Supplementary Materials

Larabi et al. Insight and emotion regulation in schizophrenia: a brain activation and functional connectivity study

1. Methods

1.1 Demographic and clinical characteristics and insight. SPSS 20 (SPSS Inc., Chicago, IL, USA) was used for behavioral data analyses. First, groups were compared on demographic characteristics and Pearson correlations between demographic and illness-related variables (age, sex, estimates of premorbid intelligence, handedness, illness duration and standardized antipsychotic dose) and (cognitive and clinical) insight were calculated. Premorbid IQ was estimated with the Dutch Adult Reading Test (DART) (Schmand et al., 1991). A threshold of $p < 0.05$, two-tailed, was used as the standard for statistical significance and all correlations between demographics and insight were evaluated at an FDR-corrected level (corrected for 12 tests) (Benjamini and Hochberg, 1995). Second, we examined the association between symptomatology and insight. Pearson correlations between PANSS scores on negative symptoms, positive symptoms, general psychopathology and illness severity (PANSS total minus item G12) and (cognitive and clinical) insight were calculated. All correlations were evaluated at an FDR-corrected level (corrected for 8 tests). In addition, we calculated intercorrelations between all insight measures (i.e. PANSS G12, SAI-E and BCIS) with clinical (i.e. PANSS scores on negative symptoms, positive symptoms, general psychopathology, PANAS (affect), ERQ (emotion regulation strategy) or cognitive (i.e. estimate of premorbid intelligence) measures.

1.2 Emotion regulation questionnaire. We examined a priori differences in emotion regulation strategies between groups with two separate ANOVAs for the two subscales of the ERQ (Reappraisal and Suppression). A threshold of $p < 0.05$, two-tailed, was used as the standard for statistical significance.

1.3 Affect. We also performed an ANOVA to examine a priori differences in affect between groups: PANAS scores were entered as within-subject variable and group as between-subject variable. A threshold of $p < 0.05$, two-tailed, was used as the standard for statistical significance.

1.4 Emotion regulation task. The degree of negative affect (rating) and the reaction times (RTs) of these ratings during the emotion regulation task were examined with repeated measures ANOVA. We entered condition (attend neutral, attend negative, reappraise, suppress and increase) as a within-subject factor, and group (HC and SZ) as a between-subject factor. A threshold of $p < 0.05$, two-tailed, was used as the standard for statistical significance.

2. Results

2.1 Behavioral results

2.1.1 Demographic and clinical characteristics and insight. No significant differences in age, sex, level of education, handedness and estimates of premorbid intelligence were found between patients and HC. No significant correlations were found between insight and demographic or clinical variables after FDR-correction for multiple testing.

No significant correlation was found between SAI-E subtotal scores and BCIS composite index scores ($r = .125$; $p = .522$; $n = 30$). A significant correlation was found between SAI-E subtotal scores and BCIS self-reflectiveness scores ($r = -.550$; $p = .002$), indicating that patients with better clinical insight had lower self-reported self-reflection abilities. In addition, a significant correlation was found (after FDR-correction for 6 tests) between SAI-E Awareness of illness subscale scores and BCIS self-reflectiveness subscale scores ($r = -.620$; $p_{FDR} < .001$).

Intercorrelations between all insight measures (i.e. PANSS G12, SAI-E and BCIS) with clinical (i.e. PANSS scores on negative symptoms, positive symptoms, general psychopathology, PANAS (affect), ERQ (emotion regulation strategy)) or cognitive (i.e. estimate of premorbid intelligence) measures can be found in Supplementary Table S1.

Table S1. Intercorrelations between insight measures and clinical and cognitive measures.

	SAI	BCIS	POS	NEG	GLO	PPO	PNE	REA	SUP	IQ
G12	.717*	.280	-.284	-.393*	-.480*	.138	.105	-.394*	.110	-.079
SAI		.125	-.344	-.114	-.251	.167	.095	-.125	.405*	-.275
BCIS			.035	-.066	-.189	.156	-.190	.009	.110	-.099
POS				.152	.672*	-.097	.122	-.070	-.144	.206
NEG					.573**	-.112	.118	-.015	.101	-.390*
GLO						-.276	.228	-.012	-.003	.010

PPOS	-.104	.578*	.370	.376
PNE		-.320	-.386	-.128
REA			.324	-.031
SUP				-.270

Abbreviations: G12 = Positive and Negative Syndrome Scale (PANSS) item G12 (rescored); SAI = Schedule for the Assessment of Insight – Expanded (SAI-E) subtotal; BCIS = Beck Cognitive Insight Scale (BCIS) composite index score; POS = PANSS positive symptoms; NEG = PANSS negative symptoms; GLO = PANSS global psychopathology; PPOS = Positive and Negative Affect Schedule (PANAS) positive affect; PNE = Positive and Negative Affect Schedule (PANAS) negative affect; REA = Emotion Regulation Questionnaire (ERQ) reappraisal; SUP = Emotion Regulation Questionnaire (ERQ) suppression; IQ = premorbid estimate of IQ measured with Dutch Adult Reading Test (DART).
*Correlations significant at the 0.05 level (2-tailed; uncorrected for multiple testing).

2.1.2 Emotion regulation questionnaire. Mean scores on this questionnaire can be seen in Supplementary Table S2. Data of one HC was missing because of technical issues. An ANOVA did not reveal significant differences between groups in the use of reappraisal as emotion regulation strategy ($F(1,42) = 0.170$, $p = 0.682$). A difference at trend-level was found between groups for the use of suppression ($F(1,42) = 2.921$, $p = 0.095$), meaning that patients reported to use this emotion regulation strategy more frequently than HC.

2.1.3 Affect. Mean affect scores can be seen in Supplementary Table S2. An ANOVA revealed a priori differences in affect (as measured with the PANAS) between groups. Patients scored higher on negative affect ($F(1,39) = 5.69$, $p = 0.022$), and lower on positive affect ($F(1,39) = 6.65$, $p = 0.014$) compared to HC.

2.1.4 Emotion regulation task. Ratings and RTs for affect during emotion regulation are presented in Supplementary Materials Table S2 and Supplementary Materials Fig. S1. A repeated measures ANOVA (with Greenhouse-Geisser correction for non-sphericity) revealed a main effect for condition on rating of affect ($F(3.32, 142.65) = 117.19$; $p < 0.001$). Pairwise

comparisons demonstrated that affect ratings were significantly different after all conditions, except for reappraise versus suppress conditions. This suggests that the task was successfully executed; both regulation strategies successfully reduced negative feelings compared to attend trials. A main effect for group on affect ratings was also found ($F(1,43) = 4.74$; $p = 0.035$), with patients scoring higher on negative affect than controls. No significant interaction effect (group*condition) was found on affect ratings. A repeated measures ANOVA for reaction time of negative affect rating revealed a main effect for condition ($F(4,172) = 14.59$; $p < 0.001$), as well as an interaction effect between condition and group ($F(4,172) = 6.13$; $p < 0.001$). The combined group of HC and SZ was fastest after increase, followed by attend neutral, reappraise, suppress and attend negative. Post-hoc tests with Bonferroni correction showed that their RTs were significantly faster after increase than after suppress or attend negative; faster after attend neutral, than after suppress and attend negative; and faster after reappraise than after suppress. Less variation was seen in RTs of SZ patients, compared to HC. No main effect for group was found.

Table S2. Affect, emotion regulation strategies and affect ratings after emotion regulation.

Variable	Schizophrenia patients (mean (SD))	Healthy controls (mean (SD))
PANAS[a]		
Positive	30.89 (5.98)	35.60 (4.97)
Negative	17.77 (7.85)	12.80 (2.27)
Total	48.65 (9.36)	48.40 (5.74)
ERQ[b]		
Reappraisal	4.69 (1.42)	4.87 (1.02)
Suppression	3.34 (1.23)	2.66 (1.24)
Rating negative affect after emotion regulation		
Attend neutral	1.28 (0.25)	1.08 (0.09)
Attend negative	2.77 (0.55)	2.45 (0.47)
Reappraise	2.27 (0.62)	2.11 (0.49)
Suppress	2.45 (0.53)	2.22 (0.51)
Increase	3.12 (0.54)	2.91 (0.36)
RT negative affect after emotion regulation (ms)		
Attend neutral	1215.26 (514.16)	931.75 (333.67)
Attend negative	1317.20 (491.13)	1323.25 (478.55)

Reappraise	1190.10 (534.82)	1169.87 (355.72)
Suppress	1245.87 (517.73)	1385.40 (398.76)
Increase	1117.51 (487.23)	1064.75 (310.45)

[a]n = 41 (PANAS information was missing for 4 SZ patients).
[b]n = 44 (ERQ information was missing for 1 HC).
Abbreviations: PANAS = Positive and Negative Affect Schedule; ERQ = Emotion Regulation Questionnaire; RT = reaction time.

2.2 Results - Main task effects

The contrast reappraisal > attend negative showed activation in bilateral superior frontal gyrus/medial frontal gyrus (supplementary motor area), bilateral middle frontal gyrus, bilateral inferior frontal gyrus, bilateral insula, left middle temporal gyrus, left inferior parietal lobule (angular gyrus) and left middle temporal gyrus. These areas have been shown to support reappraisal in a meta-analysis of Buhle and colleagues (2014) (Buhle et al., 2014). Other activated areas were midline middle cingulate cortex, right superior temporal pole, right vermis of the cerebellum, right caudate, right middle temporal gyrus and left precuneus. The reverse contrast attend negative > reappraisal did not show any activation after cluster-level FWE-correction ($p < 0.05$).

The contrast suppression > attend negative showed activation in the midline superior frontal gyrus/medial frontal gyrus (supplementary motor area), bilateral inferior frontal gyrus and insula and right supramarginal gyrus. The reverse contrast attend negative > suppression showed activation in the midline calcarine sulcus/cuneus/lingual gyrus, right superior and middle occipital gyrus and right inferior temporal gyrus. An earlier study by our group (Van der Meer et al., 2014) comparing brain activation during emotion regulation between schizophrenia patients and non-affected siblings did not find any significant activation during suppression (with an initial threshold of $p < 0.001$ and p_{FWE}-cluster level correction at $p < 0.05$). Brain activation found in our study is consistent with other studies in healthy individuals (Goldin et al., 2008; Hayes et al., 2010; Van der Velde et al., 2015), however, confirming the validity of this condition. Lack of findings in our previous study may be explained by a lack of power,

since main effect analyses were conducted with data of only 20 individuals (45 in this study) and a complex general linear model was made consisting of 32 regressors (14 regressors in this study).

Lastly, the contrast increase > attend negative revealed activation in the midline medial frontal gyrus and superior frontal gyrus, left middle temporal gyrus, left superior temporal gyrus, bilateral inferior frontal gyrus and insula. These areas have been shown to support reappraisal in a meta-analysis of Buhle et al. (Buhle et al., 2014). Activation was also found in the right vermis of the cerebellum and the left thalamus. The reverse contrast attend negative > increase showed activation in cuneus/calcarine sulcus and lingual gyrus. A full overview of these results can be seen in Supplementary Table S3.

2.3 Results - Group differences

With regard to reappraisal > attend negative, HC showed more activation in the left middle temporal gyrus compared to SZ patients. The reverse comparison (SZ > HC) did not reveal any significant differences tresholded at cluster-level FWE-corrected $p < 0.05$. The other contrasts (suppression > attend negative and increase > attend negative) did not show significant differences between groups with these thresholds. These results can be seen in Supplementary Table S3.

Table S3. Main effects of reappraisal, suppression and increase on BOLD responses and comparisons between groups.

			MNI coordinates			
	Hemisphere	k voxels	x	y	z	*Z*
Reappraisal > attend negative						
Midline superior frontal gyrus/medial frontal gyrus (supplementary motor area), midline middle cingulate cortex, L middle frontal gyrus, L inferior frontal gyrus, L insula	Midline and L	5601	-2 -6 -44	10 18 24	62 48 -4	6.67 6.44 6.27

			MNI coordinates			
	Hemisphere	k voxels	x	y	z	*Z*
Inferior frontal gyrus, insula, superior temporal pole	R	466	50	14	-14	5.56
			56	26	6	4.39
			54	4	-20	4.34
Middle temporal gyrus	L	268	-50	0	-20	5.53
			-58	-6	-12	4.92
			-42	4	-28	4.24
Cerebellum (vermis)	R	412	32	-64	-28	5.12
			24	-64	-30	4.39
			26	-76	-28	4.39
Inferior parietal lobule (angular gyrus), middle temporal gyrus	L	1621	-38	-68	42	4.76
			-50	-36	-2	4.74
			-48	-60	28	4.60
Superior frontal gyrus, middle frontal gyrus	L	118	-22	50	20	4.71
Middle cingulate gyrus	L/R	159	-4	-14	38	4.49
			-2	-24	28	3.70
Caudate	R	113	12	14	8	4.29
			10	6	4	4.16
			20	20	6	3.28
Middle frontal gyrus	R	133	42	20	42	4.22
			44	14	50	3.76
Middle temporal gyrus	R	238	48	-34	-4	4.03
			52	-18	-12	4.03
			60	-40	-2	4.00
Precuneus	L	103	-2	-60	22	3.75
			-4	-46	16	3.68
Reappraisal > attend negative HC > SZ						
Middle temporal gyrus	L	109	-50	-48	8	4.01
			-40	-42	16	3.75
Suppression > attend negative						
Superior frontal gyrus/medial frontal gyrus (supplementary motor area)	Midline	1288	2	2	60	5.01
			12	18	38	4.61
			-4	16	46	4.51
Inferior frontal gyrus, insula	R	547	44	14	6	4.53
			44	12	-4	4.41
			60	12	20	4.15
Supramarginal gyrus	R	192	62	-46	36	4.52
			62	-38	40	3.94
			52	-38	34	3.50
Insula, inferior frontal gyrus (pars opercularis)	L	298	-42	12	2	4.49
			-32	16	-6	4.07
			-48	8	6	3.87
Attend negative > suppression						
Calcarine sulcus, cuneus, lingual gyrus	Midline	3339	-8	-86	2	5.46
			-4	-88	12	5.24
			-30	-82	22	5.24
Superior occipital gyrus, middle	R	1063	28	-78	32	4.93

			MNI coordinates			
	Hemisphere	k voxels	x	y	z	*Z*
occipital gyrus			32	-70	30	4.79
			24	-74	22	4.68
Inferior temporal gyrus	R	130	48	-54	-16	4.75
Increase > attend negative						
Medial frontal gyrus, superior frontal gyrus	Midline	1954	-2	20	60	5.96
			-4	4	62	5.95
			6	6	66	5.23
Cerebellum (vermis)	R	481	20	-68	-28	5.51
			36	-60	-28	4.77
			32	-78	-28	3.94
Middle temporal gyrus, superior temporal gyrus	L	745	-54	-54	6	5.43
			-58	-36	42	4.17
			-46	-36	-6	4.15
Inferior frontal gyrus, insula	L	1328	-38	14	0	5.23
			-32	26	2	5.10
			-52	12	-2	5.10
Inferior frontal gyrus, insula	R	219	50	18	-8	4.32
			44	18	-14	4.27
			36	16	-6	4.10
Thalamus	L	113	-4	-20	6	4.26
			-4	-36	0	3.79
			-4	-28	4	3.43
Attend negative > increase						
Cuneus, calcarine sulcus	L	362	-10	-88	22	5.08
			-6	-84	14	4.95
Lingual gyrus	L	243	-12	-70	-4	4.89
			-20	-66	-6	3.51

All results of main effects analyses are shown with an initial threshold of $p < 0.001$ (uncorrected) and cluster-level FWE-correction at $p < 0.05$. Degrees of freedom = [1.0 44.0]. Abbreviations: L = left; R = right.

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