From the Knight to the Right: an Event-related fMRI Study of Schizophrenic Thinking

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Introduction

Loosening of associations with tangential or 'knight's-move' thinking – the generation of inappropriate links between unrelated sentences and concepts – is a fundamental feature of schizophrenia [1]. Lesion studies suggest that the right hemisphere plays a role in generating inferences that link sentences together into a coherent whole [2]. Schizophrenia is characterized by widespread structural changes [3], functional abnormalities [4] and abnormal interactions [5] within a temporal-prefrontal network and there are some reports of abnormal symmetries between the two hemispheres [6].

Hypothesis: the inappropriate tendency of schizophrenia patients to generate links between unrelated concepts is reflected by the inappropriate engagement of the right hemisphere to causally unrelated (relative to causally related) sentences.

Design [7]

Condition	Explanation	Example
(1) Causally- related sentences	The final sentence is causally related to its preceding context.	_"Mark and John were having an argument. Mark began to hit John hard. The next morning John had many bruises."_
(2) Inference-requiring sentences	Instead of the final sentence being directly related with its context, it is indirectly related such that the reader needs to make an inference to connect the second and final sentences.	_"Mark and John were having an argument. Mark got more and more upset. The next morning John had many bruises."_
(3) Causally-unrelated sentences	The final sentence comes from another scenario in another list. It is now causally unrelated to its preceding context.	_"Mark and John were having an argument. Mark began to hit John hard. The next morning the sun rose over the Sahara"_

240 three-sentence scenarios (80 per condition) counterbalanced over three lists.

Sentences 1 & 2: each presented for 3.4 sec. (ISI:100 msec).

Sentence 3: presented word by word (500msec, 100msec ISI).

Task: to press one of three buttons depending on how difficult it was to connect the final sentence with its preceding context.

Participants

Parameter	Controls (n =15)	Patients (n =15)
Gender (M/F)	12/3	11/4
Race (C/AA//His)	13/1/1	12/3/0
Age (years)	40.8 (11.1)	43.2 (8.2)
Education (years)	13.8 (1.8)	12.1 (3.8)
Hollingshead Index	2.7 (1)	2.9 (1.3)
Premorbid verbal IQ	117.4 (5.6)	105 (12.9)
CPZ equivalent	-	440 (272)
Duration of illness (years)	-	19 (18.4)
BPRS total	-	20.8 (11.2)
SAPS total	-	13.4 (12)
SANS total	-	31.8 (4.9)

Behavioral Results

Legend:
- ■ Causally-related
- ■ Inference-requiring
- ■ Causally-unrelated

Group by condition interaction:
$F(2,56) = 5.3, p < 0.011$
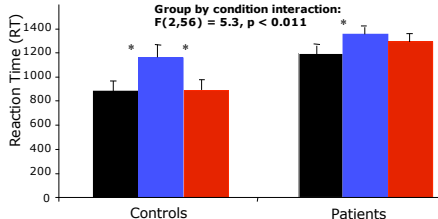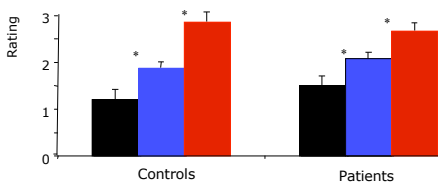
fMRI Data Acquisition

- Structural scans: 1.5 T; 3D MPRAGE sequence (128 sagittal slices, 1.3mm thickness, TR = 7.25 ms, TE = 3 ms, flip angle = 7 degrees, bandwith = 195 Hz/pixel, in-plane resolution = 1.3 mm x 1 mm).
- Functional imaging: 3.0T; 3 functional runs; T2*-weighted gradient-echo pulse sequence (TR = 2s, TE = 25ms, and flip angle = 90°); 33 transverse slices (125 images per slice, 3 mm thickness, 0.9 mm between slices).
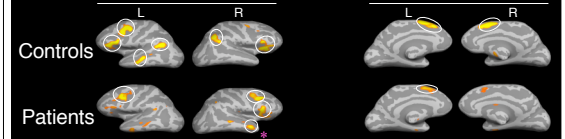
Analysis: SPM-HRF modeling

The HRF for each condition was modeled using two components: one for the first 8 sec of the trial, and one for the last 4 sec of the trial.

Each component consisted of an SPM-HRF convolved with a box car of the appropriate length.

The first component was modeled as a single regressor across all conditions as the differences between conditions did not occur until 8 sec. The second component was modeled separately for each condition. Hypothesis testing was performed on the regression weights of the 2nd component.

Each subject's functional data was resampled into a common spherical space [8] derived from each individual's cortical surface [9] and then averaged using a random effects model within and between subject groups.
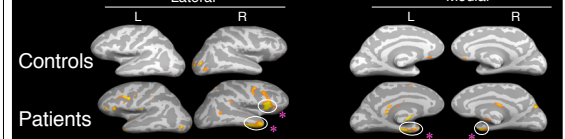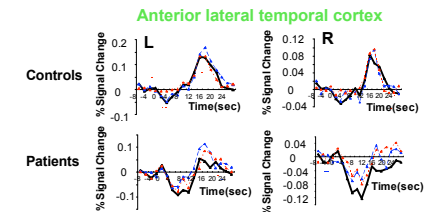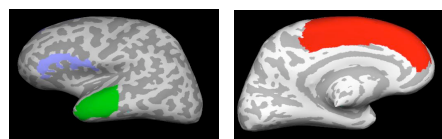

○ Significant clusters with a size of 300 mm2 and are threshold for rejection of the null hypothesis at p < 0.05 were identified on the basis of a Monte Carlo simulation
* Significant on direct comparison between patients and controls
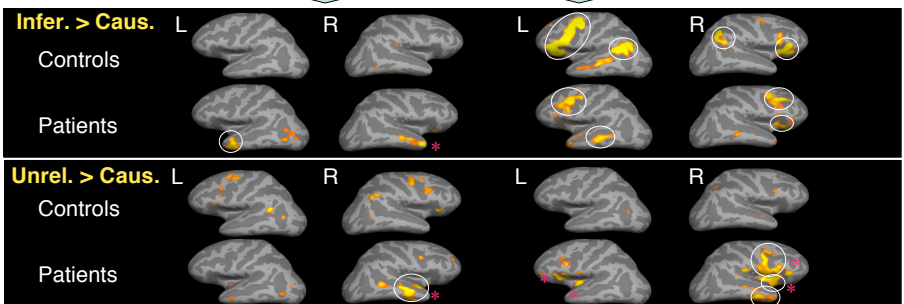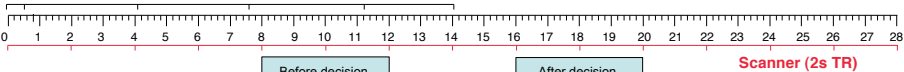
Analysis: Regions of Interest

Automatic cortical parcellation on each individual's cortical surface [10].

Analysis: FIR

FIR: estimate % signal change at each TR: shape of hemodynamic response not assumed [16].

Conclusions

- _Inference-requiring vs. causally-related sentences_: Both patient and control groups exhibited more activity to inference-requiring than causally-related sentences within (a) left temporal-prefrontal cortices, (b) right inferior prefrontal and inferior parietal cortices, and (c) bilateral medial superior prefrontal cortices.
- Patients inappropriately activated the right anterior temporal cortex to the inference-requiring sentences, beginning before they made their relatedness judgments.
- _Unrel. vs. causally-related sentences:_ Patients inappropriately engaged right anterior temporal and right inferior prefrontal cortices to the unrelated sentences. Again, the right anterior temporal activity began before subjects made their judgments, but all hemodynamic differences were maximal after the presentation of the final sentence that differentiated between the three experimental conditions.

The inappropriate increase in right temporal and prefrontal activity, to causally unrelated (relative to related) sentences might contribute to the bizarre, knights-move thinking that characterizes the schizophrenia syndrome.

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