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## How far to go in deconstructing negative symptoms? Behavioural and neural level evidence for the amotivation domain

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## How far to go in deconstructing negative symptoms? Behavioural and neural level evidence for the amotivation domain

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### ABSTRACT

Negative symptoms in schizophrenia are conceptualised as loading onto two factors: amotivation and diminished expression, which relate to different behavioural and neural markers. This distinction has proven useful for understanding the cognitive, motivational and neural mechanisms involved in negative symptoms, and for the development of treatments. Recently, it has been advocated that an even finer distinction into five subdomains is needed to understand the mechanisms underlying negative symptoms, and to prevent masking specific treatment and intervention effects. However, it is currently unclear whether such a fine-grained approach offers additional insights grounded in theory. In the present work, we focused on the factor amotivation, which has been shown to selectively correlate with the propensity to discount rewards in the face of effort and with the activity in the ventral striatum during reward anticipation. In a reanalysis of these studies we explored whether subdomains of amotivation – avolition, asociality, anhedonia – showed preferential correlation with these previously identified behavioural and neural markers. We show that for both behavioural and neural markers, a fine-grained model with the three subdomains did not better explain the data than a model with the amotivation factor only. Moreover, none of the three subdomains correlated significantly more or less with the behavioural or neural markers. Thus, no additional information was gained on amotivation in schizophrenia by selectively looking at its three subdomains. Consequently, the two-factor solution currently remains a valid option for the study of negative symptoms and further research is needed for behavioural and neural validation of the five-factor model.

### 1. Introduction

Negative symptoms in schizophrenia represent a challenge for both fundamental research and treatment development. Currently, treatment options for negative symptoms remain limited, and patients with such symptoms have restricted everyday functioning, worse clinical outcomes and lower quality of life (Bègue et al., 2020; Correll and Schooler, 2020). The lack of effective treatment might be the consequence of the traditional view of these symptoms as a unitary phenomenon. Thus, in clinical trials, improvement in one symptom domain could be masked if a global negative symptom score is reported, slowing down treatment development.

The current DSM-5 distinguishes between two domains of negative symptoms in schizophrenia: amotivation and diminished expression

(Fig. 1). This distinction is based on several factor-analytic studies run on negative symptom rating scales, such as the Brief Negative Symptom Assessment Scale, (BNSS, Strauss et al., 2012a, 2012b), Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1982), Clinical Assessment Interview for Negative Symptoms (CAINS, Krings et al., 2013). These studies show that negative symptoms are not a unitary phenomenon, but consist of two factors (Blanchard and Cohen, 2005; Kirkpatrick, 2014). Moreover, the two-factor structure is further corroborated by experimental studies, which show dissociations in the way the two factors relate to behaviour and brain function (Bègue et al., 2020; Krings and Barch, 2014).

Recently, it has been advocated that fundamental and clinical investigations could benefit from an even more detailed distinction of negative symptoms – one separating all of the five domains stipulated in

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the NIMH-MATRICES consensus statement (Kirkpatrick et al., 2006): avolition, asociality, anhedonia, blunted affect and alogia (Ahmed et al., 2018; San Ang et al., 2019; Strauss et al., 2018). A confirmatory factor analysis has indeed shown the best fit for a model containing five factors corresponding to the five domains (Strauss et al., 2018). Such a distinction, if supported experimentally, would prove beneficial for exploring the underlying separate mechanisms and targeting specific negative symptoms therapeutically.

Importantly, however, theoretical models supported by empirical data remain limited for the five individual symptom domains. At the same time, quite a solid database of findings and theoretical accounts has built up for the two factor distinction. The factor amotivation, composed of avolition, asociality and anhedonia, received the most attention from empirical research. Amotivation is often conceptualised as a reduction in goal-directed behaviour and as an impairment in associated decision-making processes. Within this framework, deficits in reward anticipation – the capability to represent expected positive outcomes and use these representations to guide behaviour – have received the most attention. Several well-replicated tasks have been used to show that patients with higher scores of amotivation, but not of diminished expression, show lower activity in the ventral striatum during reward anticipation and are less willing to engage in physical effort to obtain a monetary reward (Hartmann et al., 2014; Hartmann et al., 2015; Kirschner et al., 2017; Stepien et al., 2018; Waltz et al., 2010; Wolf et al., 2014). A complementary line of research shows that the second factor, diminished expression, is associated with deficits in emotion processing and imitation of facial expressions (Gur et al., 2006; Lepage et al., 2011).

It is possible that the models we currently use to explore the mechanisms underlying the two factors amotivation and diminished expression are better suited to study some of the five constituent symptoms independently of the others. For example, it could be that deficient reward discounting and diminished neural activation during reward anticipation are more strongly associated with one of the constituent domains of the factor amotivation – anhedonia, avolition or asociality. Such preferential associations would help further refine the study of negative symptoms and would empirically support the five factor distinction as opposed to the two-factor solutions currently used.

However, it has proven quite difficult up to now to find selective neural and behavioural markers for the individual subdomains of amotivation. The majority of studies do not report selective correlations

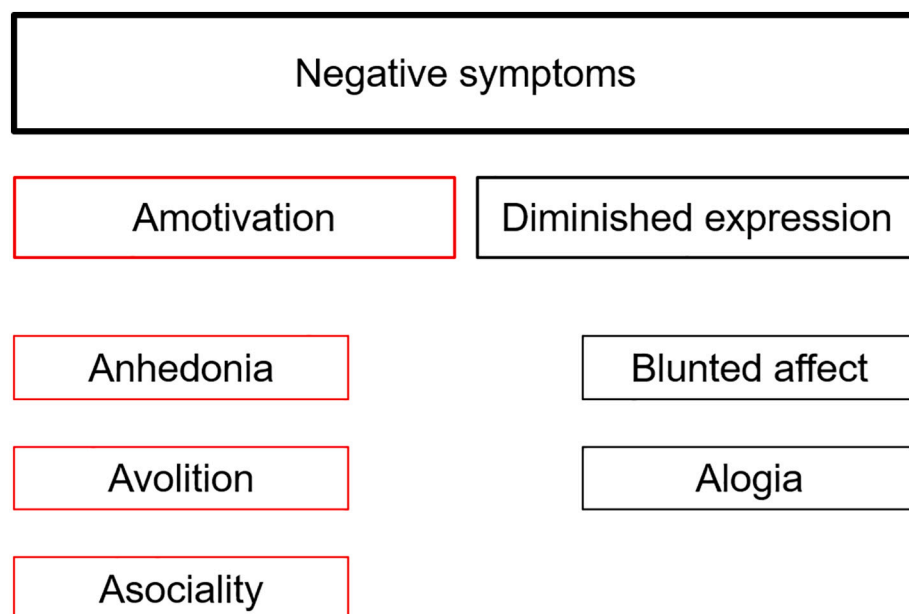
with the subdomains, and when they do, all the three subdomains show similar correlations with the dependent variable (i.e., brain activity or behavioural performance) as the amotivation factor (Giordano et al., 2018) (or even the total negative symptom score) (Strauss et al., 2015). Still, some studies do report selective correlations within the amotivation subdomains (primarily for different measures of anhedonia, in particular, for self-rated anhedonia) (Dowd et al., 2016; Mucci et al., 2015; Waltz et al., 2009; Wynn et al., 2010).

In the present work, we systematically explored whether indeed there is a benefit of considering each of the three domains constituting amotivation separately with respect to previously identified behavioural and neural correlates. For this, we conducted two sets of analyses on data from previously published studies that used the Brief Negative Symptom Assessment Scale (BNSS) to evaluate negative symptoms. One study investigated effort-based decision-making (Hartmann et al., 2015) and demonstrated that amotivation was associated with reduced willingness to exert effort for reward (i.e., increased effort discounting). The second line of research (Kirschner et al., 2017; Stepien et al., 2018) showed a negative correlation between amotivation and activity in the ventral striatum during reward anticipation. We reanalysed these data to test whether the associations with reward anticipation and reward discounting were stronger for the individual subdomains of amotivation.

## 2. Methods

### 2.1. Participants

Clinical and demographic characteristics are presented in Table 1. All patients were recruited from inpatient and outpatient units of the Psychiatric Hospital of the University of Zurich. In all patients in the original studies the diagnosis of schizophrenia was confirmed by the Mini-International Neuropsychiatric Interview for DSM-IV (MINI). Patients were not included in the studies if one of the following was present: other DSM-IV Axis I disorders (most importantly, major depressive disorder or current substance use disorder); increased psychotic symptomatology (i.e., a score exceeding 4 on the positive subscale of the PANSS); extrapyramidal side-effects (total score > 2 on the Modified Simpson-Angus Scale), as well as the prescription of more than 1 mg lorazepam per day. The aim of these criteria was to reduce the influence of secondary negative symptoms on the results of the experiments (Kirschner et al., 2017).



**Fig. 1.** The structure of negative symptoms. A two-factor approach distinguishes between amotivation (composed of anhedonia, avolition and asociality) and diminished expression (comprising blunted affect and alogia). A five-factor approach considers anhedonia, avolition, asociality, blunted affect and alogia separately. The present work only considers the amotivation factor and its subdomains (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 1**  
Demographic, psychopathological and clinical characteristics of patients.

	Behavioural (N = 31)	Neural (N = 43)
Age, years (SD)	30.4 (8.7)	32.2 (8)
Sex	25 males	32 males
Education, years	9.8 (1.7)	12.1 (2.6)
Duration of illness, months	115.5 (97.5)	115.3 (81.5)
Chlorpromazine equivalent, mg/d	568.2 (409.97)	514.2 (457.26)
Calgary depression scale for schizophrenia	2.42 (2.41)	2.15 (2.15)
BNSS score		
Amotivation	16.6 (7.5)	15.09 (7.8)
Avolition	4.7 (2.1)	4.6 (2.3)
Asociality	4.1 (2.1)	3.9 (2.4)
Anhedonia	7.9 (3.6)	6.6 (4.4)
Diminished expression	10.4 (6.97)	9.07 (7.6)

## 2.2. Clinical assessment

The Brief Negative Symptom Assessment Scale (BNSS) was used to evaluate negative symptoms in all studies. In addition, patients were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990), the Global Assessment of Functioning scale (Frances et al., 1994), and the Personal and Social Performance Scale (Schaub and Juckel, 2011).

## 2.3. Statistical analysis

The factor amotivation of the BNSS was computed using the factor solution by Mucci et al. (2015), which corresponds to the factor solution proposed by the developers of the scale without the item “lack of normal distress” (Kirkpatrick et al., 2011; Strauss et al., 2012a). The individual subdomains were composed by the sum of their constituent items (3 items for anhedonia and 2 items each for avolition and asociality).

For each analysis, we first computed two linear regression models (using the `lm` function in R). Both models included the behavioural or neural outcome of interest as the dependent variable (DV). The models differed with respect to the independent variables (IV). In model 1 the only IV were the BNSS amotivation scores, while in model 2 we used the three BNSS amotivation subdomain scores (anhedonia, avolition, asociality) as IV. These two models were then compared in an ANOVA in order to establish whether one model yielded a better fit (detailed results for each regression can be found in the Supplementary material).

In order to make our results comparable to other studies we also correlated each DV with BNSS amotivation, avolition, asociality and anhedonia. Pearson correlations were performed using Jamovi (The jamovi project (2019), *jamovi* (Version 0.9)). To establish whether any subdomain showed a stronger correlation with the DV than the others, the `cocor` R package was used to compare the correlation strengths (comparison of two overlapping correlations based on dependent groups, (Diedenhofen and Musch, 2015)). The significance level was set to  $p = 0.05$ .

## 2.4. Behavioural level

The goal of this analysis was to establish whether effort discounting correlated more strongly with one of the three domains of amotivation.

## 2.5. Participants

We used the data from the 31 patients reported in the study by Hartmann et al., 2015. Twenty-five patients had the diagnosis of schizophrenia and six – of schizoaffective disorder.

## 2.6. Effort task

Participants in the original study performed an effort-based decision-making task assessing how much monetary reward was discounted by physical effort required to obtain it. On each trial, participants chose between two alternatives: either to exert no effort and receive a small constant reward (1 CHF) or engage in a specific level of physical effort and receive a larger reward (up to 5 CHF). To quantify physical effort we used a handgrip which participant squeezed with the dominant hand for three and a half seconds. If participants chose the no-effort condition, they simply waited for 3.5 s before receiving the default 1 CHF reward. When an effortful choice was made, participants had to squeeze the dynamometer with either 40%, 60%, 80% or 100% of their maximal strength. The latter was calculated at the start of the experiment during two calibration trials: participants squeezed the handgrip as hard as they could for 3.5 s with no strength feedback. The rewards on effortful trials were: 1.5, 2, 2.5, 3, 5 CHF (1 CHF  $\approx$  1 \$). There were 80 trials in total (four repetitions of each effort level for a given reward).

The main output of the task are the so called indifference points – reward amounts for which participants are equally likely to make an effortful and a no-effort choice (i.e. are “indifferent” between them). The indifference points were obtained by using the fraction of effortful choices to fit a logistic function for each reward amount. Based on this, the relative subjective value (SV) of reward was calculated for each participant. SV represent how much the four different effort levels devalue reward. SV equals the default reward of 1 CHF divided by the indifference point for a given effort level. The area under the SV curve (AUC) for the four effort levels was used to quantify the proneness to engage in physical effort. Smaller AUC values mean that larger rewards were needed for participants to exert effort.

## 2.7. Statistical analysis

In the study by Hartmann et al. (2015), patients with higher amotivation scores showed stronger effort discounting. In the present analyses, we first compared two regression models, with AUC as the DV in both. In the first model, only amotivation was included as the IV. In the second model, avolition, asociality and anhedonia were included as the IV, but not amotivation. We then correlated patients' effort discounting with avolition, anhedonia and asociality and compared the strength of these correlations.

## 2.8. Neural level

The goal of this analysis was to estimate whether the three subdomains of amotivation correlated differently with the activity in the ventral striatum (VS) during reward anticipation.

## 2.9. Participants

Data of 27 subjects were taken from the study by Kirschner et al. (2017) and data of 16 subjects – from the study by Stepien et al. (2018). Two subjects from the first study also took part in the second study, and so were removed from this analysis, resulting in a total of 41 participants.

## 2.10. fMRI task design

An adapted version of the Monetary Incentive Delay Task (MID) (Simon et al., 2015) was used in both studies. Each trial began with a cue indicating the biggest reward amount that could be obtained on that trial (0 CHF, 0.40 CHF or 2 CHF). Next, participants indicated, by pressing the left or right button as quickly and accurately as possible, whether an outlying stimulus appeared on the right or on the left of the screen. At the end of every trial feedback on how much they won was presented and depended on participants' reaction times. There were 72

trials in total.

### 2.11. Functional magnetic resonance imaging

Both studies were run using a Philips Achieva 3.0 T magnetic resonance scanner with a 32-channel SENSE head coil at the University of Zurich Psychiatric Hospital MR Zentrum. The MID task was divided into two blocks; 195 images were taken in each block. A gradient-echo  $T_2^*$ -weighted echo-planar image (EPI) sequence was used with 38 slices acquired in ascending order. The acquired in-plane resolution used was  $3 \times 3 \text{ mm}^2$ , 3 mm slice thickness and 0.5 mm gap width over a field of view of  $240 \times 240 \text{ mm}$ , repetition time was set to 2000 ms, echo time 25 ms and a flip angle  $82^\circ$ . In both studies, the first 5 scans were discarded to eliminate the influence of the  $T_1$  saturation effects. Alignment of slices with the anterior–posterior commissure was performed. Anatomical data were acquired with the help of an ultrafast gradient echo  $T_1$ -weighted sequence in 160 sagittal plane slices of  $240 \times 240 \text{ mm}$  resulting in  $1 \times 1 \times 1 \text{ mm}$  voxels.

### 2.12. fMRI analyses

The original fMRI analyses for both studies were performed with SPM8. Reward anticipation was set as the regressor of interest and was composed of the cue and the delay phases of each trial. Consequently, the three reward ranges (anticipation of 0 CHF, 0.40 CHF or 2 CHF) constituted three regressors of interest. In both studies, the ventral striatum was defined as the region of interest during reward anticipation based on a meta-analysis (Knutson and Greer, 2008). Thus, the following coordinates were used: left: x, y, z = -12, 10, -2; right: x, y, z = 10, 8, 0. To extract the mean percent signal change the REX toolbox was used (<http://web.mit.edu/swg/software.htm>).

### 2.13. Statistical analysis

In both studies, neural activity in the VS was negatively correlated with their BNSS amotivation score. We pooled the data from the two studies and compared two regression models using VS activity as the DV. In the first model only amotivation was included as the IV. In the second model, avolition, asociality and anhedonia were included as the IV, but not amotivation. We then correlated patients' VS activity with the scores of avolition, anhedonia and asociality.

## 3. Results

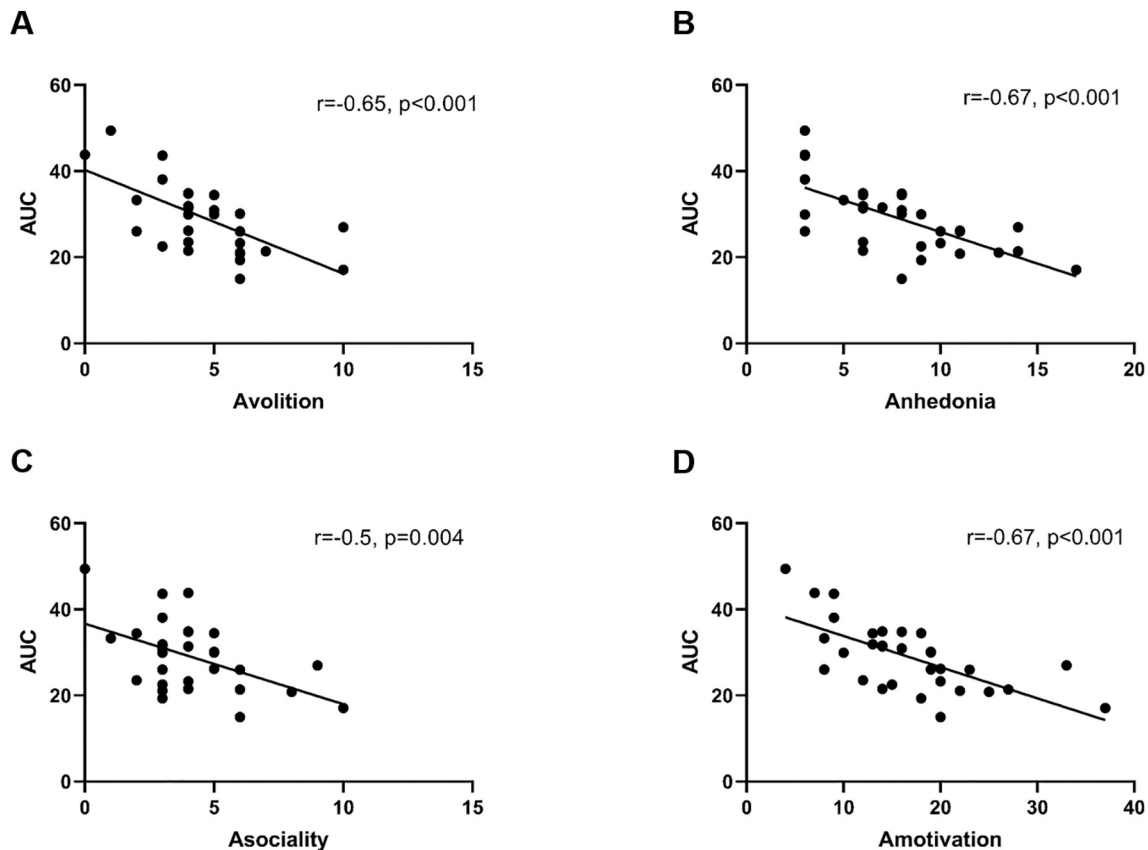
### 3.1. Behavioural level: effort based decision-making and amotivation

#### 3.1.1. Regression model

We ran two regression models, one assessing the relation between AUC and BNSS amotivation ( $F(29) = 23, p < 0.0001, R^2 = 0.42$ ), and the other assessing the relation between AUC and the three subdomains ( $F(3,27) = 7.96, p = 0.0006, R^2 = 0.41$ ). Multicollinearity was assessed for the three subdomains and all the VIFs were below 5, suggesting no correction was necessary (Cohen et al., 2013). An ANOVA comparing the fits, showed no significant difference, indicating no preference of one model over the other ( $F(2,27) = 0.69, p = 0.51$ ). In other words, the more fine-grained model including the three domains did not statistically explain more variance than the model including only the amotivation factor score.

#### 3.1.2. Correlations

The three subdomains correlated with each other as follows: anhedonia-asociality  $r = 0.73, p < 0.001$ ; avolition-asociality  $r = 0.76, p < 0.001$ ; avolition-anhedonia  $r = 0.86, p < 0.001$ .



**Fig. 2.** Pearson correlations between effort discounting (measured as area under the (discounting) curve (AUC); smaller values correspond to stronger effort discounting) and the factor amotivation of the BNSS (D), as well as its subdomains avolition (A) asociality (C) and anhedonia (B).

Fig. 2 shows the correlations between AUC, BNSS amotivation and the three subdomains. Numerically, AUC correlated to the same extent with BNSS amotivation and BNSS anhedonia ( $r = -0.67$ ), followed by BNSS avolition ( $r = -0.65$ ), and BNSS asociality ( $r = -0.5$ ).

Comparing the three pairs of correlations between AUC and the BNSS subdomains revealed no significant differences: AUC/BNSS avolition vs AUC/BNSS asociality Pearson and Filon's  $z = -1.46$ ,  $p = 0.15$ ; AUC/BNSS avolition vs AUC/BNSS anhedonia Pearson and Filon's  $z = 0.32$ ,  $p = 0.75$ ; AUC/BNSS asociality vs AUC/BNSS anhedonia Pearson and Filon's  $z = 1.6$ ,  $p = 0.11$ .

### 3.2. Neural level: relation between amotivation and the activity in the ventral striatum during reward anticipation

#### 3.2.1. Regression model

Similar to the analyses on the behavioural level, two separate regression models were run. One model assessed the relation between left VS activity and BNSS amotivation ( $F(39) = 17.96$ ,  $p = 0.0001$ ,  $R^2 = 0.3$ ) and the other assessed the relation between left VS activity and the three subdomains ( $F(3,37) = 6.83$ ,  $p = 0.001$ ,  $R^2 = 0.3$ ), all VIFs < 5). An ANOVA comparing the two regressions showed no preference for either fit ( $F(2,37) = 1.18$ ,  $p = 0.32$ ), meaning, as above, that a model including the three subdomains separately did not provide a better fit.

#### 3.2.2. Correlations

The three subdomains correlated with each other as follows: anhedonia-asociality  $r = 0.46$ ,  $p = 0.004$ ; avolition-asociality  $r = 0.47$ ,  $p = 0.002$ ; avolition-anhedonia  $r = 0.67$ ,  $p < 0.001$ .

The correlations between the VS and the BNSS variables are shown in Fig. 3. Numerically, the strongest correlation was found between left VS

activity and BNSS avolition ( $r = -0.55$ ), followed by amotivation ( $r = -0.53$ ), anhedonia ( $r = -0.42$ ) and asociality ( $r = -0.36$ ).

Pairwise comparisons of the activity in the left VS and the three BNSS subdomains showed no significant differences: left VS/BNSS avolition vs left VS/BNSS asociality Pearson and Filon's  $z = -1.4$ ,  $p = 0.2$ ; left VS/BNSS avolition vs left VS/BNSS anhedonia Pearson and Filon's  $z = -1.2$ ,  $p = 0.2$ ; left VS/BNSS asociality vs left VS/BNSS anhedonia Pearson and Filon's  $z = 0.38$ ,  $p = 0.7$ . These findings converge with the behavioural findings in suggesting that none of subdomains had more explanatory power than the others.

## 4. Discussion

In the present work, we sought to explore whether the three subdomains of negative symptoms constituting the factor amotivation are differentially associated with behavioural and neural markers previously identified for this factor. We observed no such selective distinction. Neither anhedonia, nor avolition or asociality showed preferential correlations with effort discounting or activity in the ventral striatum. Additionally, regression models using the three subdomains did not show a better fit than models using only the factor amotivation.

It is important to acknowledge the potential limitations of our work that could have prevented us from detecting selective associations of the amotivation subdomains at the behavioural and neural levels if they, in fact, did exist. First of all, we only conducted retrospective analyses, using data from tasks which were not specifically designed to study such selective associations, but where the original hypothesis of these studies concerned associations with the factor amotivation. Nevertheless, the studies we have chosen for the reanalysis applied well-validated experimental approaches based on theoretical models of negative

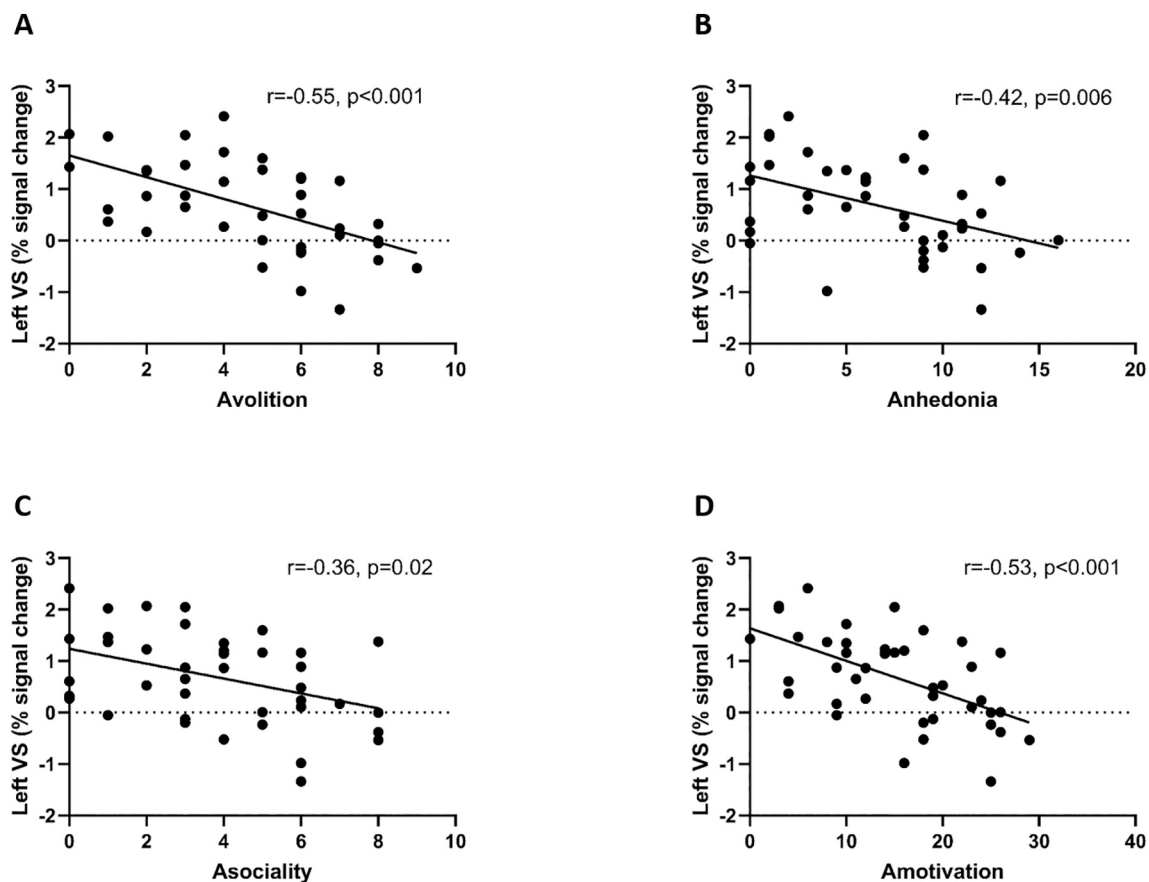


Fig. 3. Pearson correlations between the percent signal change reflecting reward anticipation in the left ventral striatum and the BNSS factor amotivation (D), as well as its subdomains, avolition (A), anhedonia (B) and asociality (C).

symptoms. Our analyses appear to indicate that no additional information is gained for the understanding of the lack of motivation and pleasure in patients with schizophrenia when considering avolition, asociality and anhedonia separately using such well-established experimental and theoretical approaches. Another reason for the co-occurrence of subdomain (e.g. asociality) and general factor correlations with the variables of interest might also be the modest sample sizes in both studies used for this reanalysis and the majority of studies in the literature. Even though we combined data from two studies for the correlations at the neural level, we failed to show an advantage of the 3-subdomain model. It is then possible that much larger sample sizes are needed to distil distinct relationships between individual subdomains, and between their relation to behaviour and brain function. However, effect sizes of such fine-grained associations of amotivation subdomains would be rather small, and added value for treatment development might be very limited.

Coming back to our specific findings, in our behavioural level analyses, one could hypothesize that effort discounting would be preferentially associated with the avolition subdomain. However, social interactions assessed in the asociality domain also represent an effortful endeavour in terms of initiating and maintaining social contact, thus the correlation with asociality appears unsurprising. Finally, in the BNSS, the score for anhedonia is dependent on the activities the patient engages in, and is thus closely related to the score for avolition and asociality. This type of anhedonia can be considered as motivational anhedonia.

At the neural level, in the study by [Kirschner et al. \(2017\)](#) avolition appeared to correlate significantly with activity in the left ventral striatum, while anhedonia and asociality did not. In the larger pooled dataset used in the present study we did not find evidence for a specific association with avolition. All three subdomains correlated significantly and to the same extent with left VS activity, even though numerically the correlation with avolition remained the strongest. It is thus important to highlight that smaller sample sizes might suggest specificity, which cannot be reproduced in larger samples.

Reward anticipation could also be thought of as preferentially related to anhedonia, in particular anticipatory anhedonia corresponding to the anticipation of future pleasure. However, anticipation of a reward is also necessary for the motivation to engage in goal-directed activities, and the reduction of this motivation results in avolition and asociality. Thus, for both associations with effort discounting and with reward anticipation, the conceptual and observed differences might be less important than proposed by the 5-factor model.

Similarly to our results, previous studies, even when specifically designed to assess a particular subdomain, have observed correlations not only with the subdomain of interest, but also with the general negative symptom score. For example, using electrical brain microstates [Giordano et al. \(2018\)](#) showed selective correlation with the amotivation factor but not the diminished expression factor. Importantly, the three subdomains of amotivation (avolition, asociality and anticipatory, but not consummatory anhedonia) also showed individually significant correlations with the same microstate ([Giordano et al., 2018](#)). Similarly, weakened levels of activity in patients with schizophrenia correlated with the factor amotivation to the same extent as with its subdomains ([Kluge et al., 2018](#)). Finally, plasma oxytocin levels were hypothesised to be related to measures of asociality, which was indeed the case. Nonetheless, oxytocin levels also correlated with total negative symptom scores (assessed by the BNSS) ([Strauss et al., 2015](#)) as well as PANSS total, general and positive symptoms ([Rubin et al., 2010](#)). Such results are unsurprising given the high intercorrelations between the amotivation subdomains. In a sample of 192 patients [Strauss et al. \(2018\)](#) show that avolition, asociality and anhedonia correlated with each other with correlation coefficients between 0.73 and 0.8. Even though our analysis at the neural level shows lower intercorrelations, we still fail to detect differences between the correlations of each subdomain with VS activity. Importantly, previous work has indicated that intercorrelation

values of this magnitude preclude an adequate estimation of factor values in regression models, and this, independently of sample size ([Friedman and Wall, 2005](#)).

Still, multiple studies using self-evaluation scales to assess anhedonia show selective correlations or selective absence of correlation with this subdomain and behavioural and neural markers. For instance, [Waltz et al. \(2009\)](#) showed that brain activation during a prediction error task correlated with avolition (as measured by the SANS) but not with anhedonia (as measured with Scales for Physical and Social Anhedonia: ([Chapman et al., 1976](#)); ([Waltz et al., 2009](#))). In a study by [Vignapiano et al. \(2016\)](#), the EEG response to large rewards and large losses correlated negatively with social anhedonia (measured by the Chapman Social Anhedonia Scale ([Chapman et al., 1976](#))) but no correlations were found with amotivation or diminished expression (assessed by the PANSS) ([Vignapiano et al., 2016](#)). Further, [Mucci et al. \(2015\)](#) found no correlation between anhedonia (Revised Physical Anhedonia Scale, PAS; [Chapman & Chapman, 1978](#)) and avolition (assessed by the Schedule for the Deficit Syndrome (SDS; [Kirkpatrick et al., 1989](#))). Activity in the dorsal caudate also only correlated with the latter but not the former. Thus, anhedonia measured by self-assessment as compared to anhedonia measured by a clinical interview seems to represent a different aspect of the patients' pleasure experience. By extension, self-assessed anhedonia could be an interesting selective target for the study of clinical, behavioural and neural correlates. In addition, work in healthy participants has also identified separate correlates for different aspects of goal directed behaviour, such as the VS for reward learning and the dorso-medial prefrontal cortex for effort learning ([Hauser et al., 2017](#)). These regions could thus constitute potential selective correlates of the different amotivation subdomains.

We would like to emphasize that the present results do not invalidate the 5-factor solution found in psychometric studies. Nevertheless, bearing in mind the above limitations, several methodological issues should be considered if indeed the clinical, behavioural or neural underpinnings of the five separate factors were to be studied separately. First, it is important that studies using well-established approaches to amotivation and the two-factor distinction report exploratory analyses for each of the five subdomains, while also reporting their intercorrelations. For example, multiple studies have been conducted on the relationship between social cognition and negative symptoms. However, the interesting link between social cognition and asociality has not been directly evaluated, and thus no direct conclusion could be drawn as to the relationship between social cognition and the motivation of patients with schizophrenia to engage in social interactions ([Marder and Galderisi, 2017](#)). It is important to note, however, that such an approach could considerably increase the number of tests run and thus the potential of Type I errors. This is especially concerning given that the sample sizes of clinical studies are often limited. Thus, specific theoretical models and empirical procedures for each of the five subdomains should be developed and hypotheses for a specific domain specified a priori. The latter point is particularly challenging as most previous models show that if a correlation exists with a given subdomain of interest, there is also a significant correlation with the factor amotivation. This means that such specific subdomain hypotheses should most likely be tested in large patient samples. Finally, although significant and strong correlations are also reported between the amotivation and the diminished expression factors (e.g., 0.6 in our own work), these correlations are weaker than the ones between the subdomains. Thus, a more precise evaluation of models is achieved when using a two- versus five-factor approach.

In conclusion, a multilevel validation (behavioural and neural) for the five-factor distinction between the individual negative symptoms is currently lacking. Such a validation, if indeed provided, would allow studying the underlying mechanisms and evaluating a fine-grained treatment response. In the meantime, the two-factor solution may remain the best available option, providing distinct information about cognitive, motivational and neural mechanisms involved in negative



symptoms, on which intervention approaches can be built.

## Contributors

Mariia Kaliuzhna, SK & FC wrote the first draft of the manuscript. Matthias Kirschner, MNHR, MB, ES, PNT designed the constituent studies and wrote the protocol. Mariia Kaliuzhna undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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The funding sources had no role in the design of the study, nor during its execution, analyses, interpretation of results and drafting of the manuscript.

## Declaration of competing interest

The authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2021.08.007>.

## References

- Addington, D., Addington, J., Schissel, B., 1990. A depression rating scale for schizophrenics. *Schizophr. Res.* 3 (4), 247–251.
- Ahmed, A.O., Kirkpatrick, B., Galderisi, S., Mucci, A., Rossi, A., Bertolino, A., Bischof, M., 2018. Cross-cultural validation of the 5-factor structure of negative symptoms in schizophrenia. *Schizophr. Bull.* 45 (2), 305–314.
- Andreasen, N.C., 1982. Negative symptoms in schizophrenia: definition and reliability. *Arch. Gen. Psychiatry* 39 (7), 784–788.
- Andreasen, N.C., 1989. The scale for the assessment of negative symptoms (SANS): conceptual and theoretical foundations. *Br. J. Psychiatry* 155 (S7), 49–52.
- Bègue, I., Kaiser, S., Kirschner, M., 2020. Pathophysiology of negative symptom dimensions of schizophrenia-current developments and implications for treatment. *Neurosci. Biobehav. Rev.* 116, 74–88.
- Blanchard, J.J., Cohen, A.S., 2005. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr. Bull.* 32 (2), 238–245.
- Chapman, L.J., Chapman, J.P., 1978. Revised Physical Anhedonia Scale. Available from L. J. Chapman, Department of Psychology, 1202 West Johnson Street, University of Wisconsin, Madison, WI 53706.
- Chapman, L.J., Chapman, J.P., Raulin, M.L., 1976. Scales for physical and social anhedonia. *J. Abnorm. Psychol.* 85 (4), 374.
- Cohen, J., Cohen, P., West, S.G., Aiken, L.S., 2013. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. Routledge.
- Correll, C.U., Schooler, N.R., 2020. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr. Dis. Treat.* 16, 519.
- Diedenhofen, B., Musch, J., 2015. Cocos: a comprehensive solution for the statistical comparison of correlations. *PLoS One* 10 (4), e0121945.
- Dowd, E.C., Frank, M.J., Collins, A., Gold, J.M., Barch, D.M., 2016. Probabilistic reinforcement learning in patients with schizophrenia: relationships to anhedonia and avolition. *Biol. Psychiatry* 1 (5), 460–473.
- Frances, A., Pincus, H., First, M., 1994. The global assessment of functioning scale (GAF). In: *Diagnostic and Statistical Manual of Mental Disorders*, p. 4.
- Friedman, L., Wall, M., 2005. Graphical views of suppression and multicollinearity in multiple linear regression. *Am. Stat.* 59 (2), 127–136.
- Giordano, G.M., Koenig, T., Mucci, A., Vignapiano, A., Amodio, A., Di Lorenzo, G., Monteleone, P., 2018. Neurophysiological correlates of avolition-apathy in schizophrenia: a resting-EEG microstates study. *NeuroImage* 20, 627–636.
- Gur, R.E., Kohler, C.G., Ragland, J.D., Siegel, S.J., Lesko, K., Bilker, W.B., Gur, R.C., 2006. Flat affect in schizophrenia: relation to emotion processing and neurocognitive measures. *Schizophr. Bull.* 32 (2), 279–287.
- Hartmann, M.N., Hager, O.M., Reimann, A.V., Chumbley, J.R., Kirschner, M., Seifritz, E., Kaiser, S., 2014. Apathy but not diminished expression in schizophrenia is associated with discounting of monetary rewards by physical effort. *Schizophr. Bull.* 41 (2), 503–512.
- Hartmann, M.N., Kluge, A., Kalis, A., Mojzisch, A., Tobler, P.N., Kaiser, S., 2015. Apathy in schizophrenia as a deficit in the generation of options for action. *J. Abnorm. Psychol.* 124 (2), 309.
- Hauser, T.U., Eldar, E., Dolan, R.J., 2017. Separate mesocortical and mesolimbic pathways encode effort and reward learning signals. *Proc. Natl. Acad. Sci.* 114 (35), E7395–E7404.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13 (2), 261–276.
- Kirkpatrick, B., 2014. Developing concepts in negative symptoms: primary vs secondary and apathy vs expression. *J. Clin. Psychiatry* 75 (suppl 1), 0-0.
- Kirkpatrick, B., Buchanan, R.W., McKenney, P.D., Alphas, L.D., Carpenter, W.T.Jr., 1989. The Schedule for the Deficit Syndrome: an instrument for research in schizophrenia. *Psychiatry Research* 30, 119–123.
- Kirkpatrick, B., Fenton, W.S., Carpenter, W.T., Marder, S.R., 2006. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr. Bull.* 32 (2), 214–219.
- Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. *Schizophr. Bull.* 37 (2), 300–305.
- Kirschner, M., Hager, O.M., Bischof, M., Hartmann, M.N., Kluge, A., Seifritz, E., Kaiser, S., 2017. Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. *J. Psychiatry Neurosci.* 41 (3), 152.
- Kluge, A., Kirschner, M., Hager, O.M., Bischof, M., Habermeyer, B., Seifritz, E., Kaiser, S., 2018. Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. *Schizophr. Res.* 195, 176–182.
- Knutson, B., Greer, S.M., 2008. Anticipatory affect: neural correlates and consequences for choice. *Philos. Trans. R. Soc. B* 363 (1511), 3771–3786.
- Kring, A.M., Barch, D.M., 2014. The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. *Eur. Neuropsychopharmacol.* 24 (5), 725–736.
- Kring, A.M., Gur, R.E., Blanchard, J.J., Horan, W.P., Reise, S.P., 2013. The clinical assessment interview for negative symptoms (CAINS): final development and validation. *Am. J. Psychiatr.* 170 (2), 165–172.
- Lepage, M., Sergerie, K., Benoit, A., Czechowska, Y., Dickie, E., Armony, J., 2011. Emotional face processing and flat affect in schizophrenia: functional and structural neural correlates. *Psychol. Med.* 41 (9), 1833–1844.
- Marder, S.R., Galderisi, S., 2017. The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry* 16 (1), 14–24.
- Mucci, A., Dima, D., Soricelli, A., Volpe, U., Bucci, P., Frangou, S., Maj, M., 2015. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychol. Med.* 45 (8), 1765–1778.
- Rubin, L.H., Carter, C.S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., Maki, P.M., 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophr. Res.* 124 (1–3), 13–21.
- San Ang, M., Rekhii, G., Lee, J., 2019. Validation of the brief negative symptom scale and its association with functioning. *Schizophr. Res.* 208, 97–104.
- Schaub, D., Juckel, G., 2011. PSP-Skala-Deutsche version der personal and social performance scale. *Nervenarzt* 82 (9), 1178–1184.
- Simon, J.J., Cordeiro, S.A., Weber, M.-A., Friederich, H.-C., Wolf, R.C., Weisbrod, M., Kaiser, S., 2015. Reward system dysfunction as a neural substrate of symptom expression across the general population and patients with schizophrenia. *Schizophr. Bull.* 41 (6), 1370–1378.
- Stepien, M., Manoliu, A., Kubli, R., Schneider, K., Tobler, P.N., Seifritz, E., Kirschner, M., 2018. Investigating the association of ventral and dorsal striatal dysfunction during reward anticipation with negative symptoms in patients with schizophrenia and healthy individuals. *PLoS One* 13 (6), e0198215.
- Strauss, G.P., Hong, L.E., Gold, J.M., Buchanan, R.W., McMahon, R.P., Keller, W.R., Carpenter, W.T., 2012. Factor structure of the brief negative symptom scale. *Schizophr. Res.* 142 (1–3), 96–98.
- Strauss, G.P., Keller, W.R., Buchanan, R.W., Gold, J.M., Fischer, B.A., McMahon, R.P., Kirkpatrick, B., 2012. Next-generation negative symptom assessment for clinical trials: validation of the brief negative symptom scale. *Schizophr. Res.* 142 (1–3), 88–92.
- Strauss, G.P., Keller, W.R., Koenig, J.I., Gold, J.M., Ossenfort, K.L., Buchanan, R.W., 2015. Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia. *Schizophr. Res.* 162 (1–3), 57–61.
- Strauss, G.P., Nuñez, A., Ahmed, A.O., Barchard, K.A., Granholm, E., Kirkpatrick, B., Allen, D.N., 2018. The latent structure of negative symptoms in schizophrenia. *JAMA Psychiatry* 75 (12), 1271–1279.
- Vignapiano, A., Mucci, A., Ford, J., Montefusco, V., Plescia, G., Bucci, P., Galderisi, S., 2016. Reward anticipation and trait anhedonia: an electrophysiological investigation in subjects with schizophrenia. *Clin. Neurophysiol.* 127 (4), 2149–2160.
- Waltz, J.A., Schweitzer, J.B., Gold, J.M., Kurup, P.K., Ross, T.J., Salmeron, B.J., Stein, E.A., 2009. Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology* 34 (6), 1567–1577.
- Waltz, J.A., Schweitzer, J.B., Ross, T.J., Kurup, P.K., Salmeron, B.J., Rose, E.J., Stein, E.A., 2010. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology* 35 (12), 2427–2439.
- Wolf, D.H., Satterthwaite, T.D., Kantrowitz, J.J., Katchmar, N., Vandekar, L., Elliott, M.A., Ruparel, K., 2014. Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures. *Schizophr. Bull.* 40 (6), 1328–1337.
- Wynn, J.K., Horan, W.P., Kring, A.M., Simons, R.F., Green, M.F., 2010. Impaired anticipatory event-related potentials in schizophrenia. *Int. J. Psychophysiol.* 77 (2), 141–149.