


The relationship of separation anxiety with the age of onset of panic disorder

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Abstract

Aim: This study aimed to investigate whether separation anxiety (SA) constitutes a dimension related to age at onset of panic disorder (PD), in homogeneous subgroups of outpatients with PD, based on their age of onset and symptom severity.

Methods: A sample of 232 outpatients with PD was assessed with the Panic Disorder Severity Scale (PDSS) and the Sheehan Disability Scale (SDS) for functional impairments. Separation anxiety was evaluated using structured interviews and questionnaires. We applied a K-Means Cluster Analysis based on the standardized “PD age of onset” and “the PDSS total score” to identify distinct but homogeneous groups.

Results: We identified three groups of patients: group 1 (“PD early onset/severe”, $N = 97$, 42%, onset 23.2 ± 6.7 years), group 2 (“PD early onset/not severe”, $N = 76$, 33%, onset 23.4 ± 6.0 years) and group 3 (“PD adult onset/not severe”, $N = 59$, 25%, onset 42.8 ± 7.0 years). Patients with early onset/severe PD had significantly higher scores on all SA measures than PD late-onset/not severe. Regression analyses showed that SA scores, but not PDSS scores, were predictive of impairment in SDS work/school, social life, and family functioning domains.

Conclusions: Our data indicate a significant relationship between SA and PD with an earlier age of onset and an impact on individual functioning. This may have important implications for implementing preventive interventions targeting early risk factors for the subsequent onset of PD.

KEYWORDS

age of onset, anxiety disorders, panic disorder, separation anxiety

1 | INTRODUCTION

Research into the age of onset of panic disorder (PD) is essential for exploring factors related to its onset, understanding heterogeneity,

and, ultimately, implementing preventive and early therapeutical interventions. Data from the literature are inconsistent and sometimes contradictory. A meta-analysis of anxiety disorders reported an average age of onset of PD in adulthood of 30.3 years (95% CI 26.09 to

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34.59) (De Lijster et al., 2017): however, the relationship of separation anxiety disorder (SAD), which showed a much earlier onset (10.6 years; 95% CI 6.38 to 14.84), with PD was not investigated. A subsequent meta-analysis of the age of onset of anxiety disorders provided evidence of a peak of onset of PD at 15.5 years of age: in about 30% of cases, PD appeared before 18 years, and 45% of cases before 25 years of age (Solmi et al., 2022). These authors did not report whether typical conditions of childhood, that is, separation anxiety (SA) or other childhood conditions, were temporally related to or predictive of the observed early age of onset of PD. Clarification of these associations is essential for implementing prevention and therapeutic strategies. Other relevant data from large samples indicate that the observed earliest median ages of onset of psychiatric disorders (8–13 years) are those of phobias/SA, attention-deficit/hyperactivity disorder, and social anxiety disorders, followed by eating disorders (12–15 years) and, finally by mood, panic and psychotic disorders (20–30 years) (Fusar-Poli, 2019; Fusar-Poli et al., 2019; Solmi et al., 2022). Consistent with these epidemiological data, the association of early-onset PD with more severe psychopathology and comorbidity, greater avoidance behaviour, and higher rates of suicide is well documented (Noyes Jr., 1991; Tietohl-Santos et al., 2019).

A meta-analysis based on 25 individual studies reported an increased odds ratio of 3.45 (95% CI: 2.37–5.03) for children with SAD to develop PD later in life. Four studies provided information about the age at onset of SAD, but none examined the influence of this variable on the age of onset of future PD (Kossowsky et al., 2013). Other authors found that 75% of adults with anxiety disorders seeking treatment at anxiety disorders clinics reported having had SAD in childhood, and that patients with a history of SAD have greater disability than do other anxiety disorder patients routinely treated in anxiety disorder clinics. However, the impact of SA on age of onset of PD was not reported in these studies (Milrod et al., 2014; Roberson-Nay et al., 2012).

Although threats of separation from close attachment figures may lead to extreme anxiety and to panic attacks (Bandelow et al., 2001), whether there is continuity from SAD to PD is still inadequately researched. PD is sometimes described as a disorder with an abrupt onset, although antecedents often are traceable (Busch & Milrod, 2015). In DSM-5-TR (APA, 2022), the median age of PD is reported to be 20–26 years, with a later onset recognized as possible, further complicating the potential relationship between PD and SA. It has also been argued that early SA and childhood SAD can continue into adulthood, manifesting as an adult form of SAD with significant impact on individual's functioning (Pini et al., 2021; Silove et al., 2015). However, in most of these cases, symptomatic overlap with PD leads to the latter diagnosis being prioritized (Rochester & Baldwin, 2015).

In sum, whether SA might anticipate the onset of PD in adult patients suffering from PD remains unclear (Cassano et al., 1997). To investigate this issue, we re-analysed data from our previous study (Gesi et al., 2016), which investigated the prevalence and clinical correlates of SAD in a large ($n = 235$) sample of patients with PD: 125 (53.2%) were categorized as having SAD and 110 (46.8%) as not. Patients with SAD were more likely to be female and younger; they showed higher rates of childhood SAD and higher PDSS scores than

subjects without SAD: but groups did not differ regarding onset of PD (28.2 ± 11.8 vs. 29.8 ± 11.9 years, $p < .57$). However, the fact that the group with SAD was significantly younger (40.2 ± 12.3 vs. 43.5 ± 12.7 , $p < .05$) suggests a potential role of SA in anticipating later clinical manifestations of PDs (Gesi et al., 2016).

In the present study, we adopted a different strategy to explore age of onset of PD using the sample of Gesi et al. Our aims were, first, to investigate, using K-Means Cluster Analysis, homogeneous subgroups of PD subjects based on their age of onset and symptomatic severity. Second, we explored the notion that SA might represent a dimension strictly related to PD, hypothesizing a connection with an earlier and more severe form of PD. This hypothesis stems from the suggestion of a specific longitudinal relationship between SAD in childhood, and the later appearance of PD/agoraphobia in the same individual, as proposed by Klein (1993, 1995) and Gittelman-Klein (1995) on the basis of clinical observation.

2 | METHODS

A total sample of $N = 232$ (mean age 41.7 ± 12.3 years, female $N = 155$, 66.8%) outpatients with a DSM-IV-TR principal diagnosis of PD consecutively recruited between 2015 and 2018 at the Adult Outpatient Clinic of the Department of Psychiatry of University of Pisa (Italy) were included within this analysis. Patients with psychotic disorders or substance use disorders were excluded. The presence of other co-occurring anxiety or mood disorders was not an exclusion criterion. Details of the study methods are reported elsewhere (Gesi et al., 2016). All participants were assessed with the Structured Clinical Interview based on DSM-IV criteria (SCID-I) (First, 1997) to establish axis I primary diagnosis. Age of onset of PD was defined as the age at first diagnosis of PD according to the SCID-I. We used the Panic Disorder Severity Scale (PDSS) to assess the current severity of PD (Shear et al., 1997). Interference with daily activities was evaluated by the Sheehan Disability Scale (SDS), a scale developed to assess functional impairment in three inter-related areas; work/school, social life/leisure activities, and family life/home responsibilities (Sheehan, 1983). In the SDS, separate scores for each of the three domains can be obtained and analysed both in young and adult populations (Coles et al., 2014). All interviews were performed face-to-face by experienced psychiatry residents.

2.1 | Assessment of separation anxiety

The diagnosis of SAD was evaluated with the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS) (Childhood and Adult sections). This semi-structured interview evaluates each of the eight DSM-IV criterion symptoms of SA, separately for Childhood (SCI-SAS-C) and Adult symptoms (SCI-SAS-A). The SCI-SAS displays excellent psychometric properties, including good internal consistency, a clear factor structure, and exceptional levels of convergent and discriminate validity (Cyranowski et al., 2002).

Separation anxiety was also assessed retrospectively with the Separation Anxiety Symptom Inventory (SASI). The SASI, a 15-item self-report inventory, was developed to assess adults' memories of SA experienced during childhood. This questionnaire showed good psychometric properties, including high internal consistency and test-retest reliability (Silove et al., 1993).

Adult SA was evaluated dimensionally with two instruments: the Adult Separation Anxiety Questionnaire (ASA-27) (Manicavasagar et al., 2003) and the Panic-Agoraphobic Spectrum Scale (PAS-SR) domain "Separation Anxiety" (Rucci et al., 2009). Both questionnaires showed excellent psychometric properties (Frank et al., 2011; Pini et al., 2010).

The study was carried out under the Declaration of Helsinki and with the approval of the University of Pisa Ethical Committee. All participants were informed of the nature of the study procedures and provided written informed consent.

2.2 | Statistical analyses

The K-Means Analysis based on the iterative and Euclidean distance method was used to identify distinct but homogeneous groups.

The K-means method was chosen over the hierarchical one for the following reasons: (a) K-means operates a simple division of the set of data objects into a non-overlapping subset (clusters) such that each data object is in exactly one subset; (b) K-means tends to create compact clusters (the distance between every two points is small). In our case, it determined small within-cluster variability compared to the differences between the centroids of the clusters, with cluster sizes each greater than 10% of the total sample; (c) the hierarchical method, which is especially useful when the target is to arrange the clusters into a natural hierarchy, is more arbitrary compared to the K-means because one can stop at any number of clusters by interpreting the dendrogram.

Groups were identified based on the "PD age at onset" and the "PDSS total score". Both discriminatory variables were first standardized. To ensure maximum efficiency in identifying the final centroids, we started from the centroids initially found, using a random test sample consisting of 50% of the total sample. To verify the stability of the solution, we repeated the analysis after sorting the data in different ways. The solution for $K = 3$ (i.e., three clusters) was the most satisfactory. It determined small within-cluster variability compared to the differences between the centroids of the clusters, with cluster sizes each greater than 10% of the total sample.

The ANOVA without correction for multiple comparisons to not losing power (Saville, 1990) was used to compare groups on continuous variables and the Chi-square test for categorical variables. Linear regressions were used to analyse the predictive effect of the PDSS severity scale score and SCI-SAS adult score on SDS domains as dependent variables. Statistical analyses were conducted using SPSS (SPSS Science, Chicago, Illinois; software version 25.0).

3 | RESULTS

3.1 | K-Means cluster analysis

Table 1 shows the initial cluster centers and the final cluster centers in the three groups. The K-Means Cluster Analysis applied to the entire sample met criterion 0 of convergence at the eighth iteration. We defined the obtained three sub-groups of subjects as follows: Group 1 ("PD early onset/severe", $N = 97$, 42%), Group 2 ("PD early onset/not severe", $N = 76$, 33%), and Group 3 ("PD adult onset/not severe", $N = 59$, 25%). The mean PD age of onset was 23.2 ± 6.7 years in Group 1, 23.4 ± 6.0 years in Group 2 and 42.8 ± 7.0 years in Group 3 (ANOVA, $F = 196.12$, $p = .001$), post-hoc Tukey's test: $1 < 3$ ($p = .000$), $2 < 3$ ($p = .000$). The current age was 34.6 ± 10.4 years in group 1, 36.9 ± 11.6 years in group 2, and 49.0 ± 8.3 years in group 3 (ANOVA, $F = 38.95$, $p = .001$).

The solution found proved to be stable even after sorting data in different ways.

The distances between the final cluster centers were: 1.69 between group 1 and group 2; 1.830 between Group 1 and Group 3; and 2.161 between Group 2 and Group 3. The average distance of cases from their classification cluster center was 0.80 ± 0.38 . Finally, in the dispersion analysis the "SCID PD age at onset" presented the greatest influence in forming the clusters. (see F values in Table 1).

3.2 | Measures of separation anxiety

In Table 2, measures of SA in the three groups of subjects categorized on the basis of the K-Means Cluster Analyses are reported. Post-hoc tests for ANOVAs showed that the "PD early onset/severe" ($N = 97$) had significantly higher scores than group 3 ("PD adult onset/not severe", $N = 59$) on all scales measuring childhood and adulthood SA and also than group 2 ("PD early onset/not severe", $N = 76$) regarding measures of adult SA.

As shown in Table 3, the results of regression analyses indicate that the PDSS total score ($p = .026$) and SCIS-SAS-Adult score ($p = .023$) were both predictive of the SDS Work/School subscale. The SCI-SAS-Adult score ($p = .003$) and duration of illness (years) score ($p = .031$) were predictive of impairment in the SDS social life subscale. The SCI-SAS-Adult score ($p = .041$) was predictive of impairment in the SDS family life subscale.

4 | DISCUSSION

In a previous study conducted in a large sample of adult outpatients with PD, we found that the categorical diagnosis of SAD was associated with greater severity of PD, and a younger mean age at the time of assessment, but not with an earlier age of onset of PD compared to subjects without SAD (Gesi et al., 2016). Using the same sample, the present study explored the relationship between dimensional

TABLE 1 K-Means Cluster Analysis features. Initial cluster centers and Final Cluster Centers after 8 iterations in “Early onset PD/severe” (N = 97), “Early onset PD/not severe” (N = 76), and “Late-onset PD/not severe” (N = 59) groups (total sample N = 232). Dispersion analysis.

	Initial cluster centers		
	Early onset PD/not severe	Early onset PD/severe	Late-onset PD/not severe
SCID-I ^a PD age of onset	−0.16401	−0.55723	1.64320
PDSS ^b total score	−0.81059	0.80805	−0.25425
	Final cluster centers		
	Early onset PD/not severe	Early onset PD/severe	Late-onset PD/not severe
SCID-I PD age at onset	−0.46634	−0.48289	1.30179
PDSS total score	−0.82521	0.86257	−0.35513
	Dispersion analysis		
	Cluster mean square (SE)	F	P
SCID-I PD age of onset	69.501 (0.354)	196.123	<.001
PDSS total score	65.683 (0.435)	150.965	<.001

^aStructured Clinical Interview for DSM-IV-TR (First, 1997).

^bPanic Disorder Severity Scale (PDSS) (Shear et al., 1997).

TABLE 2 Measures of separation anxiety in three panic disorder groups categorized with K-Means Cluster Analysis of age of onset (Total sample N = 232).

	Group 1 (Early onset with severe symptoms) (N = 97)	Group 2 (Early onset with no severe symptoms) (N = 76)	Group 3 (Adult onset with no severe symptoms) (N = 59)	F value ^a	P value	Post-hoc tests (Tukey's)
PD age of onset (mean)	23.2 ± 6.7	23.4 ± 6.0	42.8 ± 7.0	196.12	.001	1 > 3 (p = .000), 2 > 3 (p = .000)
Duration of illness (years)	11.4 ± 10.3	13.5 ± 11.7	6.4 ± 5.4	8.798	.001	1 > 3 (p = .000), 2 > 3 (p = .007)
SAD age of onset*	14.7 ± 12.0	12.8 ± 10.3	12.9 ± 15.5	0.174	.0841	ns
SASI score	17.0 ± 10.2	14.2 ± 8.5	11.9 ± 8.8	5.696	.004	1 > 3, p = .001
SCI-SAS-C score	6.9 ± 4.5	5.7 ± 3.9	4.3 ± 3.9	7.257	.001	1 > 3, p = .001
SCI-SAS-A score	8.3 ± 4.1	6.6 ± 3.4	6.4 ± 3.9	5.827	.003	1 > 3, p = .011, 1 > 2, p = .015
ASA-27 total score	37.3 ± 18.0	30.3 ± 14.5	30.1 ± 15.7	4.908	.008	1 > 3, p = .044, 1 > 2, p = .015
PAS-SR SA Factor	7.7 ± 3.5	6.6 ± 3.6	4.7 ± 3.9	9.857	.001	1 > 3, p = .000
	N (%)	N (%)	N (%)	Chi-square	P value	
Childhood Separation Anxiety Disorder ^b	46 (47.4)	27 (35.5)	16 (27.1)	6.780	.034	—
	Adjusted Standardized Residuals					
Adult Separation Anxiety Disorder ^c	2.4	−0.6	−2.1	8.313	.016	
	Adjusted Standardized Residuals					
	2.9	−2.1	−1.1			

Abbreviations: ASA-27, Adult Separation Anxiety Questionnaire (Manicavasagar et al., 2003); ns, not significant; PAS-SR SA factor, Panic-Agoraphobic Spectrum Self-report Separation Anxiety Factor (Rucci et al., 2009); SAD, Separation Anxiety Disorder; SASI, Separation Anxiety Symptom Inventory (Silove et al., 1993); SCI-SAS-C/A, Structured Clinical Interview for Separation Anxiety – Childhood/Adult Section (Cyranowski et al., 2002).

^aDegrees of Freedom = 231.

^bPearson Chi-Square 6.780, df = 2, p = .034 - Likelihood Ratio 6.861, df = 2, p = .032.

^cPearson Chi-Square 8.313, df = 2, p = .016 - Likelihood Ratio 8.363, df = 2, p = .015.

TABLE 3 Linear regressions of predictive variables (PDSS, SCI-SAS-C score, SCI-SAS-A score, PD age of onset and duration of illness (years) with the Sheehan Disability Scale (SDS) subscales scores (Work/school, Social Life, Family Life) as dependent variables.

		*B	Std. Error	**Beta	t	Sig.
Model ^a	(Constant)	3.755	1.468		2.558	.012
	PDSS total	.132	0.059	.223	2.255	.026
	SCI-SAS-C	-.024	0.084	-.030	-0.288	.774
	SCI-SAS-A	.220	0.095	.250	2.315	.023
	SCID-I PD age of onset	-.043	0.034	-.123	-1.234	.220
	Duration of illness	.014	0.042	.035	.348	.728
Model ^b	(Constant)	5.871	1.352		4.341	.000
	PDSS total	.024	0.054	.044	0.443	.659
	SCI-SAS-C	-.058	0.078	-.078	-0.745	.458
	SCI-SAS-A	.268	0.088	.328	3.052	.003
	SCID-I PD age of onset	-.056	0.032	-.176	-1.770	.080
	Duration of illness	-.084	0.038	-.220	-2.185	.031
Model ^c	(Constant)	1.888	1.362		1.386	.169
	PDSS total	.072	0.054	.134	1.323	.189
	SCI-SAS-C	.003	0.078	.004	0.037	.970
	SCI-SAS-A	.184	0.089	.228	2.073	.041
	SCID-I PD age of onset	.010	0.032	.031	0.299	.766
	Duration of illness	.046	0.039	.122	1.179	.241

Note: Bold = significant at $p < .05$.

Abbreviations: PDSS, Panic Disorder Severity Scale (Shear et al., 1997); SCI-SAS-C/A, Structured Clinical Interview for Separation Anxiety – Childhood/Adult Section (Cyranowski et al., 2002).

^aDependent Variable: SDS Work/School.

^bDependent Variable: SDS Social Life.

^cDependent Variable: SDS Family Life.

*Unstandardized Coefficients.

**Standardized Coefficients.

measures of SA and age of onset of PD using a different statistical approach. We used the K-Means Cluster Analysis to identify comparable groups of individuals based on the age of onset of PD and severity of PD. We found three groups of subjects: (1) one with an earlier age of onset of PD and greater severity of symptoms compared to the other two groups; (2) a group with an early age of onset but with less severe symptoms and (3) a group with a far later age of onset (43 years) and with less severe symptoms. Overall, these findings provide information regarding identifying normal distributions of peaks of onset of PD in an adult clinical population. Our data are also meaningful for interpreting data from epidemiological studies. For example, Solmi et al. (2022) in a worldwide meta-analysis, found that anxiety/fear-related disorders have peaks age at onset at 5.5 and 15.5 years (Solmi et al., 2022). They also found that the median age of PD was at 27 years of age. However, they did not report whether or not there were different age at onset distributions within the PD sample analysed.

Previous applications of cluster analysis to anxiety disorders resulted in cut-offs of 27 years for PD (Tibi et al., 2013). Such a cut-off showed that comorbidity rates and other severity indicators were higher in early-onset PD (Tibi et al., 2013). Other studies clustered PD patients based on different factors related to response to treatment or panic/agoraphobic symptomatology but did not include the age of

onset of PD in the analyses (Shioiri et al., 1996; Zilcha-Mano et al., 2015).

None of these studies, however, explored the association of SAD with the age of onset and severity of PD in adult patients. Our data indicate a significant relationship between SA and a potential subgroup in PD which is characterized by an early age of onset and more significant functional impairment. They are consistent with an earlier study reporting the presence of childhood SAD to influence age at onset in patients' PD when applying a stepwise survival analysis (Battaglia et al., 1995).

From a heuristic and developmental point of view, these findings strongly corroborate the hypothesis of a continuity (at least for more severe forms) between SAD and PD/agoraphobia, as previously proposed (Gittelman & Klein, 1984; Gittelman-Klein, 1995; Preter & Klein, 2008; Pini et al., 2014; Shear et al., 2006) and demonstrated by meta-analysis (Kossowsky et al., 2013). From a clinical perspective, the role of SA may constitute a key factor for the early-onset forms of PD, which notably impact adult individuals' autonomous functioning and problems or resistance to therapeutical interventions (Chambless et al., 2017; Keefe et al., 2021).

In our study, both childhood and adulthood SA were associated with the earlier onset of PD. In addition, the co-occurrence of PD with adult SA significantly impacted most important individual areas of

functioning. These findings indicate that the prevailing view of PD as having a sudden onset, often with “out-of-the-blue” panic attacks starting in adulthood, should not distract clinicians from exploring retrospectively younger, pre-pubertal, and potentially relevant manifestations, such as SA, which might otherwise be overlooked.

5 | LIMITATIONS

A number of limitations should be considered. First, we found that the groups with early onset of PD were younger than those with late-onset. Therefore, an older sample could be associated with later age of onsets due to recall bias and a longer period of being at risk of developing the disorder. On the other hand, no data in the literature indicate that younger age is associated with reported anticipation of the onset of mental disorders (Green et al., 2010; Sandanger et al., 1999). Second, it is known that prospective studies tend to report lower age of onset of anxiety disorders, when compared to retrospective studies. As this is a retrospective study, this factor could also have led to biased estimates of the age of onset (Green et al., 2010). Third, all individuals in our study had a principal diagnosis of PD, and the potential effect of the presence of lifetime or current comorbidity on PD age of onset and on the severity of panic symptomatology was not examined in this study. Related to this, we did not explore the impact of externalizing disorders on the onset and phenomenology of PD (Knapp et al., 2022). Therefore, we cannot exclude that SA interacts with other factors in determining a more general vulnerability to adult psychopathology. Further studies using comparison samples with different diagnoses are warranted from such a perspective.

5.1 | Clinical implications

If further studies confirm the relevance of the association between SAD and the subsequent onset of PD (integrating data deriving from prospective studies with children/adolescents), this may have important implications for implementing preventive interventions that can effectively target early risk factors for later psychopathology (Danese, 2022; Domschke, 2021). Within this framework, preventive interventions focusing on interoceptive sensitivity have been shown to decrease SA via reducing anxiety sensitivity (Bandelow et al., 2017;). Moreover, our data stimulate further studies on the development trajectory of SA from childhood into adult life to understand whether SA may persist across the lifespan as an independent clinical entity (Kossowsky et al., 2013; Rochester & Baldwin, 2015; Schiele et al., 2021) (Schiele et al., 2020).

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CONFLICT OF INTEREST STATEMENT

KD is a member of the Steering Committee Neurosciences, Janssen Pharmaceuticals, Inc., however, this is not relevant to the subject of this article. All other authors report no financial or other relationship relevant to the subject of this article.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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