%$_b$ [178]		
Affective	22.2%$_a$ [30]		15.3%$_a$ [15]		36.9%$_b$ [104]		
Baseline							
BPRS suicidality	2.15$_b$ [127]	1.50	2.81$_a$ [94]	1.75	2.30$_b$ [260]	1.62	H=9.24*
BPRS Depression	3.24 [127]	1.75	3.78 [94]	1.69	3.51 [260]	1.67	H=5.90
Month 6							
SAPS total	7.74$_b$ [121]	10.61	15.65$_a$ [88]	10.42	5.53$_c$ [257]	9.61	H=82.34*
SANS total	27.99$_a$ [121]	12.50	25.34$_a$ [88]	11.44	11.19$_b$ [257]	9.62	H=180.79*
CDSS total	1.64$_b$ [121]	3.20	4.08$_a$ [88]	4.29	2.01$_b$ [257]	3.37	H=28.51*
BPRS suicidality	1.27$_b$ [117]	.72	1.88$_a$ [87]	1.32	1.27$_b$ [246]	.76	H=28.76*
BPRS depression	1.97$_b$ [117]	1.36	3.03$_a$ [87]	1.77	2.03$_b$ [245]	1.32	H=28.25*
CPZ equivalent	184.57 [130]	197.07	251.8$_a$ [97]	269.22	176.9$_b$ [276]	187.85	H=7.27*
Month 12							
SAPS total	5.78$_b$ [125]	6.93	17.57$_a$ [95]	13.84	6.04$_b$ [259]	10.21	H=89.22*
SANS total	26.02$_a$ [125]	12.44	26.37$_a$ [95]	13.51	9.16$_b$ [259]	8.94	H=212.33*
CDSS total	1.10$_b$ [125]	1.95	3.92$_a$ [95]	4.24	1.26$_b$ [259]	2.56	H= 53.79*
BPRS suicidality	1.12$_b$ [113]	.417	1.80$_a$ [89]	1.42	1.21$_b$ [236]	.77	H=36.70*
BPRS Depression	1.75$_b$ [113]	1.07	2.82$_a$ [89]	1.73	1.72$_b$ [236]	1.12	H=36.31*
CPZ equivalent	212.51$_b$ [128]	247.49	308.49$_a$	323.27	152.4$_c$ [269]	161.37	H=30.61*

Abbreviations: SD=standard deviation, [n]= number of participants for whom data was available, PNS=persistent negative symptoms; sPNS= secondary persistent negative symptoms, DUP=duration of untreated psychosis, IQ=intelligence quotient. SAPS=Scale for the Assessment of Positive Symptoms, SANS=Scale for the Assessment of Negative Symptoms, CDSS= Calgary Depression Scale for Schizophrenia, BPRS=Brief Psychiatric Rating Scale, CPZ=chlorpromazine. Subscript letters denote significant post-hoc group comparisons after Bonferroni adjustment and should be interpreted horizontally (e.g., a, b, and c indicate that all comparisons are significantly different). * Denotes significant test results (p<.05).

Table 2. PNS Group Differences in Suicidality.

	Adjusting for age and sex			**Adjusting for age, sex, and depression**		
	Estimate	**SE**	**P-value**	**Estimate**	**SE**	**P-value**
sPNS – PNS	.64	.10	<.001*	.42	.11	<.001*
sPNS – non-PNS	.51	.09	<.001*	.30	.10	.004*
non-PNS – PNS	.13	.08	.11	.11	.09	.22

Note. PNS= Persistent Negative Symptoms, sPNS= Secondary Persistent Negative Symptoms, SE= standard Error. *p<.017 (bonferroni correction for 3 comparisons)

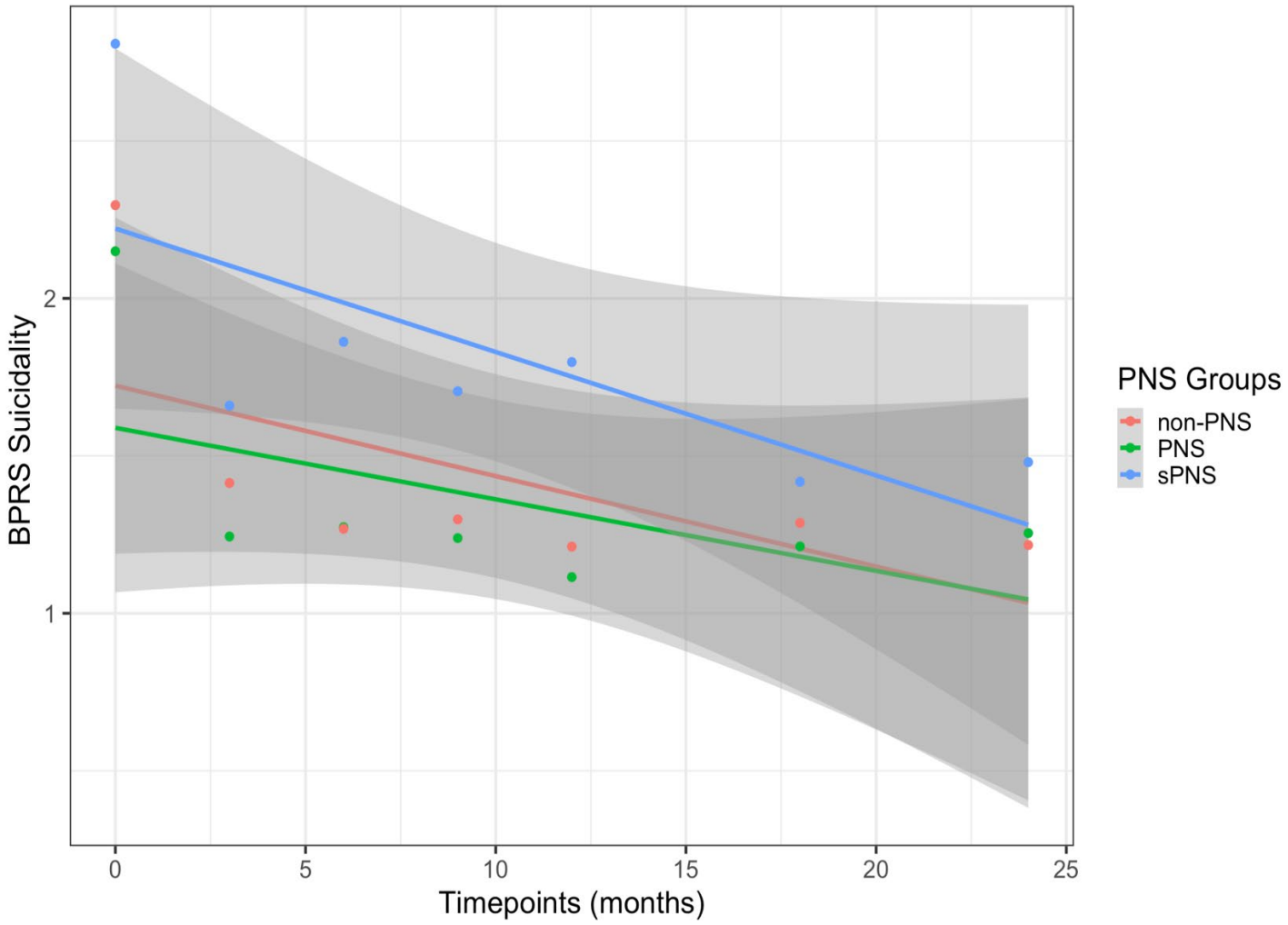

Figure 1. Trajectory of suicidality over 24 months per PNS group

BPRS= Brief Psychiatric Rating Scale, PNS=Persistent Negative Symptoms, sPNS= secondary Persistent Negative Symptoms.