The Clinical Importance of Affective Temperaments in Panic Disorder

PhD Thesis

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List of abbreviatons

AFT: affective temperament

ANXD: anxiety disorder

AG: agoraphobia

AT: anxious temperament

BD: bipolar disorder

CT: cyclothymic temperament

DT: depressive temperament

GAD: generalized anxiety disorder

HT: hyperthymic temperament

IT: irritable temperament

MDD: major depressive disorder

OCD: obsessive-compulsive disorder

PD: panic disorder

Introduction

Panic disorder (PD) is an episodic anxiety disorder associated with intense fear and at least four autonomic or cognitive symptoms of anxiety, anticipatory anxiety about the recurrence of attacks, and – in about 2/3 of the cases – avoidance behaviour (agoraphobia; AG) (Savino et al., 1993; Merikangas, 2009; Kessler et al., 2006). According to international data, the lifetime and one-year prevalence of PD without AG are 3.7-4.0% and 1.6%, respectively. The one-year prevalence of PD with AG was measured 1.1% (Grant et al., 2004; Kessler et al., 2006). In Hungary, the lifetime, one-year and past-month prevalences of PD were found 4.4%, 3.1% and 2.0%, respectively (Rihmer and Angst, 2009c; de Jonge et al., 2016; Szádóczky et al., 2000, 2004).

In the case of PD, the presence of a comorbid psychiatric condition is the rule rather than the exception. PD is most commonly associated with mood disorders, which can occur inter- and intra-episodically (de Jonge et al., 2016; Szádóczky et al., 2000; Perugi and Akiskal 2002; Kessler et al., 1998; Kaufman and Charney, 2000; Fistikçi et al., 2013). In 30-90 percent of the cases, PD is associated with major depressive disorder (MDD) or bipolar disorder (BD), especially with BD-II (Maser and Cloninger, 1990; Savino et al., 1993; Perugi and Akiskal, 2002; DSM-5, 2013; Wittchen et al., 2000; Roy-Byrne et al., 2006). The comorbidity of PD and affective disorders is bilateral. Accordingly, among patients with BD the most common anxiety disorder is PD (with a lifetime prevalence of 15-20%), while the prevalence of PD in subjects with MDD is 10% (Maser and Cloninger, 1990; Perugi and Akiskal, 2002; MacKinnon et al., 2007; Perugi and Toni, 2012; Rihmer et al., 2001).

Affective temperaments (AFTs) correspond to a behavioral endophenotype, the biological core of the personality, which are manifested from childhood and are partly genetically determined. The AFTs are affective attitudes stable over time that provide emotional colour to different experiences, as well as determine behavioral and emotional reactions, biological rhythms, and activity levels (Akiskal and Akiskal, 1992a; Tomassini et al., 2009; Gonda et al., 2009; Rihmer et al., 2010; Silva et al., 2017). AFTs carry the advantages and disadvantages of emotional reactivity, whereas their extreme variants predispose to mental disorders (Vazquez et al., 2018).

AFTs significantly influence the development, symptomatology, and outcome of psychiatric disorders, and some types of temperament may be risk or protective factors of suicidal behavior (Akiskal, 2000; Rihmer et al., 2010; Karam et al., 2010; Rihmer and Gonda, 2016).

As a result of decades of research, Akiskal and his team developed a self-rating questionnaire, TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego), which consists of 110 (109 for males) simple yes-or-no items (Akiskal et al., 2005a; Akiskal et al., 2005c; Vazquez and Gonda, 2013; Rozsa et al., 2008). The items of TEMPS-A cover five types of temperaments (depressive [DT]; cyclothymic [CT]; hyperthymic [HT]; irritable [IT] and anxious [AT]) (Akiskal et al., 2005a; Akiskal et al., 2005c; Vazquez and Gonda, 2013; Rozsa et al., 2008). AFTs can be considered as subsyndromal forms and harbingers of mood disorders and they play an important role in the development of minor and major affective disorders, including the direction of the polarity of the affective episode and the symptoms of the current episode. In addition, AFTs may influence the long-term course of affective disorders as well as the treatment response, the compliance and suicidality (Akiskal, 2003; Akiskal et al., 2005a; Akiskal et al., 2005c; Rihmer et al., 2009; Pompili et al., 2013; Pompili et al., 2018). The relationship between mood disorders and AFTs has been extensively studied, but little is known about the association between anxiety disorders (including PD) and different types of affective temperament (Savino et al., 1993; Perugi and Toni, 2012; Akiskal, 2003; Rihmer et al., 2010; Karam et al., 2010; Pompili et al., 2018; Pompili et al., 2013; Akiskal et al., 2006; Zobel et al., 2004; Mendlowicz et al., 2005).

The primary objective of our study was to investigate the distribution of AFTs among outpatients with PD. MDD is typically associated with DT, while patients with BD mostly show HT and CT features (Rihmer et al., 2010). Our hypothesis, based on the fact that PD is an anxiety disorder, was that the presence of AT among panic patients will be typical, but, due to the high comorbidity of PD with MDD and BD, DT, HT, and CT will also be common.

Materials and methods

One hundred and eighteen (80 female and 38 male) DSM-5 diagnosed PD patients with or without AG but without any other major psychiatric disorders (see exclusion criteria below) who visited our adult outpatient department between 30 September 2016 and 30 September 2017 were included. All patients were followed up till 31 March 2019 in order to detect the onset of any major affective disorders, substance use disorders and suicide attempts.

To determine the affective temperaments we used the Hungarian version of TEMPS-A (Akiskal et al., 2005a; Akiskal et al., 2005c; Rozsa et el., 2008).

The distribution of AFTs (i.e. the rate of "dominant" affective temperaments; see defined later) and data on cross-sectional and lifetime comorbidity (agoraphobia, MDD, BD-I and II, cyclothymic disorders, addictive disorders, suicide attempts) and family history data for first- and second-degree relatives in regard to affective, anxiety and substance-use disorders and completed suicide were gathered and analyzed. Affective temperaments were determined according to their z-scores in each subscale: an affective temperament was considered to be manifested as "dominant" if its z score was at least 2SD above the z-score of the normative sample (Rozsa et al., 2008).

The exclusion criteria at study inclusion were current or previous psychotic disorders, MDD, bipolar and bipolar spectrum disorders, OCD, GAD, other anxiety disorders (except for PD and/or agoraphobia), neurocognitive disorders and concomitant severe somatic diseases. Altogether fifty-seven patients (40 females and 17 males; mean age: 48.5 years) were excluded at study entry because they had lifetime comorbid psychiatric disorder(s) other than agoraphobia. In details, 29 and 28 subjects were excluded due to BD and MDD, respectively (12% of them also had a comorbid substance-use disorder). Thus, the total number of contacted patients was 175 (118 included and 57 excluded subjects) in our study. The presence of current psychiatric disorders was established based on the clinical interview of patients. The presence of previous psychiatric disorders was established based on the medical history (i.e. on patient documentation and patients' own reports). Participants were not under guardianship and, since we excluded subjects with neurocognitive disorders, the participants' ability to consent was retained. The data from the study group was statistically compared with normative data for Hungarian population obtained from the study by Rozsa et al. (2008) which validated the Hungarian version of TEMPS-A (Rozsa et al., 2008).

Furthermore, the 118 cases were also frequency-matched by age and sex to 118 controls from the sample of the abovementioned validation study (Rozsa et al., 2008). A similar comparison was carried out between those 23 PD patients who remained free from any comorbid major affective disorders during the follow-up and an age- and gender-matched control group whose 23 members were choosen from the sample of the validation study by Rozsa et al. (2008).

The statistical comparison was made by two sample t-test for continuous variables, and Chi-square statistics for categorial variables. Alpha level was set at 5%.

Statistical analysis was done with SPSS20. Participation was voluntary and anonymous and patients gave their written informed consent to participate in the study.

The study was approved by the local ethical board of the University Hospital of Szabolcs-Szatmár-Bereg County, Nyíregyháza, Hungary.

Results

Out of the 118 PD patients, 80 (68%) were females and 38 (32%) males. The average age at inclusion was 44.4 years (range: 19-73 years) (**Table 1**.). The average duration of PD was 10.1 years (ranging from 0.2 to 26 years). Seventy-seven patients (60 females and 17 males) had agoraphobia at baseline and 10 patients (6 females and 4 males) experienced newly developed agoraphobia during the 1.5-2.5 year follow-up period (**Table 1**.). Six patients (5%) had made a prior suicide attempt. During the follow-up, newly developed MDD, bipolar spectrum disorder (BD-I or -II, cyclothymic disorder) and substance use disorder were observed in 64%, 22% and 9.5% of patients, respectively. The majority of patients with newly developed bipolar spectrum disorders had BD-II (19/26=73%). None of the patients made a suicide attempt during the follow-up. Family history of any anxiety and major affective disorders among the first- and second-degree relatives was 71% and the same rate for substance use disorders was 22%. Thirteen percent of patients reported completed suicide among first- and second-degree relatives (**Table 1**.).

Table 1. Demographic, clinical and family history data of our 118 panic disorder outpatients

	Females	**Males**	**Total**
Number of patients (%)	80 (68 %)	38 (32%)	118 (100%)
Average age in years (range)	44.82 (22-60)	44.07 (19-73)	44.44 (19-73)
Duration of PD in years (range)	10.8 (0.2-26)	9.5 (0.3-25)	10.1 (0.2-26)
Comorbidity at baseline			
Agoraphobia, n (%)	60 (75%)	17 (45%)	77 (65%)
Comorbidity at follow-up			
Agoraphobia, n (%)	6 (7.5%)	4 (10%)	10 (8.5%)
Unipolar major depression, n (%)	55 (69%)	20 (53%)	75 (64%)
Substance use disorder, n (%)	3 (37.5%)	8 (21%)	11 (9,5%)
Bipolar disorder and cyclothymia, n (%)	17 (21%)	9 (24%)	26 (22%)
Previous suicide attempts, n (%)	4 (5%)	2 (5%)	6 (5%)
Family history (1- and 2-degree relatives) for anxiety and/or affective disorder n(%)	54 (67.5%)	30 (79%)	84 (71%)
Family history (1- and 2-degree relatives) for substance-use disorder, n (%)	18 (23%)	9 (24%)	26 (22%)
Family history (1- and 2-degree relatives) for completed suicide, n (%)	8 (10%)	8 (21%)	16 (13.5%)
Mean length of follow-up in month (SD)	26.3 (3.7)	26.7 (3.7)	26.4 (3.7)

Among females the "dominant" ANX and DE temperaments were about 4 and 3 times as common as in a large normative Hungarian sample, while differences for the remaining three temperament types were not significant (**Table 2**.). Similar comparisons in the group of males showed no significant differences (in fact, only 3 of the 38 male patients had a dominant temperament; all three had a dominant DT).

Table 2. Distribution of dominant affective temperaments (average score + 2 SD) in our PD sample and in a large normative Hungarian sample – Females

Temperaments	**Female patients** (n=80)		**Normative Hungarian sample, females** (n=797[Rozsa et al., 2008])		**Difference**
	N	%	N	%	
Depressive	8	10	27	3.4	2.9x ($p<0.01$)
Cyclothymic	5	6.3	28	3.5	1.8x (not significant)
Hyperthymic	1	1.3	16	2.0	0.65x (not significant)
Irritable	0	0	15	1.9	-
Anxious	16	20	38	4.8	4.2x ($p<0.0001$)

Females with PD obtained significantly higher scores on ANX, DE and CT subscales of the TEMPS-A, whereas males with PD showed significantly higher scores on ANX, DE and HT subscales compared to a gender- and age-matched control group (n=118) and a large normative Hungarian sample (n=1132) as well (**Table 3**.).

Table 3. TEMPS subscale scores (means [M]; standard deviations [SD]) among and their comparisons (differences; t-test) between panic disorder patients (PD), age- and gender-matched controls (MC) and members of a large normative Hungarian sample (NHS)

	Panic disorder (PD) patients (n=118)		**Age and gender. matched controls (MC) (n=118)**		**Normative Hungarian Sample (NHS) (n=1132) (Rozsa et al.,2008)**		**Difference PD vs. MC**		**Difference PD vs. NHS**	
Temperaments	**Females M (SD)**	**Males M (SD)**	**Females M (SD)**	**Males M (SD)**	**Females M (SD)**	**Males M (SD)**	**Females**	**Males**	**Females**	**Males**
Depressive	0.49 (0.17)	0.39 (0.17)	0.39 (0.17)	0.31 (0.14)	0.33 (0.15)	0.31 (0.15)	p<0.001	p<0.05	p<0.001	p<0.01
Cyclothymic	0.39 (0.25)	0.35 (0.22)	0.28 (0.20)	0.28 (0.24)	0.35 (0.20)	0.33 (0.22)	p<0.01	n.s.	p<0.05	n.s.
Hyperthymic	0.46 (0.20)	0.60 (0.24)	0.42 (0.20)	0.48 (0.20)	0.47 (0.20)	0.53 (0.22)	n.s.	p<0.05	n.s.	p<0.05
Irritable	0.28 (0.17)	0.30 (0.19)	0.23 (0.17)	0.30 (0.22)	0.29 (0.18)	0.31 (0.20)	n.s.	n.s.	n.s.	n.s.
Anxious	0.50 (0.22)	0.32 (0.19)	0.32 (0.19)	0.18 (0.16)	0.30 (0.18)	0.20 (0.16)	p< 0.001	p< 0.001	p< 0.001	p< 0.001

In comparison with age-matched control subjects, females with "pure" PD (i.e. females with PD but without the onset of a comorbid major affective disorder during the follow-up) scored significantly higher in ANX and CT subscales ($p<0.001$ and $p<0.05$, respectively), while males with "pure" PD scored significantly higher on the HT subscale ($p<0.05$). These results are similar to those of the total PD sample, but for both genders some of the findings from the total sample cannot be detected here (these differences may be explained by the low number of subjects with "pure" PD [n=23]).

Discussion

The relationship between anxiety disorders (ANXDs) and temperaments was investigated previously primarily with the use of the temperament dimensions (novelty seeking, reward dependence, harm avoidance, persistence) of Cloninger's psychobiological model. According to this, patients with ANXDs – including PD – show marked and state-dependent patterns of harm avoidance behavior (Cloninger et al., 1993; Kampman et al., 2014). On the other hand, there have only been a few studies that used the AFT concept of Akiskal in patients with ANXDs (Akiskal et al., 2005a; Akiskal et al., 2005c). For example, a Turkish study compared the temperament profiles of 42 patients with PD and 44 patients with obsessive-compulsive disorder (OCD) measured by TEMPS-A. Authors found that dominant DT was more common in the OCD group, whereas HT temperament scores were higher in the PD group. Dominant HT was not confirmed in either group and no comparison with control group was carried out (Fistikçi és mtsai., 2013). Another study from Turkey sought to investigate the relationship between PD, AFTs, and impulsivity, for which only a few contradictory data were available (Beşirli, 2018). Author found that PD patients (n=70) had significantly higher scores on the DT, CT, and IT and AT subscales as measured by TEMPS-A, and also had higher scores on attentional impulsivity compared with healthy controls (n=58) (Beşirli, 2018). A third Turkish study confirmed previous findings on higher scores on the DT, CT, IT, and AT subscales in the group of PD patients (n=60) than in the age-, gender-, and education-matched control group (n=37). The HT scores did not differ significantly between patients and controls (Altınbaş et al., 2015). An Italian study examined 64 outpatients with PD and 44 healthy controls matched by gender, age, education, work, and marital status. In the PD sample, significant lifetime comorbidity was confirmed for cyclothymia (31.2%), and these patients had high scores on the CT subscale. Del Carlo's results were consistent with Savino's previous data that bipolar spectrum characteristics are common in the PD patient group (Savino et al., 1993; Del Carlo et al., 2013).

Examining temperament characteristics, higher scores were confirmed in PD patients on the depressive, cyclothymic, anxiety, and irritable TEMPS-M subscales (Del Carlo et al., 2013). Del Carlo hypothesized that PD is associated not only with bipolar spectrum disorders (e.g. with cyclothymia), but also with impulsivity as a state-dependent and trait feature.

The resulting complex clinical picture may be characterized by rapid mood swings, impulse control, addictive and eating disorders (Del Carlo et al., 2013).

Schiele et al. studied 109 patients with PD (34 out of them also had comorbid MDD). Panic patients scored significantly higher on the DT, CT, IT, and AT subscales, and achieved lower scores on the HT subscale compared to healthy controls (n = 536). Females had significantly higher scores on the DT and AT subscales in both the patient and healthy control groups. In addition to AT, CT was common in the examined PD sample, although less considerably. CT was associated with comorbid cyclothymia and other bipolar spectrum disorders, confirming previous findings on the genetic overlap between PD and BD (Savino et al., 1993; Akiskal et al., 2006; MacKinnon et al., 1997; MacKinnon et al., 2002; Schiele et al., 2020).

In our study, we sought to assess the distribution of AFTs among outpatients with PD. Compared to similar prior investigations, we were able to include a relatively large number of PD patients (n=118) into our study. PD subjects were compared with age- and gender-matched controls (n=118) as well as with a large normative Hungarian sample (n=1132). Furthermore, we recorded the family history data on the presence of anxiety disorders [ANXDs] and/or major affective disorders, psychoactive substance use disorders and completed suicide among first- and second-degree relatives. In the follow-up phase of the study (with an average duration of 26.4 months) we registered newly developed major affective disorders (MDD and bipolar spectrum disorders) and AG as well as the occurrence of suicide events. Furthermore, we gathered information about the prevalence of agoraphobia (AG) at study entry and data on previous suicide attempts.

According to our results, the proportion of female patients (68%) was more than twice the proportion of male patients (32%), which is in line with the epidemiological data on the gender distribution of PD (Rihmer and Angst, 2009c; de Jonge et al., 2016; Szádóczky et al., 2000, 2004). The mean age of the patients was 44.4 years and they had PD for 10.1 years on the average. 65% of patients had AG at study entry, which is consistent with literature (Savino et al., 1993; Merikangas, 2009; Kessler et al., 2006). Psychoactive substance use affected 9.5% of patients, whereas 5% of them had previous suicide attempt. During the follow-up, newly developed MDD and bipolar spectrum disorders were observed in 64% and 22% of patients, respectively. These data are in line with the findings of others on the frequent comorbidity between panic and mood disorders (Savino et al., 1993; Perugi et al. Toni, 2012; Roy-Byrne et al., 2000).

If we take all examined patients into account (i.e. the 118 included and the 57 excluded patients), the lifetime prevalence of the comorbidity between PD and BD was 31.5% (55/175).

This figure is about ten times higher than the lifetime prevalence of BD-I and -II in the general population. This result further supports the previously described strong relationship between PD and BD (Merikangas and Rihmer, 2017). The proportion of newly developed AG was 8.5%, resulting in a total of 73.5% of PD patients having AG (before inclusion and during the follow-up). No suicide event was registered among the patients during the follow-up. With regard to AFTs, we found that our female patients with PD had significantly higher scores on the AT / DT / CT subscales, while males showed significantly higher scores on the AT / DT / HT subscales compared to the gender- and age-matched control group (n=118) as well as to the normative Hungarian sample (n=1132). Since PD belongs to the group of ANXDs, and, in addition, its comorbidity with MDD and bipolar spectrum disorder is common (and it is known that HT and CT temperaments are primarily characteristic for BD-I, CT for BD-II and DT for MDD), results on AFTs are consistent with our hypotheses (Rihmer et al., 2010; Kessler et al., 2006, DSM-5, 2013; Perugi and Toni, 2012; Roy-Byrne et al., 2000). Our findings are in line with and at the same time enrich the concept that AFTs have a specific pathoplastic role in various psychiatric disorders.

Our findings suggest that the AFT profile of patients with PD differs from those of patients with MDD and BD, as the most common type of AFT in PD was AT (since PD is an anxiety disorder this result is unsurprising). Among females, the dominant AT was four times more common than in the normative Hungarian sample with a large sample size. Our data on AT support the view of Akiskal, who supplemented the four temperament types of Kraepelin (DT, CT, HT, IT) with AT (Akiskal et al., 2005a; Akiskal et al., 2005b). In our female patients with PD, dominant DT occurred three times more frequently than in the large normative sample. With regard to the group of male patients with PD, there was no significant difference in terms of dominant affective temperaments compared to the normative Hungarian sample. In consistence with previous studies, our results showed that – irrespective of gender – AT and DT were associated with PD. On the other hand, unlike findings of other studies, IT did not correlate with PD. However, high HT scores were confirmed in male patients, consistent with findings of Savino and Fisticki (Savino et al., 1993; Fistikci et al., 2013).

High CT scores were demonstrated in the group of female patients with PD, with international data suggesting that CT is also more common in the general population among females (Rihmer et al., 2010).

The so-called “pure PD” group (n=23), which consisted of PD patients who did not develop comorbid major affective disorder during the follow-up, was also compared to age- and gender-matched control subjects (n=23). Significantly higher scores were observed on the AT and CT subscales in female patients with “pure” PD, while male patients with “pure” PD scored significantly higher on the HT subscale. These results are only partially consistent with the temperament distribution of the total sample, which may be explained by the small sample size of the “pure PD” group.

Our study has several limitations. First and foremost, the relatively small sample size, especially of the male group (n=38), which largely impairs the opportunity to generalize our results. Another important limitation is that current (i.e. at the time of the inclusion) and lifetime diagnoses were not based on structured interviews (such as SCID-5-CV [Structured Clinical Interview for DSM-5 - Clinician Version]) (First et al., 2015). Another significant limitation of our research is the relatively short follow-up period, due to which the long-term development of comorbid affective disorders could not be detected. An important aspect in this regard is that the diagnosis of MDD is often not definitive, as 50% of patients with MDD develop (hypo)manic episodes during long-term follow-up, so their final diagnosis will be BD (Akiskal, 2017). Therefore, it is conceivable that the final (and correct) diagnosis is BD for a subset of participants with newly developed MDD during the follow-up.

Conclusions, new results

In this study, we investigated the distribution of AFTs in patients with PD and compared that with the AFT profile of the general population. According to our results, characteristic temperament profile of PD patients included in the study were AT / DT / CT for females and AT / DT / HT for males. These findings are in line with our expectations because PD is an anxiety disorder on the one hand, while, on the other hand, PD is quite frequently comorbid with mood (including MDD and BD) disorders.

The so-called “pure PD patients” (i.e. those free from the onset of a comorbid major affective disorder during the follow-up) had significantly higher scores on the AT and CT subscales (in case of females) and on the HT subscale (in case of males).

These results are only partially consistent with the temperament distribution of the total patient sample, which may be explained by the small sample size of the “pure” PD group. Overall, the study has confirmed that AFTs can be considered as subclinical forms of clinical affective (i.e. anxiety and mood) disorders.

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