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Understanding negative symptoms

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Chapter 3

Neural correlates of forecasting of positive emotional events in patients with schizophrenia

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Abstract

Reduced motivation and goal-directed behavior are central to negative symptoms of schizophrenia and may be mediated by reduced anticipatory pleasure. Indeed, using standardized reward paradigms, an association between reduced anticipatory pleasure and negative symptom severity has often been found. Recently, it has been shown that this association extends to the imagination of personally generated positive future events. The aim of this study was to assess the association between brain activation and functional connectivity during imagination of positive future events and severity of negative symptoms in patients with schizophrenia. We analyzed fMRI data of 27 patients with schizophrenia, with varying levels of negative symptoms (measured with the Scale for the Assessment of Negative Symptoms [SANS]). During MR-scanning, participants performed an affective forecasting task, which consisted of imagining positive future events and neutral routine events. Associations between negative symptoms and ratings of vividness and valence of these events were assessed. Furthermore, we investigated the association between negative symptom severity and brain activation and functional connectivity during the imagination of positive versus neutral events. Results showed that negative symptom severity was related to lower vividness ratings and less positive valence ratings of imagined positive future events. Imagination of positive future events (compared to routine events) was related to activation in the superior/orbital medial frontal gyrus and precuneus/PCC. Although regional brain activation was not related to negative symptom severity, we did observe a relationship between severity of negative symptoms and lower functional connectivity between the precuneus/PCC and the precuneus/paracentral lobule and cerebellum (lobule VI/Crus I). These results indicate that negative symptoms are characterized by behavioral alterations in affective forecasting, and that these differences may be underpinned by concomitant alterations in functional brain connectivity rather than level of regional activation, emphasizing the importance of neural dysconnectivity in the characterization of negative symptoms.

Introduction

Motivational problems and reductions in goal-directed behavior are central to schizophrenia (Kring & Barch, 2014). It has been proposed that a lack of anticipatory pleasure may play an important role in these disruptions (Gard et al., 2007; Levy & Dubois, 2006). Anticipatory pleasure can be described as thinking about enjoyment or pleasure of future events. It is thought to be a key requisite for goal-directed behavior, because it may increase motivation to obtain a certain pleasurable goal and may thereby promote goal planning and execution (Kring & Barch, 2014). Reduced experience of anticipatory pleasure has been consistently shown in patients with schizophrenia and may play a crucial role in the occurrence of negative symptoms (Kring & Barch, 2014).

Anticipation of pleasure has been found to depend on involvement of the mesolimbic dopaminergic circuit, including the ventral tegmental area, the ventral and dorsal striatum, amygdala, and medial prefrontal cortex, extending to the anterior cingulate cortex (ACC) (Haber & Knutson, 2009; Liu et al., 2011). Therefore, it could be hypothesized that disrupted activation and connectivity of these brain areas during the anticipation of pleasure is associated with reductions in motivation and goal-directed behavior in patients with schizophrenia.

Indeed, reduced activation during the anticipation of pleasure or reward in patients with schizophrenia has been found in the ventral striatum, (dorsal) caudate, ACC, posterior cingulate cortex (PCC), amygdala–hippocampal complex, parahippocampal gyrus, and ventromedial prefrontal cortex (VMPFC) (Dowd & Barch, 2010, 2012; Gradin et al., 2011; Radua et al., 2015; Walter et al., 2009). In relation to negative symptoms, reduced activation in the ventral striatum has consistently been reported (Radua et al., 2015). Additionally, reduced activation in the dorsal caudate (Mucci et al., 2015), and VMPFC (Dowd & Barch, 2012) during reward anticipation have been found. Furthermore, several studies have indicated that negative symptoms are associated with lower corticostriatal functional connectivity (Koch, Rus, Reess, et al. 2014; Reckless et al. 2015; Park et al. 2017), as well as lower functional connectivity between the midbrain and the insula (Gradin et al. 2013).

To date, the anticipation of reward has often been studied using standardized paradigms. While standardization enables direct comparability between participants, these paradigms leave no room for individual differences in goals and appraisal of positive stimuli. Tasks that use personally generated positive events may therefore shed new light on anticipation of pleasure in patients with schizophrenia. In line with this idea, Raffard et al. (2013) have used an affective forecasting task during which participants were asked to imagine and extensively describe pleasant and unpleasant future events. Results showed that pleasant and unpleasant future events imagined by patients were less specific and contained fewer sensory details than events imagined by healthy controls. Moreover, it has been found that during the imagination of positive events, patients with higher levels of apathy, a core negative symptom, reported less self-reference. Self-reference was measured as the self-reported degree to which the patients' imagination elicited an emotional response and feelings of pre-experiencing the event, and if the patient could imagine what he or she would do or think during the event. In line with these findings, Goodby and MacLeod (2016) have demonstrated that patients with first-episode psychosis were impaired in future thinking (i.e., quickly generating positive and negative future events). Notably, impairments in future thinking (measured by the number of generated events, ratings of how likely participants deemed the events, and valence ratings), regarding positive events, were related to the severity of negative symptoms. It thus seems that imagining positive future events may be disrupted in patients with schizophrenia, especially in patients with higher levels of negative symptoms.

In a sample of healthy subjects, affective forecasting has been associated with activation in the VMPFC, caudate nucleus, and PCC (D'Argembeau et al., 2008), consistent with the areas that have been associated with anticipation of reward. It is, however, still unknown whether activation or functional connectivity of these areas during positive affective forecasting is related to severity of negative symptoms in patients with schizophrenia.

Therefore, in this study we investigated brain activation and functional connectivity during imagination of positive future events compared with neutral routine events in patients with schizophrenia. Specifically, the association between negative symptom severity and neural activation and functional connectivity during positive affective

forecasting was investigated. We hypothesized (1) that during the imagination of positive compared to neutral events more activation would be seen in the VMPFC, caudate, and PCC, (2) that functional connectivity between these regions and the rest of the brain depends on task condition (i.e., positive compared to neutral events), and (3) that activation and connectivity would be lower in patients with higher levels of negative symptoms.

Materials and Methods

Participants

In this study, 27 patients with schizophrenia were included. Inclusion criteria were: age of 18 years or older, sufficient knowledge of the Dutch language, and a diagnosis of schizophrenia or schizoaffective disorder without a comorbid substance dependence disorder (according to the Diagnostic and Statistical Manual of Mental Disorders IV; DSM-IV). Exclusion criteria were: presence of a neurological disorder in present or past, use of medication that may influence brain activation (except antipsychotics), visual or hearing problems that could not be corrected, MR-incompatibility, and inability to undergo cognitive testing. This inability to undergo cognitive testing was assessed with the Digit Symbol Substitution Task of the WAIS-R (Wechsler, 1981). Participants had to obtain a score of at least 24, which is 2.5 standard deviations (SD) below the mean of a previous study by our group with a comparable patient sample ($M=50.28$, $SD=10.71$) (van der Meer, van't Wout, & Aleman, 2009).

All participants gave written informed consent before entering the study. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen and was carried out according to the Declaration of Helsinki.

Clinical Measures

DSM-IV diagnosis of schizophrenia, schizoaffective disorder and substance dependence disorder was based on the Mini International Neuropsychiatric Interview plus version 5.0.0 (MINI-plus) (Lecrubier et al., 1997; Sheehan et al., 1997). Furthermore, several measures were administered to assess symptom severity. Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). Additionally, the full range of symptoms of schizophrenia was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay, Opler, & Lindenmayer, 1989) and depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Schissel, 1990).

Affective forecasting task

Pre-scan interview

The affective forecasting task used in this study was an adaptation of the task developed by D'Argembeau et al. (2008). During a pre-scan interview, participants were asked to think of five neutral routine events and five positive future events. The routine events were defined as emotionally neutral repetitive tasks that were performed every day or at least multiple times per week (e.g., *brushing my teeth*), while positive future events were events that may occur in the near future (up to a month; e.g., *having dinner with my family*). Any event was allowed, given that its occurrence was plausible and that it would take place in a particular place and time, lasting maximally one day. Short

cue statements were derived from the participant's descriptions. These statements were used as a cue during the remainder of the pre-scan interview, during which they were asked to imagine every event and rate their vividness and emotional valence. Specifically, they were asked to imagine the event with as much detail as possible: taking into account the location, objects and people present during the event, what they would be doing, and how they would feel during the event. Subsequently they were asked to rate the emotional valence of their imagination (ranging from -3 = very negative to 3 = very positive), and vividness/amount of details of the imagination (ranging from 1 = vague with no details to 6 = vivid and highly detailed).

fMRI session

The task was part of a scanning protocol that also included an effort-reward task, an anatomy scan, and MR spectroscopy. Prior to the scanning session, participants were given explanations on the MR procedures and task, and the affective forecasting task was practiced. In the MR scanner, the instruction was briefly repeated, after which the affective forecasting task was presented (see *Figure 1*). The task consisted of four epochs, each containing all five neutral events and all five positive events. The order of the trials within the epochs was randomized. Each trial started with a fixation cross (1.5 s), followed by presentation of the cue statement (5 s). Then a screen appeared instructing the participant to imagine the event and close their eyes. The imagine phase lasted 15 seconds and was ended by a tactile stimulus (i.e., a tap on the lower leg by the experimenter). Subsequently, the participant was asked to rate the vividness/amount of details of the imagination on a 7-point Likert-scale (ranging from 0 = vague with no details to 6 = vivid and highly detailed), by means of a button press. Rest periods of 10 TRs (18-20 s) were presented at the beginning and end of the task and between epochs. A fixation cross was presented during all rest periods. The total task duration was 21 minutes.



Figure 1. The affective forecasting task. The task consisted of four epochs and each event was presented in every epoch. The end of the imagination phase was marked with a tactile stimulus (i.e., a tap on the lower leg by the researcher).

Image acquisition

The fMRI data were collected using a 3.0 Tesla Philips Intera MR-scanner scanner (Best, NL), equipped with a 32-channel SENSE head coil. Whole-brain functional images were acquired using a T2*-weighted echo planar imaging sequence (47 descending axial slices, TR=2000 ms; TE=22 ms; flip angle=90°; FOV (rl, ap, fh)=192 x 192 x 141 mm; voxel size 3 x 3 x 3 mm; slice thickness 3 mm; slice gap=0 mm; 642 volumes). Two participants were scanned using slightly different parameters (39 descending axial slices; TR=2000 ms; TE=30 ms; flip angle=80°; FOV (rl, ap, fh)=224 x 224 x 136.5 mm; voxel size 3.5 x 3.5 x 3.5 mm; slice thickness 3.5 mm; slice gap=0 mm; 642 volumes). Furthermore, a whole

brain T1-weighted image was acquired for anatomical reference (170 axial slices; TR=9 ms; TE=3.5 ms; FOV=232 x 170 x 256 mm; voxel size=1 mm isotropic; flip angle=8°). All images were scanned approximately 30° from the Anterior Commissure-Posterior Commissure (AC-PC) plane in order to prevent artifacts due to nasal cavities.

Analysis

Demographic and clinical data

Demographic, clinical and behavioral data were analyzed using IBM SPSS version 23.0 (IBM Corp, Armonk, NY, 2014) and MATLAB 2013a, (The MathWorks Inc., Natick, MA). Bivariate associations between demographic and clinical variables were calculated. Because bivariate normality was not met, Kendall's Tau test was used to calculate rank correlations.

Behavioral data

Mean vividness and valence ratings obtained during the pre-scan interview and mean vividness ratings during fMRI scanning were calculated separately for neutral and positive events. In order to assess a possible association between these ratings and negative symptom severity, repeated measures analyses of covariance (ANCOVA) were used with condition as the within-subject factor and mean-centered SANS total score as the covariate of interest. Because of the close relationship between negative and depressive symptoms, this analysis was repeated with mean-centered CDSS scores as covariate. Significance was set to $p < .05$.

fMRI data

Preprocessing

The data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12 version 6470; <http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB 2013a. PAR/REC-files were converted to NIfTI, using an in-house script. Anatomical and functional images were reoriented manually to the anterior commissure – posterior commissure (AC-PC) plane. Subsequently, the data were preprocessed in the following order: (1) slice timing correction to the first slice, (2) realignment to the mean image, (3) coregistration of the T1-image to the mean functional image, (4) normalization of the images to Montreal Neurological Institute (MNI) space, and (5) smoothing of the functional images using an 8 mm Full Width Half Maximum Gaussian kernel.

First-level analysis

On first-level, task regressors were defined by the onset and duration of the imagine phase, separately for positive and neutral events. In addition, instruction periods and the rating phase were defined as regressors of no interest. Furthermore, motion parameters and their first derivatives were added. In order to reduce the effects of motion, high-motion volumes ($FD > .9$) (Siegel et al., 2014) were regressed out using an additional regressor. In addition, a 128 s high pass filter was applied. For all participants, contrasts for positive imagination (positive > neutral events) and neutral imagination (neutral events > fixation cross) were taken to second level.

Second level analysis - activation

On second level, whole-brain task activation was assessed over all patients for positive

imagination and neutral imagination, using a one-sample t-test. Because of the a priori hypothesis regarding the involvement of the VMPFC, caudate nucleus, and PCC during positive imagination based on the findings of D'Argembeau et al. (2008), a small volume correction (SVC) on these regions was applied for the contrast positive > neutral. To this end, 20 mm spheres were drawn around the previously reported peak coordinates of activation in these regions during imagination of positive > negative imagination (the positive > neutral contrast was not investigated in this paper) (D'Argembeau et al., 2008). To be able to detect activation differences in non-hypothesized areas for this contrast, an additional whole-brain analysis was performed. For the contrast neutral > baseline only a whole-brain approach was used, because there were no specific hypotheses regarding regions of activation. Significance was set to $p < .05$ family wise error (FWE) cluster-level corrected for the extent of the whole brain or region of interest mask, with an initial threshold of $p < .001$, uncorrected.

In order to assess the association between brain activation during positive imagination and negative symptom severity, a regression analysis was performed with SANS total score as the independent variable and activation during positive > neutral events as the dependent variable. Again, a small-volume correction (using the same mask as for the analysis of task activation) as well as a whole-brain analysis was performed, with a threshold of $p < .05$ FWE cluster level corrected (initial threshold $p < .001$).

Because of the close relationship between negative symptoms and depression, any negative symptom-related clusters of activation were explored further. Specifically, it was assessed whether SANS-scores uniquely explained the variance in these clusters, or whether any variance explained by the SANS was also explained by CDSS scores. To this end, the first eigenvariates of the activation in the negative symptom-related clusters were extracted. These were entered into a stepwise linear regression analysis, in which CDSS and SANS scores were entered as independent variables in a step-wise manner (SANS scores were entered last). To emphasize the exploratory nature of this analysis and in order to avoid the suggestion of circular analysis, only explained variances were reported. Whether the beta-values were significantly different from zero was not examined, because this analysis was a mere exploration of the association between SANS scores and activation that was found in the main analysis. Finally, in order to assess the robustness of the effect against the subtle differences in scan parameters, all analyses were repeated without the participants with alternative scan parameters.

Second level analysis – functional connectivity

Functional connectivity of the regions activated during positive > neutral imagination was analyzed by means of a generalized psychophysiological interaction analysis (gPPI; McLaren et al. 2012). To this end, separate regions of interest (ROIs) were determined functionally as a sphere of 6 mm radius around any peak coordinates from the overall task activation, for the contrast positive > neutral events. Functional connectivity was calculated between the time courses of these regions and all other voxels in the brain during positive > neutral imagination. In addition, the association between this functional connectivity and SANS scores was examined. As in the activation analysis, any negative symptom-related clusters of connectivity were entered into an exploratory step-wise regression analysis with CDSS and SANS as the independent variables,

in order to assess whether any variance in these clusters was uniquely explained by negative symptoms over and above depressive symptoms. Significance was set to $p < .05$ family wise error (FWE) cluster-level corrected for the extent of the whole brain, with an initial threshold of $p < .001$, uncorrected.

Results

Demographic and clinical data

Demographic and clinical characteristics are shown in *Table 1*. Negative symptom severity as measured by the SANS ranged from 13 to 64 ($M=40.52$, $SD=16.00$). CDSS scores ranged from 0 to 11 ($M=2.67$, $SD=3.17$) and were correlated with SANS scores ($\tau=0.48$, $p=.001$).

Table 1. Demographic and clinical variables

	Possible range ¹	Mean (SD)	Min/max	τ_{SANS} total	<i>p</i>
N	-	27	-	-	-
Age	-	34.59 (8.61)	22/56	-.34	.02
N Male/female (% male)	-	70.37	-	-.08	.64
Education (years ²)	-	15.61 (2.48)	12/20	0.004	.98
SANS total	0/130	40.52 (16.00)	13/64	-	-
SANS blunted affect	0/45	12.93 (5.86)	5/24	.58	<.001
SANS alogia	0/30	5.93 (2.91)	0/11	.56	<.001
SANS avolition/apathy	0/25	11.33 (5.23)	1/20	.69	<.001
SANS anhedonia/asociality	0/30	10.33 (6.13)	0/21	.64	<.001
PANSS total	30/210	59.48 (13.22)	32/83	.30	.03
PANSS positive	7/49	13.81 (5.00)	7/24	-.04	.80
PANSS negative	7/49	14.52 (3.96)	8/23	.55	<.001
PANSS general	16/112	31.15 (6.99)	17/44	.32	.02
CDSS	0/27	2.67 (3.17)	0/11	.48	.001

Note. SA: Schizoaffective disorder; SZ: Schizophrenia; SANS: Scale for the Assessment of Negative Symptoms; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; ¹Higher scores indicate stronger severity. ²Including primary school.

Behavioral data

There was a main effect of condition on vividness ratings obtained during the pre-scan interview and a negative association with SANS score ($F(1, 25)=4.97$, $p=.04$ and $F(1, 25)=15.98$, $p<.001$, resp., *Figure 2A*), but no interaction between SANS and condition ($F(1, 25)=0.69$, $p=.41$). Regarding valence ratings obtained during the pre-scan interview, there was again a main effect of condition and a negative association with SANS score ($F(1, 25)=208.36$, $p<.001$ and $F(1, 25)=7.75$, $p=.01$, resp., *Figure 2B*), but no interaction ($F(1, 25)=1.02$, $p=.32$).

Due to a technical issue during scanning, vividness ratings of one participant were

not obtained. Therefore, the analyses on vividness ratings during the fMRI task were performed on the data of 26 participants. These vividness ratings showed a similar pattern as the ratings obtained during the pre-scan interview: there was a negative association with SANS scores ($F(1, 24)=8.32, p=.01$, Figure 3), However, there was no main effect of condition or an interaction effect ($F(1, 24)=1.76, p=.20$ and $F(1, 24)=0.60, p=.45$, resp.).

Repeating the analyses with CDSS score as covariate yielded no significant effects of depressive symptoms on any of the ratings (for pre-scan ratings of vividness: $F(1, 25)=2.45, p=.13$; for pre-scan ratings of valence: $F(1, 25)=1.30, p=.27$; for ratings of vividness during scanning: $F(1, 24)=2.04, p=.17$).

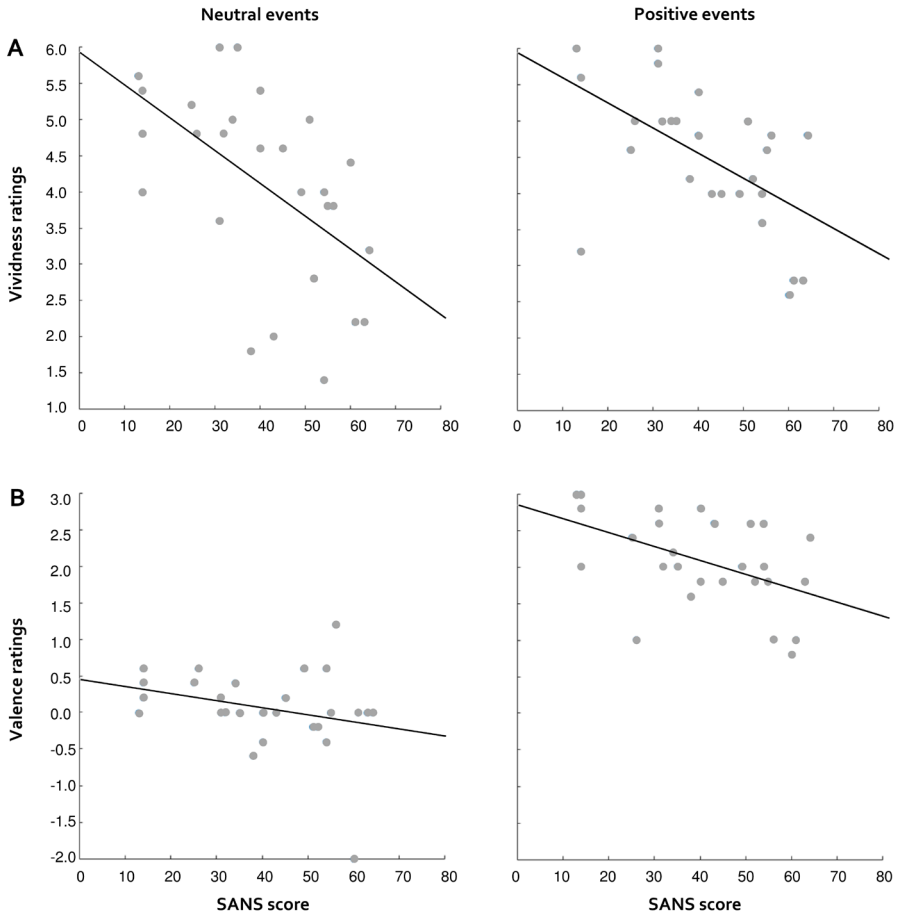


Figure 2. Scatter plots of the association between vividness (A) and valence (B) participant ratings obtained during the pre-scan interview and total SANS scores.

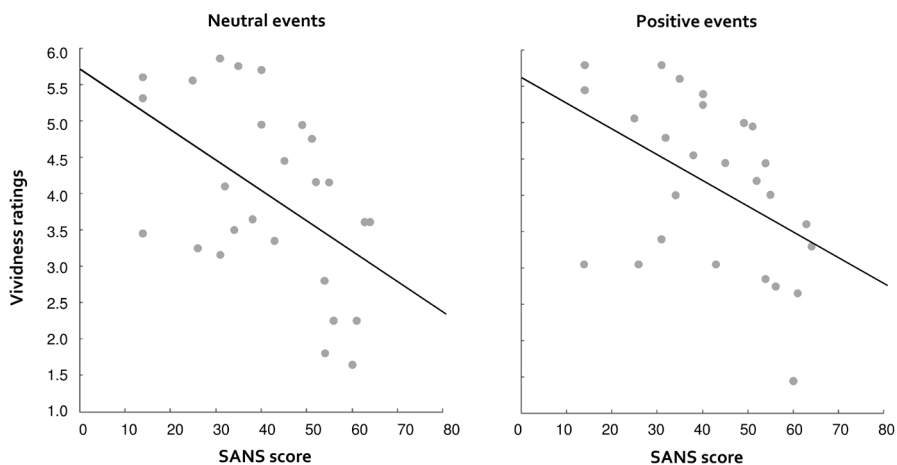


Figure 3. Scatter plots of the association between participant ratings obtained during the fMRI experiment and total SANS scores.

Table 2. Areas of brain activation during imagination of neutral and positive events

	k	side	peak coordinates			t	p (FWE)
			x	y	z		
<i>Neutral > baseline^a</i>							
Middle/superior frontal gyrus (BA6/8/9/10/24/32)	1923	L	-27	47	17	7.57	<.001
		L	-6	17	44	6.44	
		L	-42	23	35	5.73	
Middle/superior frontal gyrus (BA10)	131	R	30	35	20	5.66	.01
		R	21	47	20	4.22	
<i>Positive > neutral^b</i>							
Medial superior/orbital frontal gyrus (BA10)	47*	L	-6	56	14	4.42	.03
		L	-3	59	-7	4.18	
		L	-9	56	5	3.82	
Precuneus/PCC (BA31)	33*	L	-6	-55	23	4.02	.049
			0	-55	29	3.92	

Note. BA: Brodmann area; k: cluster extent (in voxels); FWE: Family-Wise Error corrected: ¹ Whole-brain analysis: corrected on cluster level; ² Small volume corrected analysis; * cluster extent (in voxels) within the small volume mask.

fMRI data

Activation

During neutral imagination (compared to fixation), activation was found in the left middle and superior frontal gyrus, extending to the bilateral supplementary motor area and midcingulate gyrus, and the left precentral gyrus (BA6/22/9/8; whole brain corrected, *Figure 4* and *Table 2*). Activation during positive > neutral imagination was found in the medial superior/orbital frontal gyrus (BA 10), and precuneus/PCC (BA 31) after small volume correction (*Figure 4* and *Table 2*). The whole-brain analysis yielded no significant activation for this contrast. Furthermore, there was no association, either in the whole-brain analysis or after small-volume correction, between activation and negative symptom severity (SANS total score) for both the contrasts positive > neutral and neutral > fixation. Removal of the participants with alternative scan parameters did not change the results.

Because the associations between SANS scores and valence ratings and vividness ratings (during both the pre-scan interview and the fMRI task) were irrespective of condition, an exploratory analysis was performed to assess whether negative symptoms were associated with brain activation during imagination in general. To this end, first-level contrasts of positive + neutral > baseline were taken to second level to investigate the association with SANS scores. However, no association between SANS scores and activation during positive and neutral activation was found. Again, removing participants with alternative scan parameters did not change these results.

Functional connectivity

Functional connectivity was calculated for the ROIs in the medial frontal gyrus and precuneus/PCC. Functional connectivity during positive > neutral imagination was found between the precuneus/PCC seed and the midbrain (*Figure 5* and *Table 3*). Higher SANS scores were associated with lower functional connectivity between the

3

Table 3. Functional connectivity of the precuneus/PCC region of interest (ROI) during imagination of positive > neutral events

	k	side	peak coordinates			t	p (FWE)
			x	y	z		
<i>Task-related FC</i>							
Midbrain	75	R	12	-7	-13	5.12	0.033
		R	12	-16	-19	4.88	
<i>SANS-related FC</i>							
Precuneus/paracentral lobule (BA 5/6)	231	R	9	-49	74	5.13	<.001
		R	3	-46	68	5.09	
Cerebellum (lobule VI/Crus I)	72	L	-15	-31	77	4.84	.03
		L	-21	-52	-25	4.65	
		L	-30	-64	-28	4.24	

Note. FC: functional connectivity; k: cluster extent (in voxels); FWE: Family-Wise Error cluster corrected for the whole-brain.

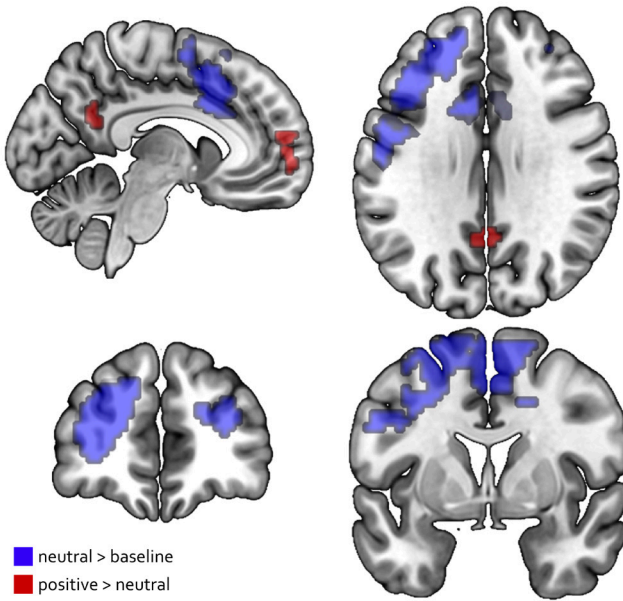


Figure 4. Task activation during the affective forecasting task. Threshold was set to $p < .05$ FWE cluster-level corrected (with an initial threshold of $p < .001$) for the whole brain for the contrast neutral > baseline (in blue) and small-volume corrected for the contrast positive > neutral (in red). For visualization purposes images were resliced to a voxel size of 0.4 mm.

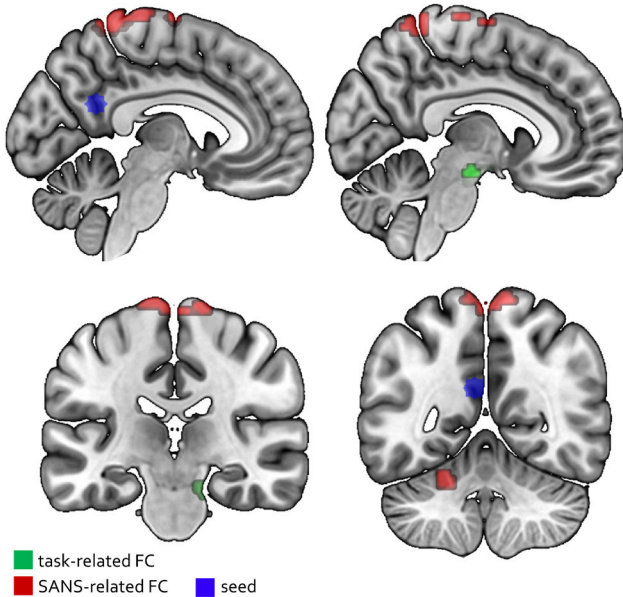


Figure 5. Functional connectivity (FC) between the precuneus/PCC region of interest (ROI; in blue) and the rest of the brain during positive > neutral imagination. Threshold was set to $p < .05$ FWE cluster-level corrected (with an initial threshold of $p < .001$) for the whole brain. For visualization purposes images were resliced to a voxel size of 0.4 mm.

precuneus/PCC and the precuneus/paracentral lobule (extending to the supplementary motor area; BA 5/6) and cerebellum (lobule VI/Crus I).

Exploration of the first eigenvariates of these clusters showed that a substantial portion

of the variance was uniquely explained by SANS-scores (25.6% for the precuneus/paracentral lobule and 21.4% for the cerebellum cluster), in addition to the variance that was explained by CDS scores (32.8% for the precuneus/paracentral lobule and 17.5% for the cerebellum). No positive association between negative symptoms and functional connectivity of the precuneus/PCC was found and no suprathreshold functional connectivity was found between the medial frontal gyrus ROI and the rest of the brain.

Discussion

In this study, we investigated whether brain activation and functional connectivity during affective forecasting of positive events is related to the severity of negative symptoms in patients with schizophrenia. Participants with more severe negative symptoms reported less vividness and less positive valence of their imagined positive future events, as well as for neutral events. Moreover, imagination of positive events elicited activation in the medial superior/orbital frontal gyrus and precuneus/PCC. Although regional activation during imagination of positive future events was not related to negative symptom severity, lower functional connectivity between the precuneus/PCC and precuneus/paracentral lobule and cerebellum (lobule 6/Crus I) was associated with more severe negative symptoms.

The findings of reduced vividness and valence of positive imagined events in relation to more severe negative symptoms is in line with previous findings in patients with schizophrenia (Goodby & Macleod, 2016; Raffard et al., 2013). In these studies, imagination of positive events was compared to imagination of negative events, showing that negative symptoms were specifically associated with problems in imagining positive events. In the current study, we compared positive with neutral events, adding to previous findings that during imagination of neutral routine events ratings of vividness and valence were associated with negative symptom severity as well. Therefore, based on previous and current findings, it may be suggested that imagination of positive and neutral, but not negative events is related to negative symptoms in patients with schizophrenia. While neutral events (e.g., *brushing my teeth*) and positive events (e.g., *having dinner with my family*) may elicit 'approach' or 'go' actions, negative events (e.g., *having a fight with the neighbor*) are more likely to elicit avoidance or 'no-go' actions. Therefore, these findings fit with the idea of negative symptoms as a result of disrupted go-learning (i.e., what to do to obtain a reward) and intact no-go learning (i.e., what not to do to avoid punishment), that has been found in patients with schizophrenia (Strauss, Waltz, & Gold, 2014) and specifically in patients with negative symptoms (Gold et al., 2008).

Moreover, the findings of reduced vividness and valence of imagined future events in association with increased severity of negative symptoms fit with known models of motivational problems in patients with schizophrenia. Specifically, a vivid representation of a positive outcome (*having dinner with your family*) is thought to be imperative for prediction of pleasure (*how much will I enjoy this dinner?*) as well as for pre-experiencing feelings of pleasure (*I feel happy thinking about having a nice dinner with my family*) (Kring & Barch, 2014). Therefore, although a temporal dependency between the two ratings cannot be assessed, it is possible that reduced vividness of imagined positive

events may lead to reduced valence ratings, i.e., reduced anticipatory pleasure. This may in turn reduce the tendency to act upon the anticipatory pleasure, leading to reduced goal-directed behavior, a disturbance central to the negative symptom cluster (Kring & Barch, 2014).

Of note, individuals with more severe negative symptoms may simply experience fewer or less pleasurable events than those with less severe negative symptoms, which may influence the reported reduction in anticipatory pleasure. Because negative symptoms are characterized by reduced goal-directed behavior, people with negative symptoms may be less inclined to seek pleasurable events and may therefore experience them less often. Indeed, negative symptoms have been associated with reduced quality of life in various domains including interpersonal relations and professional and household functioning, taking into account both frequency and subjective quality of the activity (Fervaha et al., 2014a; Rabinowitz et al., 2012). The positive events that occur in the lives of patients with more severe negative symptoms may therefore be less positive compared to those in the lives of patients with less severe negative symptoms, leading to lower valence ratings.

On the neural level, imagination of positive events in schizophrenia patients was associated with activation in the medial frontal gyrus and precuneus/PCC. This is in accordance with previous studies in healthy individuals, in which activation in similar regions was found during imagination of future events in general (Addis, Wong, & Schacter, 2007; Sharot et al., 2007), and during imagination of positive events compared to negative events in particular (Blair et al., 2013; D'Argembeau et al., 2008). Furthermore, the current results are in line with previous meta-analyses that underline the involvement of the anterior part of the medial frontal gyrus (Brodmann area 10) in mentalizing (Denny et al., 2012; Gilbert et al., 2006) and more generally in emotional processing and social cognition (Ray et al., 2015). Furthermore, the PCC and the medial frontal gyrus are core regions of the default mode network (DMN), a network of brain areas that support emotional and self-referential processing, and thinking about one's past and future (Raichle, 2015).

Given the involvement of the caudate nucleus in both reward-related processing (Liu et al., 2011) and positive imagination in healthy individuals (D'Argembeau et al., 2008), we expected to find main task activation in the caudate for the contrast positive > neutral imagination in the current study. However, this was not the case. Because altered activation in this area during reward-related processes has been found in patients with schizophrenia (Gradin et al., 2011; Morris et al., 2015; Mucci et al., 2015), this absence could perhaps be due to the fact that only patients with schizophrenia, and no healthy controls, were included in the current study and that caudate activity may have been attenuated accordingly. However, to test this hypothesis, a direct comparison between patients with schizophrenia and healthy controls is warranted.

Contrary to our expectations, brain activation in the regions involved in positive affective forecasting was not associated with negative symptom severity. Because negative symptoms were related to valence and vividness of both positive and neutral events, it may be suggested that brain activation during imagination in general, rather

than specifically positive imagination, is related to negative symptoms. However, an additional exploratory analysis showed that also activation during imagination of positive and neutral events combined was not related to negative symptom severity.

In contrast, we did observe a relationship between functional connectivity of the precuneus/PCC and severity of negative symptoms. Thus, severity of negative symptoms may be underpinned to a stronger degree by connectivity of brain areas rather than degree of local activation. Indeed, schizophrenia is commonly linked to dysconnection (i.e., disrupted connectivity) of large-scale brain networks (Stephan, Baldeweg, & Friston, 2006), which may not be fully explained by altered activity in specific brain regions (Rish et al., 2013). The association of negative symptoms with connectivity between the precuneus/PCC and precuneus/paracentral lobule may be explained by previous findings that have linked connectivity between these regions to mental simulation of goal-directed actions, most notably when participants were asked to imagine the steps necessary to obtain a goal (Gerlach et al., 2013). Given the involvement of the paracentral lobule, SMA and lobule VI and Crus I of the cerebellum in motor control and motor imagery (Zapparoli et al., 2013), the lower connectivity between these areas and the PCC/precuneus ROI may imply that individuals with negative symptoms may have difficulty translating imagined positive events to a goal-directed action, leading to apathy, a central negative symptom.

Strengths and limitations

The personalized nature of the affective forecasting task could be regarded as strength as well as a limitation. On the one hand, the current paradigm with its personalized stimuli leaves room for personal interpretation and experience of pleasurable events and personal goals. Accounting for these personal preferences possibly makes the task more sensitive and adds to its ecological validity. On the other hand, the subjective and unstandardized nature of the stimuli and participant ratings does not allow for complete experimental control. It may therefore be advisable to assess current findings in concordance with findings from more standardized paradigms, combining the strengths of both approaches.

A limitation of the current study may be the inclusion of patients using antipsychotics. Antipsychotic medication has been shown to influence the dopamine pathways that are involved in reward processing (Kapur, 2004). Indeed, in healthy individuals, a single dose of antipsychotic medication has been shown to alter reward processing (Abler, Erk, & Walter, 2007; Pessiglione et al., 2006) and to induce secondary negative symptoms (Artaloytia et al., 2006). Ideally, replication of the current study in a sample of antipsychotic medication-naïve patients may therefore be warranted to affirm the current results. This may however be challenging, given that most patients with schizophrenia are using antipsychotic medication from an early start after entering mental health care.

A second limitation is the absence of a healthy control group. Although a comparison with healthy controls is not essential given the specific hypothesis regarding negative symptoms, it does somewhat limit the interpretation of the results. Specifically, inclusion of healthy participants would allow further exploration of reasons for the

absence of task activation in the caudate nucleus and, moreover, the absence of an association between brain activation and symptom severity. In other words: can the absence of caudate activation in patients be ascribed to schizophrenia in general or to task demands of the current task, and is the absence of an association with negative symptoms due to normal levels of activation in patients, or a decrease in patients with schizophrenia in general, unrelated to the severity of negative symptoms? Therefore, we are currently recruiting a healthy control group that will be included in a subsequent version of the current manuscript.

Conclusion

To conclude, the present study showed that in patients with schizophrenia, severity of negative symptoms is related to reduced ratings of vividness and valence of imagined positive future events. Imagination of positive future events elicited activation in the superior/orbital medial frontal gyrus and precuneus/PCC. Reduced functional connectivity of the precuneus/PCC seed rather than local activation strength was related to negative symptom severity.

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PART II

Neural correlates of negative symptom dimensions: amotivation and expressive deficits

