Longitudinal resting state analysis of thalamic connectivity shows improvement in prefrontal connectivity after 12 months in first-episode psychosis

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Introduction

Previous research in resting state fMRI has shown a mixed pattern of disrupted thalamocortical connectivity in psychosis, with increased connectivity in sensorimotor and temporal regions as well as decreased connectivity in prefrontal areas and the cerebellum compared to controls [1]. The clinical meaning of these findings, however, and their stability over time remain unclear. We aimed to examine thalamic connectivity longitudinally over a one-year period in patients with recent onset psychosis.

Socio-demographics

	Baseline				Follow-up (1 year)			
	FEP	HC	Stats	*p*	FEP	HC	Stats	*p*
n	124	87			42	40		
Mean age at baseline scan	19.8 (4.1)	19.7 (3.7)	T=-0.110	0.913	19.4 (3.5)	18.8 (3.7)	T=-0.763	0.447
Gender (% male)	72.6%	59.8%	X-sq=3.253	0.071	64.3%	65.0%	X-sq<0.1	~=1
Parental education, years	14.7 (2.7)	14.7 (3.3)	T=0.113	0.910	14.2 (2.9)	15.1 (3.6)	T=0.864	0.394
	At baseline				At follow-up			
SAPS total (SD)	13.9 (14.9)	NA			7.7 (10.0)	NA		
SANS total (SD)	33.8 (16.1)	NA			25.6 (15.8)	NA		
Affective psychosis[1] (%)	21.5%	NA			23.8%	NA		

Methods

129 subjects with first-episode psychosis (**FEP**) and 87 healthy control subjects were recruited and clinically evaluated at the early psychosis program at the University of California Davis and underwent fMRI resting state scanning.
Among the initial sample, 43 FEP patients and 40 controls were re-scanned and re-evaluated 12 months later. Functional images were preprocessed using CONN Toolbox and SPM12. Preprocessing steps included slice-time correction, realignment across sessions, and direct functional normalization to an EPI template. Functional volumes were scrubbed using an FD threshold of 0.9, and the same threshold was used to discard subjects based on mean FD values. Variance associated with subject motion, white matter and CSF were removed by linear regression. The images were then smoothed using a 10mm FWHM kernel. Seed-based functional connectivity was performed using FreeSurfer-segmented bilateral thalamus seeds. A second level analysis was computed for the baseline participants and a separate repeated measures model was created with those subjects for whom follow-up images were available. Results were corrected for multiple comparisons using an initial threshold of $p < 0.001$ (voxelwise), and $p < 0.05$ (FDR cluster-corrected).

Results

<u>At baseline</u>, FEP subjects showed **increased thalamic connectivity** (compared to HC) **in somato-sensory and temporal regions** (peak cluster: k = 653, x y z=-58 -22 4, T=5.712, and **decreased connectivity to left cerebellum and right middle and superior frontal gyrus** (peak cluster: k = 201, x y z = -8 -58 -42, T=-4.700).

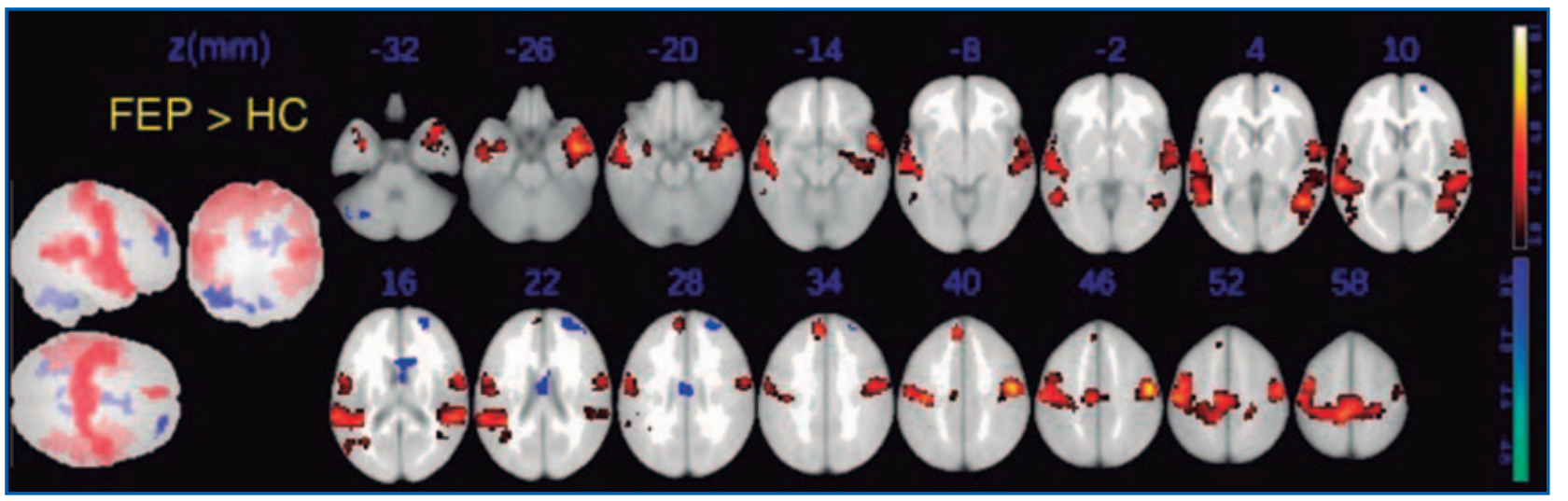

Fig 1: Between group differences in thalamic connectivity at baseline: Red range: connectivty FEP > HC, Blue range: HC > FEP. Cluster-defining threshold p<0.001 at voxel-level and cluster-extent FDR correction at p<0.05.]

<u>Longitudinal analyses</u> **revealed increased connectivity over time in FEP** subjects (i.e. follow-up higher than baseline) relative to controls in **the right middle frontal gyrus.**

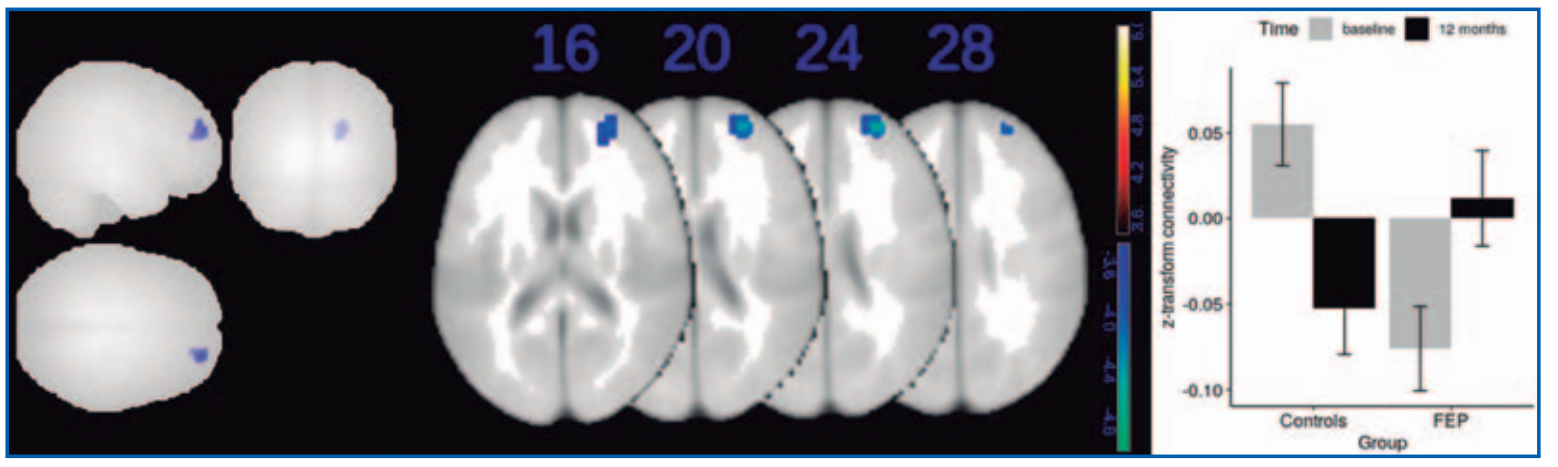

Fig 2: Group per time interaction contrast. Blue range: increase over time of thalamic connectivity in FEP > HC. Cluster-defining threshold p<0.001 at voxel-level and cluster-extent FDR correction at p<0.05. Right: Boxplot showing z-transformed averaged connectivity values per group and time (baseline or 12 months) from the significant cluster of the left figure (peak at x,y,z = +28, +56, +22).]

Conclusions

We not only replicated previous findings showing aberrant thalamic connectivity in psychosis but also showed no evidence of deterioration (indeed, partial improvement) over time. These results are in agreement with a non-degenerative model of illness in which functional changes occur early in development and do not deteriorate over time during the early phase of psychosis.

References

1. Anticevic, A., Cole, M. W., Repovs, G., Murray, J. D., Brumbaugh, M. S., Winkler, A. M., ... Glahn, D. C. (2014). Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. Cerebral Cortex (New York, N.Y.: 1991), 24(12), 3116–3130.

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