doi: 10.1192/bjp.bp.111.098046

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Online supplement

1. Methods Supplement

1.1 Clinical and socio-demographic data collection and analyses

See Fig. DS2 for a pictorial representation of the timeline regarding the collection of data and assessment of remission. Positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).[18] Evaluators have established an ICC of 0.79 on this scale; all evaluators participate in inter-rater reliability sessions at least once a year to avoid rater drift. Type and dosage of antipsychotic were recorded with dosages converted into chlorpromazine equivalents as needed.[41,42] Medication adherence, based on a 5-point scale ranging from 0 (never) to 4 (fully), was obtained from patients or, when possible, from family members. The above data were obtained at first assessment and at months 1, 2, 3, 6, 9, and 12 past first assessment; first assessment was conducted, on average, within one month after admission (days; mean=23.4, range=4.8-54.8). The following data were acquired at first assessment: education level (number of school years completed), parental socio-economic status (SES) with the Hollingshead two-factor index,[43] and handedness with the Edinburgh Handedness Inventory.[44] Full Scale IQ was measured using the Wechsler Adult Intelligence Scale[25] as part of our neurocognitive battery administered approximately 3 months after admission [months, mean (s.d.): non-remitted=2.9 (2.4), remitted=2.4 (1.4); t_{40}=0.82, P=0.416].

Among the three groups, age at scan, education level, and Full Scale IQ were compared using a one-way ANOVA, parental SES with a Kruskall-Wallis H-test, and sex

(female vs. male) and handedness (right vs. other) with cross tabulation and Chi-square tests. Between patient groups, antipsychotic dosage and symptom totals were compared using independent t-tests and medication adherence ratings using Mann-Whitney U-tests for data at first assessment, month 6, month 12, and at time of scan. All data were normally distributed.

1.2 Additional information for patients at time of scan

For patients, scanning took place only when stable enough to tolerate the scanning session with suitability to participate reassessed on a weekly basis until our clinical and research team agreed that acute symptoms would not interfere with the protocol (e.g., being able to stay still for more than one hour). On average, scanning occurred within five months after admission [months, mean (s.d.): non-remitted=4.7 (1.9), remitted=4.7 (1.7); t_{40}=-0.02, *P*=0.982].

At the time of scan, all non-remitted patients were taking antipsychotic medications [risperidone (n=15; mean=2.3mg/day, s.d.=1.1), olanzapine (n=8; mean=14.1mg/day, s.d.=7.6), quetiapine (n=4; mean=412.5mg/day, s.d.=143.6)]; 6 were taking antidepressants [citalopram (n=2; mean=40.0mg/day, s.d.=0.0), paroxetine (n=1; 20.0mg/day), venlafaxine (n=3; mean=137.5mg/day, s.d.= 94.4), 1 was taking a benzodiazepine [lorazepam, 0.5mg/day], and 3 were taking an anticholinergic [benztropine, mean=1.3mg/day, s.d.=0.8]. Only 1 of the 3 subjects taking the anticholinergic exhibited slightly below average memory impairment; the subject taking the benzodiazepine showed excessive memory impairment.

For remitted patients, 12 of 15 were taking antipsychotic medications [risperidone (n=2; mean=1.3mg/day, s.d.=0.4), olanzapine (n=7; mean=8.8mg/day, s.d.=4.6), quetiapine (n=1; 200.0mg/day), haloperidol (n=1; 1.5mg/day), risperdone injectable (n=1; 25.0mg/2weeks)] with 1 taking a second antipsychotic [riperidone, 2.0mg/day]; 1 was taking an antidepressant [bupropion, 10.0mg/day]; and none were taking benzodiazepines or anticholinergics. For the three patients refusing antipsychotic medication at the time of scan, one had refused medication only at the time of scan while the other two were antipsychotic naïve throughout the 12-month treatment period but still received psychosocial interventions as per PEPP protocol.

Behavioural fMRI results

Memory encoding

See Table DS2 for values. For accuracy performance regarding the encoding questions, there was a significant main effect of semantic relatedness ($F_{1,68}$=58.94, P<0.001), encoding strategy ($F_{1,68}$=13.43, P<0.001), and group ($F_{2,68}$=5.67, P=0.005). There was also a significant group x semantic relatedness interaction ($F_{2,68}$=6.57, P=0.002); no other interactions were significant. Univariate ANOVAs revealed there were significant group differences when responding to both related pairs ($F_{2,68}$=4.96, P=0.010) and unrelated pairs ($F_{2,68}$=6.60, P=0.002). Tukey's HSD tests revealed, for related pairs: non-remitted = remitted (P=0.969, ES=0.00), non-remitted < controls (P=0.013, ES=0.87), and remitted = controls (P=0.073, ES=0.75); and for unrelated pairs: non-remitted = remitted (P=0.192, ES=0.54), non-remitted = controls (P=0.103, ES=0.64), and remitted < controls (P=0.002, ES=1.08). Additionally, paired t-tests revealed remitted patients (t_{14}=-

6.35, P<0.001; ES=0.57) and controls (t_{29}=-6.80, P<0.001; ES=0.59) responded more accurately to related pairs than to unrelated pairs whereas non-remitted patients displayed no such difference (t_{25}=-1.60, P=0.119; ES=0.22).

For response time, there were significant main effects of semantic relatedness ($F_{1,68}$=11.28, P=0.001), encoding strategy ($F_{1,68}$=32.47, P<0.001), and group ($F_{2,68}$=4.70, P=0.012). There was also a significant semantic relatedness x encoding strategy interaction ($F_{1,68}$=22.71, P<0.001); no other interactions were significant. The semantic relatedness x encoding strategy interaction reflected that response times were shorter for related pairs than for unrelated pairs when subjects responded to the item-oriented encoding cues (t_{70}=-5.82, P<0.001; ES=0.43); response times did not significantly differ when responding to the associative encoding cues (t_{70}=1.36, P=0.177; ES=0.09).

Memory recognition – hit rate

See Table DS2 for values. For hit rate performance, there were significant main effects of semantic relatedness ($F_{1,69}$=13.47, P=0.001), encoding strategy ($F_{1,69}$=79.81, P<0.001), and group ($F_{2,69}$=6.55, P=0.002). There was also a significant group x semantic relatedness interaction ($F_{2,69}$=3.38, P=0.040); no other interactions were significant. Univariate ANOVAs revealed there were significant group differences when recognizing both related pairs ($F_{2,69}$=3.55, P=0.034) and unrelated pairs ($F_{2,69}$=8.83, P<0.001). Tukey's HSD tests revealed, for related pairs: non-remitted = remitted (P=0.382, ES=0.37), non-remitted < controls (P=0.026, ES=0.73), and remitted = controls (P=0.659, ES=0.40); and for unrelated pairs: non-remitted = remitted (P=0.348, ES=0.39), non-remitted < controls (P<0.001, ES=1.13), and remitted = controls

(*P*=0.100, ES=0.84). Additionally, paired t-tests revealed non-remitted patients (t_{25}=-2.81, *P*=0.010; ES=0.33) and remitted patients (t_{14}=-3.08, *P*=0.010; ES=0.40) recognized related pairs more than unrelated pairs whereas controls displayed no such difference (t_{30}=-0.29, *P*=0.773; ES=0.05).

For response time, there were significant main effects of semantic relatedness ($F_{1,69}$=101.35, *P*<0.001), encoding strategy ($F_{1,69}$=6.70, *P*=0.012), and group ($F_{2,69}$=6.56, *P*=0.002). There was also a significant group x semantic relatedness interaction ($F_{2,69}$=5.86, *P*=0.004); no other interactions were significant. Univariate ANOVAs revealed there were significant group differences when responding to both related pairs ($F_{2,69}$=5.98, *P*=0.004) and unrelated pairs ($F_{2,69}$=7.03, *P*<0.001). Tukey's HSD tests revealed, for related pairs: non-remitted = remitted (*P*=0.519, ES=0.31), non-remitted > controls (*P*=0.003, ES=0.97), and remitted = controls (*P*=0.189, ES=0.64); and for unrelated pairs: non-remitted = remitted (*P*=0.936, ES=0.10), non-remitted > controls (*P*<0.006, ES=0.91), and remitted > controls (*P*=0.009, ES=1.04). Additionally, paired t-tests revealed non-remitted patients (t_{25}=-3.86, *P*=0.001; ES=0.35), remitted patients (t_{14}=-8.49, *P*<0.001; ES=0.75), and controls (t_{30}=-5.77, *P*<0.001; ES=0.56) responded more quickly to the related pairs than to unrelated pairs.

Memory recognition – Pr and Br

See Table DS3 for values. For Pr, there was no significant main effect of semantic relatedness ($F_{1,69}$=0.02, *P*=0.877) nor a significant group x semantic relatedness interaction ($F_{2,69}$=1.92, *P*=0.155); however, there was a significant main effect of group ($F_{2,69}$=8.07, *P*=0.001). Tukey's HSD tests revealed: non-remitted < remitted (*P*=0.025, ES=0.62), non-remitted < controls (*P*<0.001, ES=1.02), and remitted = controls

(P=0.323, ES=0.49). For Br, there was no significant main effect of group ($F_{2,69}$=1.12, P=0.333) nor a significant group x semantic relatedness interaction ($F_{2,69}$=0.24, P=0.787). However, there was a significant main effect of semantic relatedness ($F_{1,69}$=21.12, P<0.001) representing that subjects showed a stronger novelty bias (propensity to say "new") when recognizing related pairs of images over unrelated pairs of images.

Additional references

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Table DS1 Clinical characteristics for non-remitted & remitted FES patients

	Non-remitted (n=27)	Remitted (n=15)	Analysis		
	mean (s.d.)	mean (s.d.)	Statistic	df	*P*
Positive symptoms [a]					
Baseline	23.7 (6.0)	24.9 (6.1)	t=-0.65	40	0.517
Month 6	14.2 (5.8)	8.6 (2.9)	t=3.47	40	**0.001**
Month 12	16.6 (7.2)	8.8 (2.0)	t=4.08	40	**<0.001**
At time of scan	13.2 (5.0)	9.3 (3.5)	t=2.69	40	**0.010**
Negative symptoms [a]					
Baseline	17.3 (6.3)	15.3 (4.8)	t=1.03	40	0.311
Month 6	14.8 (5.3)	10.1 (3.3)	t=3.11	40	**0.003**
Month 12	15.5 (5.5)	10.0 (2.6)	t=3.63	40	**0.001**
At time of scan	13.7 (5.5)	10.1 (3.1)	t=2.29	40	**0.028**
Antipsychotic total [b]					
Baseline	169.8 (173.0)	179.5 (132.8)	t=-0.19	40	0.853
Month 6	240.3 (257.9)	118.7 (97.0)	t=1.75	40	0.088
Month 12	240.2 (267.7)	102.9 (103.3)	t=1.90	40	0.065
At time of scan	224.3 (190.1)	125.4 (111.0)	t=1.82	40	0.076
Medication adherence [c]					
Baseline	3.4 (1.4)	3.1 (1.5)	U=160.0	40	0.289
Month 6	2.9 (1.4)	2.9 (1.4)	U=198.5	40	0.911
Month 12	3.0 (1.6)	3.1 (1.4)	U=197.5	40	0.878
At time of scan	2.9 (1.5)	2.9 (1.6)	U=200.5	40	0.964

[a] Symptom totals from the Positive and Negative Syndrome Scale (PANSS).

[b] Antipsychotic totals presented in chlorpromazine equivalents in mg/day.

[c] Medication adherence: 0 (never adherent) to 4 (fully adherent).

Table DS2 Results for contrast between associative encoding > item-oriented encoding [a]

Cluster Size	*t*-value	Coordinates			Side	Region (Broddman Area)	Parameter estimates			
		x	y	z			Associative		Item-oriented	
Remitted > Non-Remitted							R	NR	R	NR
No significant differences in activation							--	--	--	--
Non-Remitted > Remitted										
No significant differences in activation							--	--	--	--
Controls > Non-Remitted							C	NR	C	NR
No significant differences in activation							--	--	--	--
Non-Remitted > Controls										
No significant differences in activation							--	--	--	--
Controls > Remitted							C	R	C	R
220	5.69	2	-67	53	R	Precuneus (7)	0.82	-3.71	1.84	2.11
167 [b]	3.94	2	-35	35	R	Middle Cingulate (31)	-1.53	-5.31	-1.58	-2.72
167 [b]	3.83	-4	-39	39	L	Middle Cingulate (31)				
167 [b]	3.69	-14	-39	39	L	Middle Cingulate (31)				
Remitted > Controls										
No significant differences in activation							--	--	--	--

[a] The cluster size represents the number of voxels. The x, y, and z coordinates of local maxima are listed according to the Talairach coordinate system. The parameter estimates reported in the last columns were extracted from within each group for each comparison.

[b] These peaks belong to the same cluster of activation.

Table DS3 Results for contrast between successful encoding > unsuccessful encoding[a]

Cluster Size	*t*-value	Coordinates			Side	Region (Broddman Area)	Parameter estimates			
		x	y	z			Successful		Unsuccessful	
Remitted > Non-Remitted							R	NR	R	NR
No significant differences in activation							--	--	--	--
Non-Remitted > Remitted										
No significant differences in activation							--	--	--	--
Controls > Non-Remitted							C	NR	C	NR
No significant differences in activation							--	--	--	--
Non-Remitted > Controls										
269 [b]	4.35	-57	-30	13	L	Superior Temporal (42)	-1.51	-1.16	-0.55	-1.46
269 [b]	4.05	-57	-21	3	L	Superior Temporal (41)				
269 [b]	3.90	-51	-34	18	L	Insula (13)				
Controls > Remitted							C	R	C	R
No significant differences in activation							--	--	--	--
Remitted > Controls										
No significant differences in activation							--	--	--	--

[a] The cluster size represents the number of voxels. The x, y, and z coordinates of local maxima are listed according to the Talairach coordinate system. The parameter estimates reported in the last columns were extracted from within each group for each comparison.

[b] These peaks belong to the same cluster of activation.

Table DS4 Correlations of left posterior cingulate activation with fMRI behavioural data and the 8 key symptoms of the remission definition.

	Activity For Related Images		Activity For Unrelated Images	
fMRI behavioural data	Pearson's r	*P*	Pearson's r	*P*
Encoding Accuracy				
Related images	0.290	0.065	0.323	0.039
Unrelated images	0.225	0.158	0.237	0.135
Recognition – Pr				
Related	0.003	0.983	0.057	0.726
Unrelated	-0.006	0.971	0.055	0.736
Total	-0.001	0.995	0.058	0.722
Remission Symptoms (PANSS - at scan)	Spearman's rho	*P*	Spearman's rho	*P*
Delusions (P1)	0.033	0.839	0.048	0.767
Conceptual disorganization (P2)	0.022	0.892	-0.089	0.582
Hallucinatory behaviour (P3)	0.191	0.231	0.075	0.640
Blunted affect (N1)	-0.096	0.550	-0.189	0.237
Social withdrawal (N4)	0.012	0.941	-0.022	0.892
Lack of spontaneity (N6)	0.158	0.323	0.103	0.521
Mannerisms and posturing (G5)	-- [a]	--	-- [a]	--
Unusual thought content (G9)	0.017	0.916	-0.021	0.894

Abbreviations: PANSS, Positive and Negative Syndrome Scale

Significant results in **bold**; critical *P*-value set at 0.025 for encoding accuracy, at 0.017 for Pr, and at 0.006 for clinical symptoms.

[a] All mannerisms and posturing ratings at time of scan were rated a 1 (non-existent).

Fig. DS1 Pictorial representation of the fMRI task.

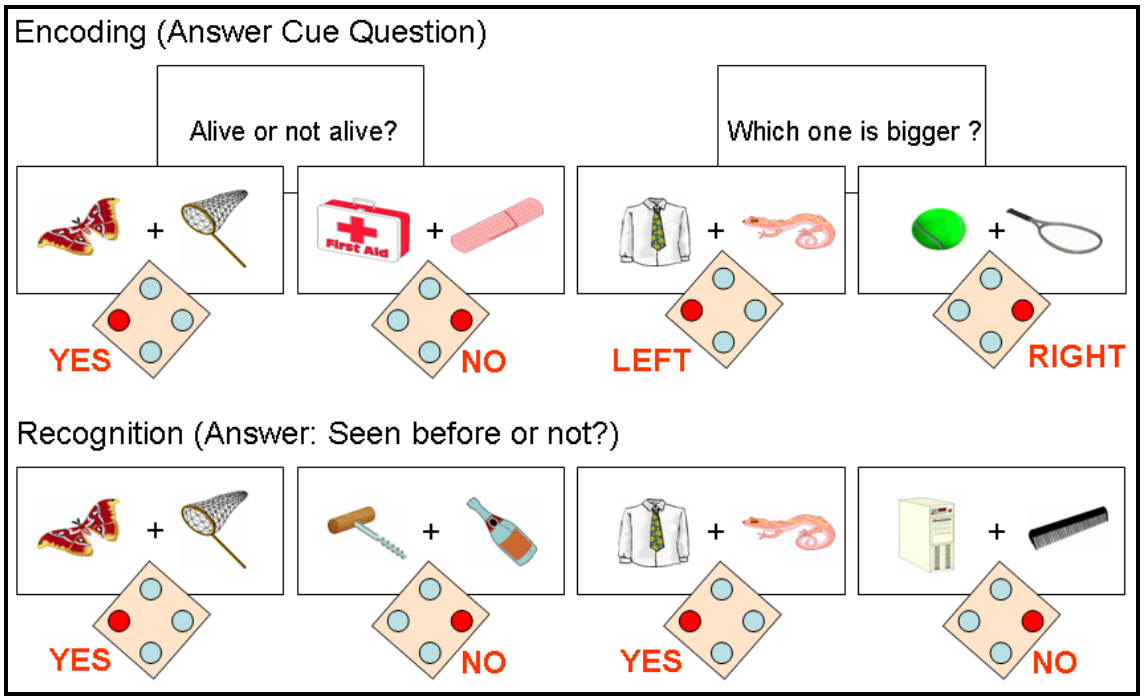
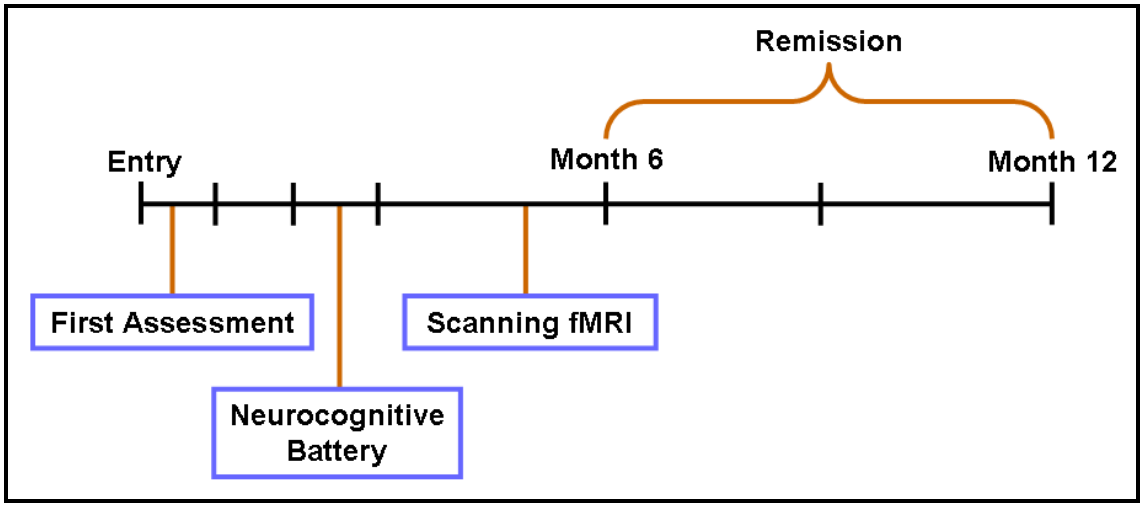


Fig. DS2 Pictorial representation of data collection and assessment of remission.



First symptom evaluation was conducted within one month after entry with subsequent evaluations taking place at months 1, 2, 3, 6, 9, and 12 past first assessment. Remission status was evaluated using symptom data collected from month 6 to month 12. Neurocognitive battery data (including Full IQ) were collected approximately 2.6 months after entry with fMRI data collected approximately 4.7 months after entry.