European Archives of Psychiatry and Clinical Neuroscience (2019) 269:911–920
https://doi.org/10.1007/s00406-018-0907-1

ORIGINAL PAPER

The cognitive, affective motivational and clinical longitudinal determinants of apathy in schizophrenia

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Received: 10 January 2018 / Accepted: 22 May 2018 / Published online: 8 June 2018

Abstract

Apathy is a frequent and debilitating condition with few treatment options available in schizophrenia patients. Despite evidence of its multidimensional structure, most of past studies have explored apathy through a categorical approach. The main objective of this study was to identify the cognitive, emotional, motivational, and clinical factors at baseline that best predicted the three subtypes of apathy dimensions at follow-up. In a longitudinal study, 137 participants diagnosed with schizophrenia underwent different assessments including clinical, motivational, affective and cognitive measurements, at 1-month (referred to as baseline) and 12-month follow-ups. Data were analyzed using partial least squares variance-based structural equation modeling. Three latent variables representing the three previously described domains of apathy reaching consensus in the literature were extracted from the Lille Apathy Rating Scale. Results showed that in addition to baseline apathy, positive symptoms, anticipatory pleasure and sensibility to punishment at baseline predicted cognitive apathy at follow-up. Likewise, both baseline apathy and sensibility to punishment predicted emotional apathy at follow-up. Finally, baseline anhedonia and episodic memory were the main variables the predicted behavioral apathy at follow-up. This is the first study to show specific associations between apathy subtypes and clinical and cognitive motivational dysfunction in individual with schizophrenia, indicating possible distinct underlying mechanisms to these demotivational symptoms. Treatment for apathy should address both types of processes. Importantly, our results demonstrate the interest of multidimensional approaches in the understanding of apathy in schizophrenia.

Keywords Apathy · Longitudinal study · Negative symptoms · Partial least squares-path modeling

Introduction

Apathy is a prominent and influential symptom in most neurological and psychiatric disorders, characterized by a quantitative reduction of goal-directed behavior [1]. While conceptualizations of apathy vary in neurological literature, there is general agreement across most definitions for a triadic substructure including cognitive/affective, behavioral, and emotional dimensions [2–4]. The emotional-affective component refers to the loss of spontaneous emotional responsiveness to positive or negative stimuli or events. Cognitive apathy refers to a loss of, or diminished, goal-directed cognitive activity such as spontaneous or environment-stimulated ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs). Finally, behavioral apathy corresponds to diminished self-initiated or environment-stimulated behavior (for example: starting a conversation,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00406-018-0907-1) contains supplementary material, which is available to authorized users.

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doing basic tasks of day-to-day living, participating in social activities). Apathy is part of the negative symptomatology of schizophrenia, which can be grouped into two dimensions: amotivation–asociality and diminished expressiveness, according to a recent consensus [5, 6]. Apathy is highly prevalent in schizophrenia [2, 7] and has detrimental effects on quality of life [8], functional outcome [9–11] and is one of the most distressing symptoms for family members [12, 13]. Despite growing interest in the assessment [14] and the consequences of apathetic symptoms in schizophrenia, the underlying pathological mechanisms are not clearly understood and few treatment options are available [15]. One reason for this is that the vast majority of questionnaires used to quantify apathy were not specifically developed to measure apathy, but to assess negative symptoms overall [15]. As discussed elsewhere, it appears that the heterogeneity of apathy in terms of prognosis and causal factors has not received adequate and systematic attention [16] despite the development of new tools such as the Clinical Assessment Interview for Negative Symptoms (CAINS; [17]) and the Brief Negative Syndrome Scale (BNSS; [18]), which are able to differentiate the two factors amotivation-asociality and diminished expressiveness. Consequently, apathy in schizophrenia has been mostly analyzed through a categorical approach in which individuals are categorized as either "apathetic" or "not apathetic". Nevertheless, current evidence suggests that apathetic manifestations are better viewed on a continuum rather than simple categorical disorders [20, 21]. Such a continuous approach has clear advantages to better capture the heterogeneity of negative and apathetic manifestations largely neglected in previous studies [22]. Another important limitation of existing literature concerns the lack of a proper definition of apathy in schizophrenia and the tendency to cover the multidimensional aspects of apathy focusing mainly on the broader term of avolition which includes asociality, anhedonia and apathy [23]. However, there is now evidence that apathy can no longer be considered as a unique construct but rather as a multidimensional psychopathological state with different underlying psychological, biological or environmental processes [20].

Regarding its underlying components, apathy has been shown to be associated with cognitive deficits such as executive deficits [10], impaired working memory and episodic memory deficits [21, 24], clinical symptoms such as positive symptomatology or depression [25]. It has more recently been associated with dysfunctional processing of reward information in effort-based decision-making and reward anticipation procedure [26, 27]. However, the specific paths and underlying mechanisms which lead these specific mechanisms to specific dimensions of apathy remain unclear. Furthermore, the existing studies on this subject are mainly cross-sectional, which limits inferences of causality. In a recent study, Raffard et al. [21] showed that impaired cognition and more specifically working memory was associated with an increased risk of severe overall apathy 1 year later.

Aims of the study

Using the same sample as the study by Raffard et al. [21], the main objective of this study was to explore the effects of a multidimensional framework of risk factors on the different subtypes of apathy, including not only cognitive factors, but also affective factors (e.g., depression, anhedonia), motivational variables (e.g., anticipatory pleasure, sensitivity to reward and punishment) and clinical factors (antipsychotic medication, psychotic symptomatology and apathy at baseline) over an 11-month follow-up in schizophrenia patients.

To achieve this aim, we used structural equation modeling (SEM) which is a robust approach to test substantive theories and is particularly well suited to test competing models about cause-effect relationships in cross-sectional designs [28, 29] but also longitudinal.

Materials and methods

Subjects

Participants with a diagnosis of schizophrenia were recruited from full- and part-time hospitalization and ambulatory care services of the Departments of Adult Psychiatry in Montpellier, Marseille, and Nice (France). Diagnoses were made by a psychiatrist or a psychologist, both fully trained, using the structured clinical interview for DSM-IV (SCID; [30]). For more detailed description of the design of the study see Raffard et al. [21].

After inclusion, participants were followed-up at 1, 3, 6, and 12 months. In all, 166 patients with schizophrenia (77% male) aged between 19 and 59 years (median age 37) completed the study between January 2011 and December 2012. The current study was carried out on the 1-month (V1) and 12-month follow-up data (V4); 137 (82.5%) patients participated at the 1-month follow-up and 82 patients (59.1%) at both follow-ups.

Patients were aged between 18 and 60 years old and had to understand, talk and read French. Exclusion criteria were: (a) known neurological disease, (b) brain injuries, or (c) axis II diagnosis of developmental disorders. Written informed consent was obtained from all participants and the local ethical committee approved the protocol.

Apathy

Apathy was assessed using the Lille Apathy Rating Scale (LARS; [31]) which has been validated in French in

schizophrenia by Yazbek et al. [32]. The global score ranges from −36 to +36, with a higher score representing a greater degree of apathy.

Clinical variables

Symptom severity was measured using the 30-item Positive and the Negative Syndrome Scale (PANSS; [33]).

Affective variables

Depression was evaluated using the Calgary Depression scale for Schizophrenia (CDSS; [34. 35]).

Anhedonia was evaluated using the Anhedonia/Asociality subscale of the Schedule for the Assessment of Negative Symptoms (SANS; [19]). This subscale consists of four items that cover recreational interests and activities, sexual interest and activities, ability to feel intimacy and closeness, and relationships with friends and peers. These 4 items, as well as a global summary score, are rated on a 0 (not at all) to 5 (extreme) Likert scale.

Motivational variables

Anticipatory and consummatory pleasure was evaluated using the French version of the Temporal Experience of Pleasure Scale (TEPS; [36, 37]). It is an 18-item self-report measure of anticipatory (10 items) and consummatory (8 items) pleasure. The mean theoretical range of the two scales goes from 1 to 6; higher scores indicate more pleasure.

Sensitivity to punishment and reward were evaluated using the French version of Sensitivity to Punishment and Reward Questionnaire short version (SPSRQ; [38, 39]). The French short version of the SPSRQ [39] includes 35 items, similar to that developed by O'Connor et al. [40], of which 17 assess SR and 18 SP. Participants have to evaluate whether these items fit their personality on a four-point Likert scale, with 1 = totally true and 4 = totally wrong, with responses summed to obtain SR and SP scores.

Cognitive assessment

Episodic verbal learning was evaluated using the California Verbal Learning Test (CVLT; [41]). We used the total number of words recalled during the first and the fifth trial of the words in list A as well as the number of words recalled in List B.

Working memory was assessed using the Letter-Number Sequencing subtest (LNS) of the Wechsler Adult Intelligence Scale-III (WAIS-III; [42]).

Multitasking was assessed with the Modified Six Elements Test (MSET; [43]). The MSET requires the individual to devise a simple plan, schedule the subtests efficiently, and keep track of the time. The dependent variable was the mean profile score, an index based on the number of tasks attempted and the number of rule breaks.

Inhibition was assessed with the Stop Signal Paradigm (SSP; [44]). In the SSP, participants perform a go task, such as reporting the identity of a stimulus. Occasionally, the go stimulus is followed by a stop signal, which instructs subjects to withhold the response. Participants completed a total of 80 stop trials and 20 go trials. A higher inhibition percentage reflects better inhibition capacity [44].

Statistical analysis

It must be noted that this study represents a secondary analysis of data already published [29] on relationships of apathy as assessed by LARS with cognitive dysfunctions.

Descriptive data (mean, standard deviation, median, min–max and frequency) was analyzed using SPSS 17.0. Likewise, paired *t* test was performed to compare V1 and V4 Apathy scores (total score, cognitive, emotional and behavioral dimensions).

Data were analyzed using Partial Least Squares Structural Equation Modeling (PLS-SEM) to take into account simultaneous relationships among multiple constructs (for more details regarding this method see supplementary data). A bootstrapping procedure based on 5.000 resamples was used to calculate a 95% bias-corrected confidence interval (BCCI).

Before running the analysis using PLS-SEM, we first checked the data for outliers and the percentage of missing data using SPSS 17.0. We employed the Path Weighting approach to deal with missing data as recommended by Hair et al. [29]. Although Smart PLS makes no assumptions about data distribution, we also checked the skewness and kurtosis, since important deviations could inflate standard errors obtained from bootstrapping. Variables with high values of skewness and kurtosis were not included in the analysis; two items of apathy at V1, two items of apathy at V4, and item 7 of the PANSS at V1 were also excluded.

Subsequently we tested three models, one for each facet of apathy. First, the variables mentioned above and potential interactions (direct and indirect effect) between them were included in the model. In total 11 cognitive, affective, clinical, and motivational LV were created and entered, in addition to age, gender, education, duration of illness and chlorpromazine equivalents (total of 16 variables). Regarding the cognitive variables, a latent variable was created for episodic memory including the number of words recalled during the first and fifth trial of list A as well as the number of words recalled in list B. Working memory was entered alone. Moreover, a latent variable was created to measure executive function with inhibition and multitasking/planning. For the other latent variables

used in the model we entered all items in the original questionnaire as initially validated. Finally, for each V4 (follow-up) apathy dimensions (e.g., cognitive apathy dimension at baseline) only the respective V1 (baseline) apathy dimension was entered in the model (e.g., cognitive apathy dimension at follow-up).

Indicators were only retained if the indicator loadings (Indicator reliability) were higher than 0.5 although for some items values above 0.4 were also accepted if the composite reliability (internal consistency reliability) was higher than 0.6 and the average variance extracted (convergent validity) was higher than 0.5. The discriminant validity (Fornell–Larcker criterion) was also checked (see supplementary tables for cross loadings).

Secondly, we examined the structural model provided by Smart PLS [45, 46], and evaluated how well it predicted the dependent latent variable (apathy). To do so, we examined the adjusted R^2, the effect size f^2, and the Q^2 index which was calculated to measure the predictive power of the models based on the cross-validated redundancy approach. The confidence intervals of the PLS-SEM coefficients were obtained by cross-validation. The best predictive model was obtained by maximizing the Q^2.

We computed a model for each type of apathy: cognitive, emotional and behavioral. The definition and the choice of the items tested in each dependent LV was defined in accordance with Arnould et al. [20]. The indicators of the remaining LVs were based on the pre-validated scales/questionnaires considering, however, that some items were excluded at the first stage of the analysis. All scales/questionnaires mentioned in the methodology were entered in the model, in addition to socio-demographic variables such as age, gender and education, as well as other clinical variables such as duration of the illness and chlorpromazine equivalents. Aforementioned, only the variables that statistically predicted the LV were kept in the model; those that had no impact on cognitive, emotional and behavioral apathy do not appear in the model.

Results

Socio, demographic, and clinical data

Descriptive information of the 82 patients included at V4 for the socio, demographic, and clinical data are presented in Table 1. Total score of apathy (LARS) did not change from V1 to V4 [$t(81) = 1.232$, $p = 0.221$]. Likewise, no significant differences between V1 and V4 were found for cognitive (novelty seeking), behavioral (initiative) and emotional (emotional responses) apathy ($p > 0.05$).

Table 1 Mean and standard deviation for the socio, demographic and clinical variables ($N = 82$)

	Median	Min–Max[a]
Variables at V1		
Age (mean/SD)	36.74	9.93
Gender (male/%)	64	78%
Education (years/mean/SD)	4.57	1.04
Chlorpromazine equivalents	600	60–4250
Age at onset	19.94	10–43
Age 1st hospitalization	22.56	15–44
Duration of the disorder	15.20	1–41 years
Substance abuse (*N*/%)		
Cannabis	31	37.8%
Alcohol	11	13.4%
Other substances	20	24.4%
PANSS score total		
Positive symptoms	13.5	7–31
Negative symptoms	18.5	9–35
General psychopathology (mean/SD)	33.35	6.69
Anhedonia (SANS/ mean/SD)	2.61	0.97
Depression	2.50	0–23
Sensitivity to reward and punishment (mean/SD)		
Reward	41.35	8.91
Punishment	45.99	8.44
Pleasure (mean/SD)		
Consummatory	44.65	8.87
Anticipatory	31.91	6.67
Apathy (LARS/ mean/SD)	− 18.59	6.98
Episodic memory (CVLT)		
CVLT first trial	6	0–14
CVLT fifth trial	11	3–16
CVLT all trials list A	46	9–78
Working memory (mean/SD)		
Mean Empan	22.33	5.81
Flexibility		
TMT B-A time	59	14–190
Inhibition		
Stop signal inhibition 350 ms	70	20–10
Multitasking		
Mean profile score	3	0–40
Variables at V4		
Apathy (LARS/ mean/SD)	− 17.65	7.23

[a]Or mean (SD) when specified

PLS-SEM analysis

Cognitive apathy model

Measurement model Reliability results and discriminant validity measures are given in Table 2. Measures of internal consistency and reliability, as indexed by the composite reli-

Table 2 Assessment of the measurement model and discriminant validity (Fornell Larcker Criterion) of variable constructs

	Composite reliability	AVE	(1)	(2)	(3)	(4)	(5)
Model 1: Cognitive apathy V4							
(1) Anticipatory pleasure	0.760	0.522	**0.722**				
(2) Cognitive apathy V1	0.825	0.703	− 0.232	**0.839**			
(3) Cognitive apathy V4	0.788	0.560	− 0.407	0.572	**0.748**		
(4) Positive symptoms	0.867	0.624	0.206	− 0.045	− 0.278	**0.790**	
(5) Sensitivity to punishment	0.765	0.521	0.144	− 0.053	− 0.309	0.220	**0.722**
Model 2: Emotional apathy V4							
(1) Emotional apathy V1	0.778	0.643	**0.802**				
(2) Emotional apathy V4	0.717	0.576	0.349	**0.759**			
(3) Sensitivity to punishment	0.805	0.581	0.090	− 0.219	**0.762**		
Model 3: Behavioral apathy V4							
(1) Behavioral apathy V1	0.801	0.573	**0.727**				
(2) Behavioral apathy V4	0.769	0.528	0.527	**0.757**			
(3) Episodic memory	0.958	0.920	− 0.450	− 0.201	**0.959**		
(4) Anhedonia	0.792	0.565	0.348	0.265	− 0.076	**0.752**	

AVE average variance extracted

ability, ranged from 0.760 to 0.867, exceeding the recommended threshold value of 0.70 [47]. Similarly, the Average Variance Extracted (AVE) exceeds 0.50 for each measure [48]. Moreover, Variances Extracted were greater in all cases than the off-diagonal elements in their corresponding row and column, supporting discriminant validity at the LV level. To test the convergent validity we extracted the factor and the cross-loadings for all indicators to their respective LV (see supplementary data).

The Structural Model displayed in Fig. 1 was statistically significant, $t = 4.625$, $p < 0.001$, with R^2 equals to 0.46. All beta paths were statistically significant ($p < 0.05$). Anticipatory pleasure, apathy at V1, positive symptoms and sensibility to punishment had a direct and significant influence on cognitive apathy.

The effect size (f^2) of each path is displayed in Table 3. Finally, the model's predictive power was examined by calculating the Q^2 index of cognitive apathy ($Q^2 = 0.201$). This indicated that the model's predictive power exceeded the recommended threshold value ($Q^2 > 0$), indicating an adequate predictive validity [46].

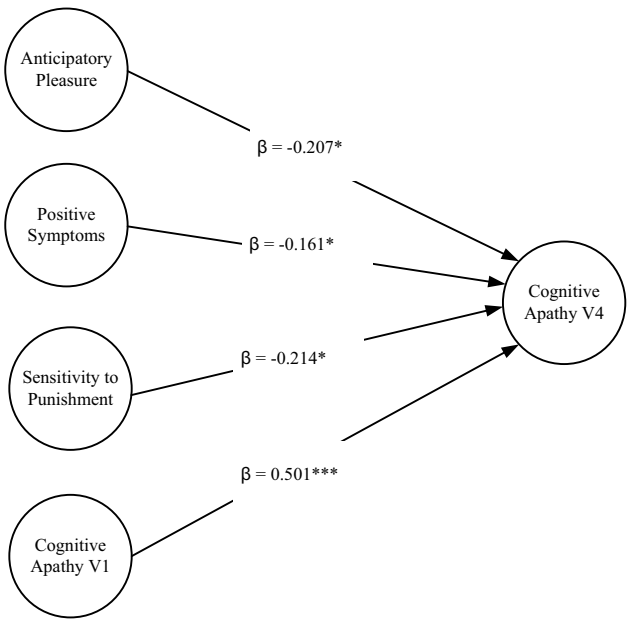

Fig. 1 Structural model results for the cognitive apathy model. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

Emotional apathy model

Measurement model Reliability results and discriminant validity measures are given in Table 2. Measures of internal consistency (composite reliability) and AVE exceeded, respectively, the recommended threshold value of 0.70 [47] and 0.50 for each measure [48]. Moreover, the square roots of the AVE (shown in the matrix diagonals) were greater than the off-diagonal elements in their corresponding row and column in all cases (discriminant validity). For the convergent validity for the emotional apathy model (See supplementary data), each item's factor loading was significant ($p < 0.05$) (Figs. 2, 3).

The structural model was statistically significant, $t = 1.964$, $p = 0.05$, with R^2 equals to 0.16. All beta paths were statistically significant ($p < 0.05$). Emotional apathy at V1 and sensitivity to punishment had a significant influence on emotional apathy.

Table 3 Effect sizes of the structural model paths

Paths	f^2	Magnitude of the effect
Model 1: Cognitive apathy		
Anticipatory pleasure	0.091	Low
Cognitive apathy V1	0.465	High
Positive symptoms	0.047	Low
Sensitivity to punishment	0.084	Low
Model 2: Emotional apathy		
Emotional apathy V1	0.169	Moderate
Sensitivity to punishment	0.077	Low
Model 3: Behavioral apathy		
Behavioral apathy at V1	0.257	High
Episodic memory	0.215	High
Anhedonia	0.077	Low

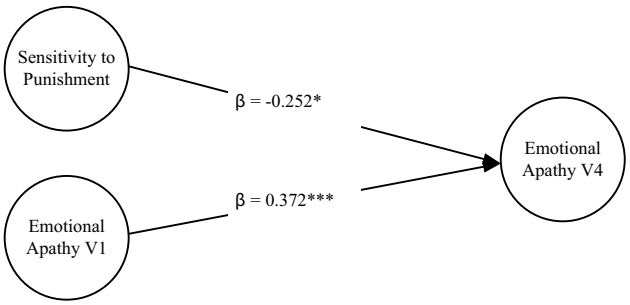

Fig. 2 Structural model results for the emotional apathy model. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

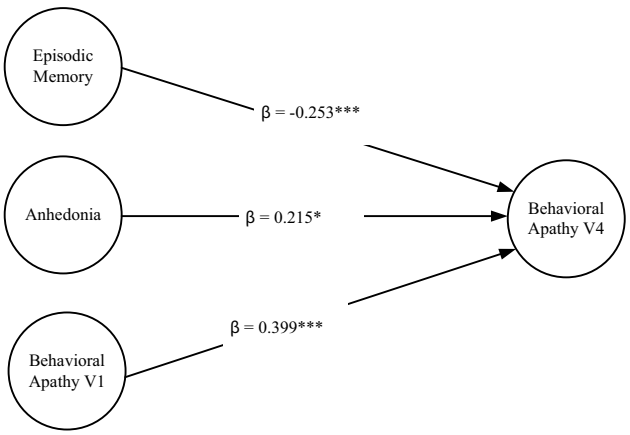

Fig. 3 Structural model results for the behavioral apathy model. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

The effect size (f^2) of each path is displayed in Table 3. The model's predictive power (Q^2 index) for emotional apathy was equal to 0.05. This exceeded the recommended threshold value ($Q^2 > 0$), indicating an adequate predictive validity [46].

Behavioral apathy model

Measurement model

Measures of internal consistency (composite reliability) and the AVE exceeded the recommended threshold value of 0.70 and 0.50, respectively (Table 2). The discriminant validity at the LV level was also supported by the square roots of the AVE (shown in the matrix diagonals). Greater values were observed in all cases compared to the off-diagonal elements in their corresponding row and column. Regarding the convergent validity for the behavioral apathy model (see supplementary data).

Results showed that the structural model was statistically significant, $t = 5.020$, $p < 0.0001$, with R^2 equals to 0.423. All beta paths were statistically significant ($p < 0.05$). behavioral apathy at V1, episodic memory and social anhedonia had a significant influence on behavioral apathy at V4.

The effect size (f^2) of each path is displayed in Table 3. The model's predictive power (Q^2 index) for behavioral apathy was 0.18. This exceeded the recommended threshold value ($Q^2 > 0$), indicating an adequate predictive validity [46].

Discussion

Even though apathy is highly prevalent in schizophrenia, the underlying risk factors are still poorly known. In addition, most past studies have investigated apathy as a unitary syndrome despite evidence of its multidimensional structure [2–4]. The main aim of the present study was to investigate different risk factors that may be associated with cognitive, emotional and behavioral apathy at 1-year follow-up in schizophrenia patients using PLS-SEM analysis. To achieve this aim, we tested three different models, one for each type of apathy. A longitudinal design combined with structural equation modeling allowed us to identify a broad range of psychological, motivational, affective, and clinical risk factors, each predicting a unique share of variance in our three path models of apathy in schizophrenia. They include episodic memory, sensitivity to punishment, anticipatory pleasure, anhedonia, positive symptoms and levels of apathy at baseline.

Overall, we observed that except for apathy at baseline, distinct mechanisms impact specific facets of apathy. The only exception is sensitivity to punishment, which predicted

both emotional and cognitive apathy. It thus corroborates the view that apathy is not a unitary construct, but rather depends on different types of mechanisms.

A first important result concerns the influence of apathy at baseline as a risk factor for the three dimensions of apathy at 1 year. Among all factors taken into account in three distinct models, severity of apathy as measured by the LARS at 1 month constitute the main latent variable predicting level of apathy at 1 year in our longitudinal design. Our results thus suggest that apathy in schizophrenia has a chronic course during the 1-year period and is mainly predicted by levels of apathy at baseline. Even if this result cannot be generalized to first-episode schizophrenia, developing interventions at an earlier and more modifiable stage of apathy development may be more effective in achieving and sustaining remission in schizophrenia patients.

Another key finding of our study concerns the negative associations between sensitivity to punishment and apathetic manifestations. Indeed, the more patients were sensitive to punishment, the lower they were at risk to develop cognitive and emotional apathy at follow-up. Past studies in schizophrenia have revealed the central role of reward processing in the development and maintenance of motivation, which requires overcoming the difficulty of translating reward information into motivated behavior [26]. Our findings highlight the central role of the behavioral inhibition system (BIS) in apathetic manifestations. This finding is in line with that of Scholten et al. [49], who found that higher BIS sensitivity correlated with lower scores on the negative PANSS subscale in a sample of schizophrenia patients. According to the reinforcement sensitivity theory (RST; [50]) the behavioral activation system (BAS) is hypothesized to control approach behavior in response to cues of reward. BIS, however, is hypothesized to be sensitive to conditioned stimuli for punishment, novel stimuli, and innate fear stimuli, and activating responses of inhibition and avoidance. Increased sensitivity to cues of threat may result in greater emotional responsiveness to negative stimuli or events (emotional component of apathy), and similarly may increase focus toward identification of emotional stimuli perceived as negative and threatening (cognitive component of apathy).

Regarding cognitive apathy, which corresponds to diminished goal-directed cognitive activity such as spontaneous ideas and curiosity for new events in our model, we found that positive symptoms, anticipatory pleasure and sensitivity to punishment were significant predictors of cognitive apathy at follow-up. The covariance between negative and positive symptoms has already been described, mainly through improvement of negative symptoms secondary to concomitant improvement of positive symptoms after initiating antipsychotic treatment [51]. However, this is the first time that a direct negative association between positive symptoms and cognitive apathy is shown. In other words the more the patients have positive symptomatology, the more they develop intellectual interest (e.g., lower cognitive apathy) for the environment. A number of theorists have hypothesized that positive psychotic symptoms may arise out of an excessive and aberrant assignment of motivational salience to internal and external objects such as actions, objects or perceptions, partly driven by an aberrant firing of the dopamine system [52–54]. Salience is a process whereby events and thoughts come to grab attention and drive action. In schizophrenia, aberrant salience syndrome leads patients to attribute exaggerated importance of certain percepts and ideas present in their mind or in their external environment. As a consequence, it is not surprising that positive symptoms in combination with distorted thinking styles such as a tendency to "jump to conclusions" have the paradoxical effect to increase interest towards novelty and environment while increasing the risk of delusions formation [55].

Another key finding of this study was the association between anticipatory pleasure and cognitive apathy. This result extends previous findings from cross-sectional studies in Parkinson's disease [56], normal aging [57] and schizophrenia [58] that have shown negative relationships between anticipatory pleasure and apathy. Importantly, we were able to replicate the results of Raffard et al. [57] that showed a specific positive relationship between difficulties in predicting future enjoyment and cognitive apathy (measured in this study by the apathy evaluation scale; [59]) in a sample of older adults. Additionally, this finding links cognitive apathy specifically to anticipatory, but not consummatory, anhedonic deficits in schizophrenia patients. Several authors [60, 61] have postulated that anticipatory pleasure deficit as measured by self-reports (e.g., the Temporal Experience of Pleasure Scale in our study) frequently found in schizophrenia could be partly considered as a form of defeatist beliefs corresponding to a reduced estimation of prospective pleasure. As there is now evidence that hedonic capacity is preserved in schizophrenia, or at least at moderate or high levels of affective input [62], our results thus show that defeatist beliefs about future emotions has a negative causal impact on the approach of novel stimuli in schizophrenia, which could be particularly problematic for patients who are at high risk of living in socioeconomically deprived neighborhoods [63].

Regarding emotional apathy, corresponding to a loss of emotional responsiveness to positive or negative stimuli or events, sensitivity to punishment was the only mechanism, outside emotional apathy at baseline, explaining emotional apathy severity at 1 year. As discussed above, this suggests that emotional apathy may be mainly the consequence of motivational systems, rather than being influenced by cognitive, psychotic symptomatology or emotional dimensions. Two recent studies in stroke [64] and older adults [57] found a positive association between poor reward sensitivity and

apathy but not between sensitivity to punishment and apathy. Consequently, specific mechanisms may be at play in schizophrenia in comparison with other non-psychiatric disorders, with a key role played by not only by the reward system [26, 54, 65], but also by the BIS in apathetic manifestations in schizophrenia.

Regarding behavioral apathy, anhedonia as measured by the SANS and episodic memory were the two mechanisms explaining behavioral apathy at the follow-up. These findings replicate and extend the associations found in previous studies in schizophrenia patients between apathy and cognitive functioning, more specifically episodic memory [21, 24]. Our study supports an independent role of episodic memory in the prediction of apathy. Significant deficit in the ability to maintain stimulus-reward relationships in memory over long delay periods [66] may lead individuals with schizophrenia to less frequently engage in behaviors aimed at obtaining rewards and pleasurable outcomes. However, due to the limited number of neuropsychological tests used in our study we cannot exclude that other cognitive functions such as social cognition [67], effort-based decision making processes [68], reinforcement leaning [69] underlie cognitive apathy or other dimensions of apathy in schizophrenia patients. In addition, in our study the higher the level of anhedonia as measured by the SANS the greater the risk of developing behavioral apathy. However, the SANS Anhedonia–Asociality subscale, which is also considered to be a measure of asociality, is thought to reflect social "performance" deficit rather than measure a hedonic deficit [70]. Indeed, limited engagement with friends, romantic partners, and family could reflect other factors than a decreased capacity to experience pleasure, such as stressful environments, poor perceived social support, or limited financial resources. Future studies are needed to clarify if it is social anhedonia per se or social performances and environment that constitute a causal factor of behavioral apathy.

Finally and importantly, we did not find a significant relationship between antipsychotic dosage and apathy. This is in keeping with Ferveha et al. [71] who previously found that antipsychotic dosage was not related to the level of goal-directed amotivation in their sample of schizophrenia patients. It must be noted that divergent (apparent) findings were found regarding anhedonia and apathy. Indeed, on one hand anhedonia was associated with behavioral apathy. On the other hand anticipatory pleasure, which could be seen as a subcomponent of anhedonia, was associated with cognitive apathy at follow-up. As previously discussed, anticipatory pleasure as measured by self-reports (i.e., the TEPS) can be mainly considered as a form of defeatist beliefs corresponding to a reduced estimation of prospective pleasure. As postulated by Horan et al. [70] the anhedonia/asociality ratings of the SANS are only based solely on patients' capacity to experience pleasant emotions, but also on the frequency, quality, and level of interest and engagement in recreational and social activities, and may, therefore, reflecting a social performance deficit more than a fundamental hedonic capacity deficit.

Limitations

Although we included important socio-demographic, psychological and clinical characteristics as possible predictors of apathy, additional key biological, environmental and health determinants may be of relevance. Indeed, while the models for cognitive and behavioral apathy explained 46 and 42% of the variance, respectively, the model for emotional apathy explained only 16% suggesting that other variables such as defeatist beliefs or reward-related tasks should be considered in further studies. Moreover, although smart PLS enables the estimation of complex cause-effect relationship models and is particularly well suited to the deal with cross-sectional data, less is known about its application to longitudinal data, which makes difficult to deal with some issues, such as, different indicators loading into the apathy at V1 and V4. In the present article we chose to prioritize the quality (reliability and validity) of the model instead of keeping the same indicators. Despite these limitations, this study have many strengths, notably the fact that we provide evidence that apathy is multidimensional phenomena and that different factors may be associated with different types of apathy. Finally and importantly, the apathy scale we used in this study, the Lille Apathy Rating Scale, has been only validated by one study [14] in subjects with schizophrenia in only one language (French), which limits the generalization of our results. Validating in individuals with schizophrenia an English version of the LARS would bring new information on the validity of our results and their generalization to other countries.

Conclusions

Motivational deficits represent a core negative symptom in patients with schizophrenia. The present findings provide valuable insight into the longitudinal predictors and the various mechanisms at play in the facets of apathy from a multidimensional perspective.

From a clinical perspective, symptom-specific strategies have been used in the development of specific therapeutic techniques for positive symptoms and have led to more effective interventions, such as CBT for persecutory delusions [72]. Similarly, apathy treatment may need to be tailored to address underlying etiological factors in schizophrenia patients.

Funding The study was financed by a University Hospital Clinical Research Grant, Montpellier (#UF8641), 2010. The University Hospital had no further role in the study design, in the collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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