The link between personality dimensions and pain perception in patients with diabetes mellitus or cancer

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Abstract

Background and aims. Diabetes mellitus and cancer are two diseases with a strong psychological impact. Personality traits modulate the perception of pain and the response to disease. The specificity of this study consists of the assessment of personality, pain and emotional impact in the two diseases.

Method. The study included 130 participants assigned to 3 groups: patients with diabetes mellitus, patients with cancer disease, and a control group. The personality traits of all the participants were analyzed using Cloninger’s Temperament and Character Inventory (TCI). For the evaluation of pain, as well as associated anxiety and depression in the diabetes and cancer groups, the Brief Pain Inventory (BPI) and the Hospital Anxiety and Depression Scale (HADS) were used.

Results. Patients with diabetes mellitus and cancer disease had significantly higher total values on the Harm Avoidance scale (HA) (p<0.001) and lower total values on the Self-Directedness scale (SD), Reward Dependence scale (RD), Cooperativeness scale (CO) (p<0.001) compared to the control group. Major anxiety was predominant in patients with diabetes mellitus (34%), and major depression was prevalent in cancer patients (17.5%). Patients with diabetes mellitus obtained a significantly higher severity score at BPI scale than patients with cancer disease (p=0.03).

Conclusions. The existence of a mutual personality profile featuring high levels of Harm Avoidance and low levels of Self-Directedness in patients with diabetes mellitus and cancer who experience pain has great implications for the therapeutic approach. A potential future avenue of management in these diseases may lie in targeting particular personality aspects of chronic pain patients.

Keywords: personality, TCI, pain, diabetes, cancer

Background and aims

Diabetes mellitus and cancer are two diseases with a strong psychological impact, either through their chronic, disabling nature and negative effect on the quality of life (diabetes) or through their discouraging, frequently fatal evolution (cancer). A common and frequent symptom is pain, especially chronic pain. It is difficult to imagine pain without emotion. Suffering associated with a nociceptive stimulus is reflected in the emotional response, which is useful in adaptive coping mechanisms and more effective in the case of acute pain [1]. However, emotions also contribute to disturbances in the affective area, as a result of chronic pain, in particular. Studies have demonstrated that pain is associated with emotions such as: anger [2], anxiety [3,4], fear [5,6], worry [7]. Psychological factors are strong predictors of pain experience [8] and psychological models are focused on characteristic cognitive, emotional and behavioral patterns that influence the perception of pain. The background in which these patterns develop is represented by personality. Personality traits and other cognitive and emotional patterns play a role in the processing and interpretation of pain experience, and they can be modeled as protective and risk factors for pain [9].

Cloninger’s model is composed of 7 dimensions of personality, having the general advantages of dimensionality and retaining at the same time the solid theoretical basis and the empirical support of previous psychobiological models (Eysenck, McCrae), being suitable for the determination of personality traits, as well as for the identification of their pathological
deviations (personality disorders). The Temperament and Character Inventory (TCI) can be more useful in clinical practice than other personality assessment questionnaires (Minnesota Multiphasic Personality Inventory, NEO-Personality Inventory) because it follows a psychobiological personality model that makes the distinction between the temperament and character dimensions [10]. The different temperament dimensions are defined in terms of basic stimulus-response characteristics. Novelty Seeking (NS) is thought to be related to the behavioral activation system, Harm Avoidance (HA) to the behavioral inhibition system, Reward Dependence (RD) to the behavioral maintenance system, and Persistence (P) to perseverance in behavior despite frustration and fatigue. Of the character dimensions, Self-Directedness (SD) refers to an individual’s ability to control and adapt their behavior in accord with chosen goals and values, Cooperativeness (CO) to their tendency towards social tolerance, empathy and compassion, and Self-Transcendence (ST) to their identification with nature and the ability to accept uncertainty [11]. According to Cloninger’s theory, temperament represents the “emotional core” of personality, genetically transmitted and considered stable throughout life regardless of the cultural or social context, while character represents the “conceptual core”, which develops in stages through the interaction between temperament, socio-cultural environment and life experiences. This theory is supposed to be relevant for the perception of pain because serotonin, the neurotransmitter correlated with Harm Avoidance (HA) [12], is one of the major transmitters in the inhibitory modulation of pain by descending pathways.

Harm avoidance is one of the four independent temperament dimensions that form the “emotional core” of personality. This dimension reflects a neurobiological predisposition to the early emotion of fear and its related automatic behavior, which can be described as inhibition [13]. Individuals with high scores of harm avoidance can easily develop avoidant responses to aversive stimuli, which makes them susceptible to fear [14]. Waddel et al. concluded in their studies that the fear of pain and the behavior associated with this fear is more disabling than the pain itself [15]. The fear-avoidance model states that avoidant movements and activities based on fear are the central mechanism in the development of chronic pain [16]. Depression and disability are consequences of these avoidant behaviors which maintain the pain experience and perpetuate the vicious circle of increasing fear and avoidance [17]. The actual pain behavior may result from an interaction between the perception of somatosensory information, personality characteristics and environmental feedback.

Cloninger’s biopsychosocial model was developed and used mainly in the field of psychiatry; few studies use this model in non-psychiatric patients, such as patients with pain [13,18-21].

The main focus of the study is to explore the link between personality dimensions and pain perception in diabetes mellitus and cancer. Specifically,

1. The hypothesis of a higher score in the Harm Avoidance (HA) temperament dimension and a lower score on the Self-Directedness (SD) character scale compared to the control group was advanced.

2. Pain and the associated degree of anxiety and depression were assessed in patients with diabetes mellitus and cancer disease.

Subjects and methods

Subjects

The study was conducted on 130 patients assigned to 3 groups: diabetes (50), cancer (40), and control (40). The first group included 50 diabetic patients admitted to the Clinical Center for Diabetes, Nutrition and Metabolic Diseases Cluj-Napoca in the period 19.02.2016-11.03.2016. Of these, 13 patients had type 1 diabetes mellitus and 37 patients had type 2 diabetes mellitus. The second group comprised 40 patients admitted to the service of Oncology of the Alba County Emergency Hospital in the period 3.05.2016-6.05.2016. Of these, 29 patients were admitted on a day care basis for chemotherapy, and 11 patients were admitted on an inpatient basis. The third group, representing the control group, included 40 patients with hypertension from Cluj-Napoca selected in the internal medicine department at the free Polyclinic “Holy family”, Cluj-Napoca and was only used to compare the groups regarding their personality traits.

Study inclusion criteria: patients diagnosed with type 1 or type 2 diabetes mellitus, with cancer disease regardless of the stage, type of treatment or date of diagnosis; absence of mental retardation, presence of the patient’s consent.

Study exclusion criteria: presence of mental retardation, presence of disabling or metastatic pain, presence of high-intensity pain at the moment of evaluation, presence of a diagnosis of anxiety or affective disorder prior to our study, absence of the patient’s consent, inadequate mental or physical state, incomplete data because of the patient’s discharge or transfer.

The patients were free to withdraw from the study at any time, without prejudice.

The study protocol was approved by the Local Ethics Committee and all patients gave their written informed consent.

Methods

Sociodemographic data form

For each patient in the diabetes mellitus and cancer disease groups, data on age, sex, background, marital status, education level, religion were collected.

Temperament and Character Inventory (TCI)

Each participant in the study was administered the Temperament and Character Inventory (TCI) for evaluation of personality traits. TCI is a self-administered questionnaire that measures the 4 temperament dimensions (NS, HA, RD, and PS) and the 3 character dimensions (SD, CO, and ST). The 240 items are answered “yes” or “no”.

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Each temperament and character dimension, except for persistence, is evaluated as the sum of scores of 3 up to 5 subscales that measure more specific traits. The subscales corresponding to each scale were analyzed.

**Hospital Anxiety and Depression Scale (HADS)**

HADS is a 14-item scale which determines the generation of ordinal data. Of the 14 items, 7 assess anxiety and the other 7, depression. Each item is scored from 0 to 3. Both anxiety and depression are considered absent at a score lower than 7, moderately present at a score between 8-10, and major at a score higher than 11.

HADS is a practical screening tool for identifying and quantifying anxiety and depression in the medical clinic for non-psychiatric patients. The Romanian version of the scale shows appropriate reliability and validity. The use of this instrument is strongly recommended to assess anxiety and depression in the chronic pain population, as it does not include items of a somatic nature that can give false positive results. In Romania, the validity of HADS was confirmed in both psychiatric [22] and medical adult patients [23] and the validation studies showed a high internal consistency of both scales: HADS-A (Cronbach’s α ranging between .68 and .93) and HADS-D (Cronbach’s α ranging between .67 and .90) [23].

**Brief Pain Inventory (BPI)**

Brief Pain Inventory (BPI) is a self-administered questionnaire originally designed to assess cancer pain, which is now also used as a generic pain questionnaire for chronic pain. It is available in a short (9 items) and long (17 items) form. The short BPI form is the most frequently used. The first, optional, item is a screening question about the respondent’s pain on the day. The questionnaire is then composed of pain drawing diagrams, four items about pain intensity (worst pain, least pain, average pain, pain right now), two items on pain relief treatment or medication, and one item on pain interference, with seven subitems (general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life) [24]. A consensus panel recommended that the two domains measured by BPI - pain intensity and the impact of pain on functioning (interference), be included as outcomes in all chronic-pain clinical trials [25].

Data collection was performed using the method of non-probabilistic, rational sampling conditioned by the inclusion and exclusion criteria presented above.

**Statistical analysis**

Statistical analysis was carried out using SPSS 25.0 and Microsoft Excel. The data in this study were described using descriptive statistical methods (means, percentagess, and standard deviations). Analyses of variance (ANOVAs) were performed to assess whether each dependent variable of TCI was statistically different between the groups. The level of significance was set at p<0.001 (Bonferroni correction). The t-test for independent samples with equal variances and Levene’s test for comparison of the results obtained on BPI (interference and severity scores) between the group of patients with diabetes mellitus and those with cancer disease were used.

**Results**

The analysis of the 130 patients included in the study showed the predominance of the female sex in all three groups (72% diabetes group, 57% cancer group, 70% control group), an average age of 60 in the cancer group, of 54 in the diabetes group and of 39 in the control group.

From a psychosocial point of view, the patients came from urban areas, had secondary education, were married and of Orthodox religion.

**Results of TCI (Temperament and Character Inventory)**

Significant results were obtained for the overall scores of the Harm Avoidance, Reward dependence, Self-Directedness and Cooperativeness scales and isolated significant scores for the Novelty Seeking (NS1) subscale.

**Domains of Temperament**

Results regarding Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), Persistence (P) scales and their respective subscales are described in Table I. No significant difference was obtained for the total mean value of the Novelty Seeking scale, however NS1 subscale had significantly lower scores in both studied groups (p<0.001).

Harm Avoidance was significantly higher (p<0.001) in both studied groups. Also, the mean value obtained on subscale HA4 was significantly higher for both studied groups compared to the control group.

The value obtained on the Reward Dependence scale and on the RD3 subscale in both studied groups were significantly lower (p<0.001) than in the control group.

No significant difference was found on the Persistence (P) scale between the 3 groups.

**Domains of Character**

Results regarding Self-Directedness (SD), Cooperativeness (CO), and Self-Transcendence (ST) and their respective subscales are represented in Table II.

Self-Directedness (SD) had significantly lower scores (p<0.001) in both studied groups compared to the control group. Furthermore SD1 and SD3 had significantly lower scores in the studied groups, in contrast to SD2 that had significantly lower scores only in the diabetes mellitus group.

Cooperativeness (CO) values were significantly lower for the subjects with cancer and those with diabetes (p<0.001), as were the values for the C2 and C5 subdimensions compared to the control group. Furthermore C1 and the C3 subscales had significantly lower scores only in the diabetes mellitus group.

The Self-Transcendence (ST) scale showed no significant difference for the total mean value between the 3 groups.
### Table I. Temperament domains of individuals with diabetes mellitus or cancer disease compared with control group.

|                        | DM Group (Mean±SE) | CD Group (Mean±SE) | CON Group (Mean±SE) | DM vs CON (ANOVA) | CD vs CON (ANOVA) |
|------------------------|---------------------|--------------------|---------------------|-------------------|-------------------|
| Novelty Seeking (NS) Total | 15.26±3.99          | 15.35±5.28         | 17.57±5.63          | .025              | .072              |
| Exploratory excitability vs. stoic rigidity (NS1) | 4.98±1.86           | 4.75±2.26          | 6.72±2.26           | .000              | .000              |
| Impulsiveness vs. reflection (NS2) | 3.48±1.79           | 3.67±2.1           | 2.97±2.06           | .219              | .140              |
| Extravagance vs. reserve (NS3) | 3.58±1.48           | 3.60±1.99          | 4.57±1.99           | .008              | .032              |
| Disorderliness vs. regimentation (NS4) | 3.30±1.74           | 3.22±1.74          | 3.22±1.75           | .830              | .949              |
| Harm avoidance (HA) Total | 19.64±6.20          | 19.85±7.63         | 13.32±6.02          | .000              | .000              |
| Worry/pessimism vs. uninhibited optimism (HA1) | 5.54±2.55           | 5.60±2.68          | 4.05±2.14           | .004              | .006              |
| Fear of uncertainty vs. confidence | 4.72±1.40           | 4.85±2.01          | 3.87±1.58           | .009              | .019              |
| Shyness with strangers vs. gregariousness (HA3) | 4.04±1.64           | 4.27±2.30          | 3.05±2.01           | .012              | .013              |
| Fatigability/asthenia vs. vigor (HA4) | 5.34±2.20           | 5.12±2.26          | 2.40±2.09           | .000              | .000              |
| Reward dependence (RD) Total | 14.34±3.5           | 14.35±3.23         | 17.35±3.2           | .000              | .000              |
| Sentimentality vs. insensitivity (RD1) | 7.00±1.87           | 7.27±2.13          | 7.80±1.66           | .037              | .224              |
| Attachment vs. detachment (RD3) | 4.60±1.96           | 4.35±1.71          | 6.27±1.81           | .000              | .000              |
| Dependence vs. independence (RD4) | 2.74±1.74           | 2.72±1.37          | 3.27±1.48           | .127              | .090              |
| Persistence (P) Total | 4.18±1.40           | 4.15±1.44          | 4.55±1.53           | .238              | .331              |

DM = Diabetes Mellitus; CD = Cancer disease; CON = control group

### Table II. Character domains of individuals with diabetes mellitus or cancer disease compared with control group

|                      | DM Group (Mean ± SE) | CD Group (Mean ± SE) | CON Group (Mean ± SE) | DM vs CON (ANOVA) | CD vs CON (ANOVA) |
|----------------------|----------------------|----------------------|-----------------------|-------------------|-------------------|
| Self-Directedness (SD) Total | 27.30±6.38          | 29.30±4.91          | 34.60±3.7            | .000              | .000              |
| Responsibility vs. blaming (SD1) | 5.08±1.95           | 4.95±1.41           | 6.82±1.05            | .000              | .000              |
| Purposefulness vs. lack of goal direction (SD2) | 4.80±1.60           | 5.47±1.58           | 6.22±1.42            | .000              | .029              |
| Resourcefulness vs. inertia (SD3) | 2.60±1.21           | 2.82±1.33           | 4.50±0.75            | .000              | .000              |
| Self-acceptance vs. self-striving (SD4) | 6.96±2.25           | 7.47±2.02           | 6.72±2.59            | .647              | .153              |
| Cooperativeness (CO) Total | 28.7±5.25           | 30.1±4.17           | 35.02±3.05           | .000              | .000              |
| Social acceptance vs. social intolerance (C1) | 5.58±1.84           | 6.25±1.54           | 7.12±1.01            | .000              | .004              |
| Empathy vs. social disinterest (C2) | 3.66±1.39           | 3.72±1.53           | 5.35±0.89            | .000              | .000              |
| Helpfulness vs. unhelpfulness (C3) | 5.48±1.35           | 6.02±1.02           | 6.75±1.29            | .000              | .007              |
| Compassion vs. revengefulness (C4) | 7.78±1.58           | 7.92±1.24           | 8.37±1.14            | .049              | .097              |
| Pure-hearted principles vs. self-advantage (C5) | 6.24±1.49           | 6.22±1.18           | 7.47±1.08            | .000              | .000              |
| Self-transcendence (ST) Total | 16.28±6.62          | 16.85±5.68          | 14.15±6.34           | .126              | .484              |
| Self-forgetful vs. self-conscious (ST1) | 5.40±2.55           | 5.50±2.43           | 3.82±2.17            | .003              | .002              |
| Transpersonal identification vs. self-differentiation (ST2) | 4.70±2.34           | 5.22±2.15           | 3.12±2.05            | .001              | .000              |
| Spiritual acceptance vs. rational Materialism (ST3) | 6.18±2.94           | 6.12±2.77           | 7.22±3.25            | .114              | .108              |

DM = Diabetes Mellitus; CD = Cancer disease; CON = control group
**Results following the application of HADS (Hospital Anxiety and Depression Scale)**

Following quantification of the anxiety and depression forms in the two study groups using the HADS scale, it was observed that major anxiety was more frequent in diabetics (34%) compared to a much lower percentage (20%) in cancer patients. Moderate anxiety was found in almost equal proportions in the two groups (22%). The absence of anxiety was more frequent in the group of cancer patients (57.5%) compared to the group of diabetic patients (44%). Regarding depression, the major form was seen in 17.5% of cancer patients compared to 16% of diabetics. Moderate depression was more frequent in diabetics (24%) compared to cancer patients (15%), and the absence of depression was more frequent in cancer patients (67.5%) compared to diabetics (60%).

**Results following the application of BPI (Brief Pain Inventory)**

Following analysis of the BPI inventory, higher severity and interference scores were obtained for the group of diabetic patients (Table III). The differences between the two groups were significant regarding the BPI severity score (t-test for independent samples, p=0.03) (Levene’s test for equal variances F=0.539, p=0.465, t-test for independent samples with equal variances, t=2.205, p=0.03) (Table IV). In the case of the interference score, there were no significant differences between the two groups (Levene’s test F=2.63, p>0.05, t-test for independent samples with equal variances, t=1.11, p>0.05).

**Table III.** Mean and standard deviation (m±sd) for BPI scores.

| Score            | Cancer     | DM        | p (Levene) | p (t-test)          |
|------------------|------------|-----------|------------|---------------------|
| BPI Severity Score | 3.42±2.55  | 4.54±2.25 | 0.39       | 0.03 (equal variances) |
| BPI Interference Score | 4.11±2.83  | 4.71±2.33 | 0.19       | 0.267 (equal variances) |

**Table IV.** Mean and standard deviation, t-test and Levene’s test for the BPI severity score.

| Group Statistics | N   | Mean | Std. Deviation | Std. Error Mean |
|------------------|-----|------|----------------|-----------------|
| Diabetes Mellitus Patients | 50  | 4.5440 | 2.25082 | 0.31831 |
| Oncology Patients | 40  | 3.4250 | 2.55842 | 0.40452 |

**Independent Samples Test**

| Levene’s Test for Equality of Variances | t-test for Equality of Means | 95% Confidence Interval of the Difference |
|----------------------------------------|------------------------------|---------------------------------------|
| F                                      | Sig.                         | t                          | Df       | Sig. (2-tailed) | Mean Difference | Std. Error Difference | Lower | Upper     |
| BPI Severity Score Equal variances assumed | .539 | .465  | 2.205 | 88      | .030   | 1.11900   | .50743   | .11060 | 2.12740   |
| Equal variances not assumed            | 2.174 | 78.343 | .033  | 1.11900 | .51474 | .09429     | 2.14371 |
Discussion

In this investigation, we have found that individuals with diabetes and cancer have significantly higher scores in the scale of Harm Avoidance and significantly lower scores in the Self-Directedness, Reward Dependence and Cooperativeness scales when compared to the to age- and gender-matched controls.

The findings of the current study suggest that personality traits can have a determinant role in integrating the concept of disease and this could explain the variability of pain perception among individuals. Even more, this study indicates that patients who experience pain may exhibit a mutual personality profile featuring high levels of Harm Avoidance accompanied by low levels of Self-Directedness, as mentioned in other studies [26,27]. In addition, our findings point out that more attention should be paid to the low scores in Reward Dependence and Cooperativeness of cancer and diabetes patients.

Harm Avoidance assessment could be useful in clinical practice as a high score predicts a negative perception of pain, a distorted representation of the disease and a worse response to antidepressant treatment in mood disorders [28,29].

Higher scores of Harm Avoidance in patients with diabetes and cancer compared to the control group suggest that these individuals could be described as cautious, tense, fearful, worrying, passive and fatigable. These traits are considered to be markers of vulnerability [30,31] of a higher severity of depression [32] but also of pain-related anxiety [33]. Furthermore, Harm Avoidance is regarded as the TCI equivalent of behavioral inhibition [32], which is considered to reflect sensitivity to stress on a behavioral level [34]. On the HA scale, significantly higher values were obtained for subscale HA4 (Fatigability and Asthenia vs Vigor). According to Cloninger’s model, with high Fatigability recover from minor illnesses and stress more slowly than average people individuals do [18]. Fatigability as a trait construct reflects the negative affectivity associated with an enhanced distress in somatic illnesses.

Low scores, as the ones we obtained on the Self-Directedness scale, reflect an individual’s tendency to blame other people and external circumstances for what is happening to them (SD1), alongside their struggle to find direction, purpose and meaning in their lives (SD2). As a consequence they generally seem to be lacking an internal locus of control, which prevents them to define, set and pursue meaningful goals [18].

Our results indicate lower scores in Reward Dependence especially in subscale RD3 in patients with diabetes and cancer. This suggests that they are reserved individuals who don’t tend to express their emotions and energy, behavior that has a negative impact on the perception of pain and disease. The low scores in Cooperativeness scale indicate the fact that these patients tend to retreat and to not ask for help, even if they are in distress. Further research should be conducted for a better understanding of the low Reward Dependence and Cooperativeness scores in patients with diabetes mellitus or cancer disease.

The low scores obtained on the Novelty Seeking scale suggest that patients in the diabetes mellitus and cancer disease groups have a tendency to be slow, indifferent, to lack curiosity and enthusiasm.

Pain and emotions are frequently associated with multiple comorbid symptoms [35]. The perception of pain is accompanied by anxiety, depression and other emotional symptoms [3,4]. Our research shows that major anxiety was more frequent in patients with diabetes. Diabetes is a growing problem that poses a major public health challenge globally. Patients with diabetes are more predisposed to depression [36,37], anxiety and personality disorders, and at the same time these conditions can increase the risk of developing diabetes. Depression is the most commonly researched factor in studies regarding diabetes. However, more research should be conducted to investigate anxiety disorders in these patients. Overviews of a study [38] suggest that diabetes is associated with 20% increased odds of having an anxiety disorder and 48% increased odds of having elevated anxiety symptoms. This elevated anxiety could be the reason why pain perception is frequently more intense in diabetes patients, as reflected in the high scores obtained in the BPI.

Major depression was more frequent in patients with cancer. It is known that both pain and depression are common in cancer patients and many studies have indicated a significant association between these two prevalent symptoms in these patients [39,40].

Even though the prevalence of chronic pain in cancer free patients is high, it remains underappreciated in comparison with the quest for survival [41]. Patients with a long history of pain disorders have increased anxiety and depression symptoms, as well as suicidal thoughts. A regular basic evaluation can help oncology staff to identify patients with clinical depression. There has been an extensive discussion in literature about the fact that patients suffering from chronic diseases and pain associated with anxiety and depression have poor emotional regulation strategies [1]. It would be more important to know the underlying mechanism of the two comorbidities—pain and emotional problems (anxiety and depression) than to focus on diagnostic and treatment modalities alone, in the hope that treating one condition can improve the other.

The limitations of this study are the relatively small number of patients, reliance on self-reported data, and the patients’ heterogeneous pain disorders that can complicate the interpretation of the results. HA scores may be susceptible to demographic factors such as gender, age and educational level.

The strengths of the study reside in there not being many studies that investigate the link between personality dimensions and anxiety in patients with diabetes or cancer.
who experience pain. Furthermore, our results were significant in the Reward Dependence and Cooperativeness scales, not just in the Harm Avoidance and Self-Directedness scales as previously studied.

Conclusions
This study reveals that there is a link between personality dimensions and pain perception in patients with diabetes mellitus or cancer and emphasizes the traits that make them vulnerable when confronting pain as well as their disease. Our results confirm the existence of a mutual personality profile featuring high levels of Harm Avoidance and low levels of Self-Directedness in patients who experience pain, as previously studied. More attention should be paid to associated anxiety in patients with diabetes mellitus or neoplasms who experience pain, whose personality is insufficiently investigated and is a major factor of treatment resistance. Our finding regarding low levels of Reward Dependence and Cooperativeness could potentially extend the personality profile of these patients, and open a gateway to future research.

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