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Video Article

Measurement of Fronto-limbic Activity Using an Emotional Oddball Task in Children with Familial High Risk for Schizophrenia

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Abstract

Adolescence is a critical developmental period where the early symptoms of schizophrenia frequently emerge. First-degree relatives of people with schizophrenia who are at familial high risk (FHR) may show similar cognitive and emotional changes. However, the neurological changes underlying the emergence of these symptoms remain unclear. This study sought to identify differences in frontal, striatal, and limbic regions in children and adolescents with FHR using functional magnetic resonance imaging. Groups of 21 children and adolescents at FHR and 21 healthy controls completed an emotional oddball task that relied on selective attention and the suppression of task-irrelevant emotional information. The standard oddball task was modified to include aversive and neutral distractors in order to examine potential group differences in both emotional and executive processing. This task was designed specifically to allow for children and adolescents to complete by keeping the difficulty and emotional image content age-appropriate. Furthermore, we demonstrate a technique for suitable fMRI registration for children and adolescent participants. This paradigm may also be applied in future studies to measure changes in neural activity in other populations with hypothesized developmental changes in executive and emotional processing.

Video Link

The video component of this article can be found at http://www.jove.com/video/51484/

Introduction

Schizophrenia is a neurodevelopmental disorder with a known genetic component[1,2] and with symptoms including deficits in both executive and emotional processing[3,4]. First-degree relatives are thought to be at an increased risk of developing schizophrenia, and have been shown to share some of these same neurocognitive deficits in both cognitive and social-emotional domains[5]. We therefore expect that brain activity in regions associated with executive and emotional processing may be altered in at-risk family members preceding the onset of clinical symptoms.

Previous studies have indicated that both adults with schizophrenia and adults at familial high risk show aberrant activity within executive and emotional processing networks; however it remains unclear how these changes come about during development. Demonstrating that these changes occur early in life will be a critical first step in understanding the pathophysiology of the disorder. Therefore, this study utilizes an emotional oddball paradigm during functional MRI (fMRI) scanning in order to measure brain activity during the completion of a task that requires both executive and emotional processing in adolescents who are at risk for developing schizophrenia. Oddball paradigms are frequently used to examine the function of fronto-striate circuitry in schizophrenia[6] and in individuals with familial high risk[7] by measuring selective attention processes allocated to task-relevant target stimuli. Here, a standard oddball task has been modified to include task-irrelevant aversive and neutral stimuli that have been shown to elicit changes in brain activity in patients with schizophrenia[8].

This paper measures functional differences between healthy adolescents and adolescents at high familial risk for schizophrenia using an emotional oddball task. The task design is similar to that used by Fichtenholtz and colleagues[9], but the selection of aversive emotional images has been modified to be appropriate for children between the ages of 9-18. The use of this task during functional MRI allowed for the identification of specific brain regions that showed patterns of hyperactivation and hypoactivation in children and adolescents with FHR for schizophrenia, in addition to age-related changes in neural activity during adolescent development.

Protocol

The research techniques used during this study were approved by the institutional review boards (IRB) of Duke University and the University of North Carolina – Chapel Hill.

1. Imaging Task Design

1. Generate an event-based behavioral task that presents infrequent target stimuli (a circle) within a sequence of more-frequent standard stimuli (scrambled images). A schematic of the task is shown in **Figure 1**. Present the task using CIGAL software[10].

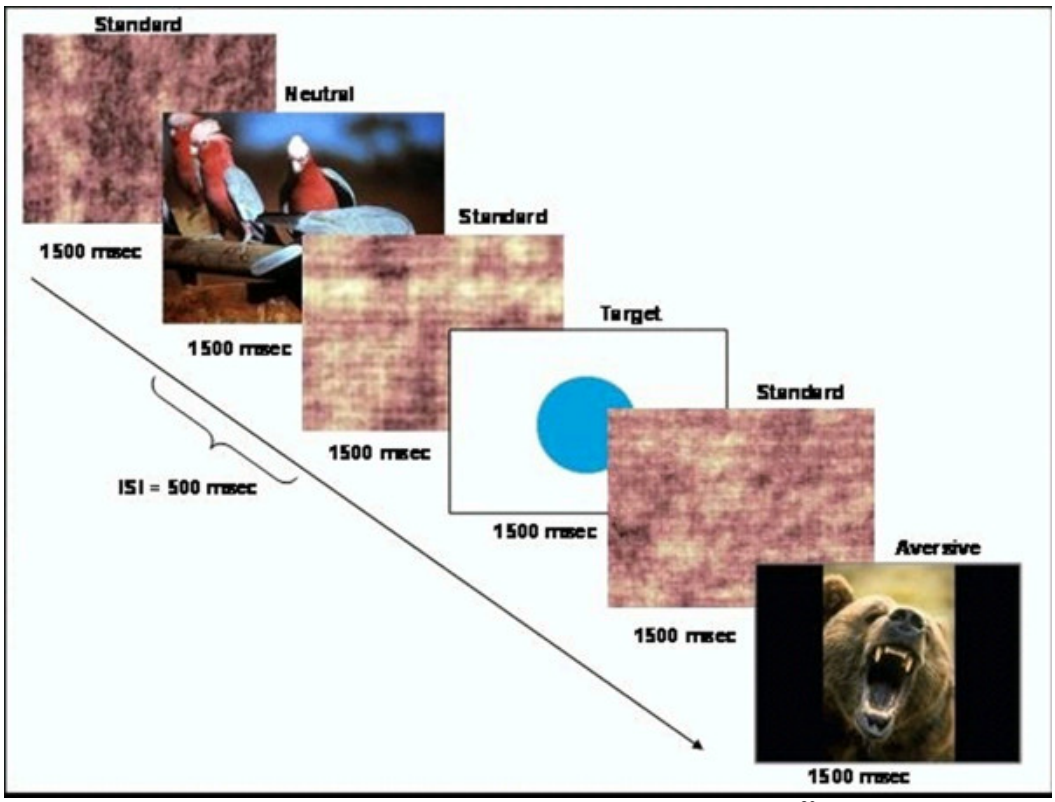

Figure 1. Schematic of Task Design. This figure has been modified from Hart *et al.*[20], with permission. Please click here to view a larger version of this figure.

1. Select a set of aversive stimuli and a set of neutral stimuli from the International Affective Picture System database (IAPS). IAPS images are rated on a scale of 1-9 in order to reflect levels of arousal and valence[11]. High numbers indicate higher positive valence and arousal. Select a set of images that are age-appropriate to the study group such as pictures of snakes, spiders, or other animals.
   Note: The task-irrelevant aversive stimuli images used for this study had an average valence rating of 3.38 (S.D. = 1.78) and an average arousal rating of 6.14 (S.D. = 2.08). The neutral stimuli images had an average valence of 6.21 (S.D. = 0.26) and an average arousal rating of 3.72 (S.D. = 2.15).
2. Program the task script such that images are presented in a pseudo-randomized order for 1,500 msec with a 500 msec mean inter-stimulus interval. Present target stimuli and task-irrelevant neutral images no more frequently than every 15 sec and make each about 4% of the stimuli. Jitter event onset times in order to provide better resolution of the hemodynamic response function.

2. Create 8 sets of images, one for each of 8 functional runs such that the participants are presented with a total of 40 targets and 40 task-irrelevant neutral images over the course of all 8 runs.

2. Participant Setup and Scanning

1. Recruit children and adolescents between the ages of 9 and 18 who are either healthy control individuals or who are at familial high risk for psychosis.
   1. Ensure that healthy individuals have no psychiatric illnesses or any first-degree family members with a psychiatric illness. Ensure that familial risk participants have at least one first-degree relative (parent or sibling) with schizophrenia. Do not exclude them for the presence of other psychiatric illnesses in first-degree relatives.
   2. Age and gender match healthy participants with familial risk group participants.

2. Acquire informed consent from participants over the age of 18. For minors, acquire informed consent from parents/legal guardians. Additionally, acquire written assent from minors who are taking part in the study.
3. Place the participants in a mock MRI scanner in order to familiarize them with the environment. Play an audio recording of scanner noise and have them complete a practice run of the behavioral task in order to ensure that they understand the task instructions.
4. Place the participant in the MRI Scanner and acquire any necessary brain localization scans and/or anatomical images.
5. Using an MRI-safe input box, tell participants to press one button with their index finger in response to all target stimuli and another button with their middle finger for all other stimuli.

6. Following fMRI scanning, collect subjective ratings of arousal and valence for the images used in the study from a subset of participants. The current study obtained ratings from 15 controls and 13 with familial high risk.

3. Image Acquisition

1. Place participants into a 3.0 Tesla MRI scanner. First, acquire a set of structural images including a 3D coplanar anatomical T1-contrast image using a spoiled gradient-recalled acquisition pulse sequence (TR: 5.16 msec; TE: 2.04 msec; FOV: 24 cm; image matrix: 256 × 256; Flip Angle: 20; voxel size: 0.94 mm × 0.94 mm × 1.9 mm; 68 axial slices).
2. Acquire functional imaging data using a gradient echo echo-planar imaging sequence with full-brain coverage (TR: 2,000 msec; TE: 27 msec; FOV: 24 cm; image matrix: 64 × 64; Flip Angle: 60; voxel size: 3.75 mm × 3.75 mm × 3.8 mm; 34 axial slices) so that brain activity can be measured during the performance of the behavioral task. Run this imaging sequence for each run of the behavioral task. Each run should consist of 120 imaging time points.
3. Present the task in 8 functional runs, each lasting approximately 4 min.

4. Analyses

1. Image Preprocessing: Open fMRI Expert Analysis Tool (FEAT) in FSL[12]. Select First-level analysis and Pre-stats.
    1. On the "*Data*" tab, select the number of input images and enter the path to each of the MR images you are going to process. Set the Output directory. Enter the *Total volumes,* number of discarded acquisitions, and the TR.
    2. On the *"Pre-stats*" tab, set motion correction to *MCFLIRT,* Spatial smoothing FWHM to 5 mms, and *"Slice timing correction".* Select *"BET brain extraction"* and "*Highpass*" temporal filtering but do not select B0 unwarping (uness you have a gradient field map) or "I*ntensitiy normaization*". [12,14].
    3. On the *"Registration*" tab, select *"Main structural image".* Enter the path to the subject's skull-stripped T1-weighted image. Use a linear normal search with at least 6 DOF. Select the *Standard space* check box. Enter the path to the MNI atlas image. Use a normal, linear search with 12 DOF. Press *Go*.
    4. Exclude participants with greater than 3 mm head motion in the X, Y, or Z directions.

2. Level 1: Compare data between task conditions within a single run. Open FEAT. Select *"First-level analysis"* and *"Stats + Post-stats".*
    1. On the *Data* tab, set the number of inputs and enter the path to each of the MR images. Enter a path for the *"Output directory".* Enter the *"Total volumes",* number of discarded acquisitions, and the TR.
    2. On the "*Stats*" tab, select the "*Use FILM prewhitening*" check box[16]. Press the "*Full model setup*" button. Set the "*Number of original EVs*" to the number of task conditions. For each condition, select "*Custom (3 column format)*" from the basic shape drop-down menu and "*Double-Gama HRF* from the "*Convolution*" drop-down menu[17,18] and select a text file containing the task timing.
        1. Format this text file in 3 columns with one entry for each "event" of the given type. The first column should contain the onset time (in seconds), the second should contain the duration (in seconds), and the third should contain the event weight. On the *Contrasts & F-tests* tab, create one contrast for each task condition and one for each comparison.
    3. On the *"Post-stats"* tab, select *"Cluster*" on the *"Thresholding"* drop-down menu and set the *"Z threshold"* and *Cluster P* threshold to 2.3 and 0.05 respectively[8,19].
    4. On the *"Registration*" tab, select *"Main structural image".* Enter the path to the subject's skull-stripped T1-weighted image. Use a linear normal search with at least 6 DOF. Select the *"Standard space"* check box. Enter the path to the MNI atlas image. Use a normal, linear search with 12 DOF. Press *"Go"*.

3. Level 2: Compare data between runs for each task condition. Open FEAT. Select "Higher-level analysis" and "Stats + Post-stats" from the drop down menu.
    1. On the Data tab, select *"Inputs are lower-level FEAT directories*". Set the number of inputs and enter the path to each of the MR images. Enter a path for the *"Output directory"*.
    2. On the *"Stats"* tab, change the *"Mixed Effects: FLAME1*" selection box to *"Fixed Effects*". Press the *"Model setup wizard"* button. Select *"single group average"* and click the *"Process"* button.
    3. On the *"Post-stats*" tab, select *"Cluster*" on the *"Thresholding*" drop-down menu and set the *"Z threshold*" and "*Cluster P*" threshold to 2.3 and 0.05 respectively[8,19]. Press *"Go"*.

4. Level 3: Compare data between subjects for each task condition across all runs. Open FEAT. Select "*Higher-level analysis*" and "*Stats + Post-stats*" from the drop down menu.
    1. On the Data tab, select "*Inputs are 3D cope images from FEAT directories*." Set the number of inputs and enter the path to each of the MR images. Enter a path for the *"Output directory*".
    2. On the *"Stats"* tab, Press the *"Full model setup"*. Set the number of EVs equal to the number of group variables and covariates such as diagnostic group, age, sex, etc. Enter the values for each subject (Input 1 – Input n) for each EV. You can use the *"Paste"* window in order to copy a spreadsheet of these values.
        1. On the *"Contrasts & F-tests*" tab, add a contrast for each test variable and for each contrast (*e.g.,* diagnostic group). For each test variable, set the contrast by selecting the value 1 in the column under the appropriate EV. For each contrast, set the first value to 1 and the second to -1. Select *"Done"*.
    3. On the *"Post-stats*" tab, select *"Cluster"* on the *"Thresholding"* drop-down menu and set the *"Z threshold*" and *"Cluster P"* threshold to 2.3 and 0.05 respectively[8,19]. Press *"Go"*.

Representative Results

There were no differences between groups based on demographic characteristics[20]. Behavioral data indicated that the target detection task is at an appropriate level of difficulty for children and adolescents between the ages of 9-18. In the current study, controls correctly identified 82.36% of targets (*S.D.* = 0.14), and the familial risk group correctly identified 76.8% of targets (*S.D.* = 0.17). Both groups showed decreased accuracy when identifying emotional pictures compared to neutral pictures ($F(1,40) = 5.63$, $p = 0.03$).

The imaging data indicated that the experimental conditions led to significant activation in regions expected to be recruited during executive and emotional processing. Activation was seen in prefrontal, anterior caudate, insular, and posterior parietal areas during target trials and in the right amygdala, bilateral orbitofrontal cortex, fusiform cortex and visual cortical areas during aversive trials in both groups. Table 1 shows areas of significant activation in controls for each condition.

This paradigm also elicited significant differences in activation between controls and individuals with familial high risk for schizophrenia. The familial high risk group showed decreased activation in fronto-striate circuitry in response to target stimuli. Controls, in contrast, showed greater activation in the middle frontal gyrus and insula. Group differences between conditions are shown in Table 2 and **Figure 2**. The familial high risk group also showed different patterns of age-related activation compared with controls in response to target and aversive stimuli (**Figure 3**).

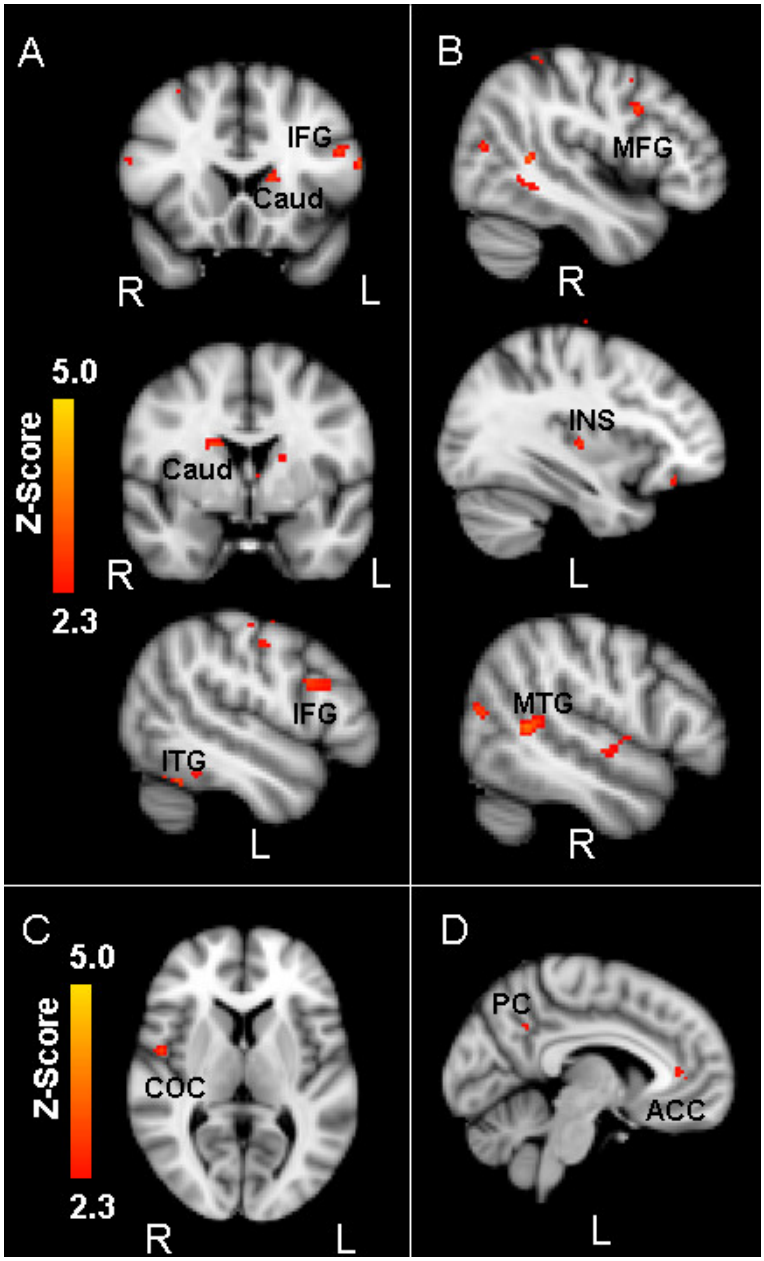

Figure 2. Activation Maps of Between-Group Differences. (**A**) Areas where the familial high risk group (n=21) showed greater activation than controls (n=21) during target processing. CAUD = Caudate; IFG = Inferior frontal gyrus; ITG = Inferior temporal gyrus. (**B**) Areas where controls showed greater activation than the familial high risk group during target processing. INS = Insula; MFG = Middle frontal gyrus; MTG = Middle temporal gyrus. (**C**) Areas where the familial high risk group activated more than controls during the Aversive > Neutral contrast. COC = Central opercular cortex. (**D**) Areas where the controls activated more than the familial high risk group during the Aversive > Neutral contrast. ACC = Anterior cingulate cortex; PC = Precuneus. This figure has been modified from Hart et al.[20], with permission. Please click here to view a larger version of this figure.

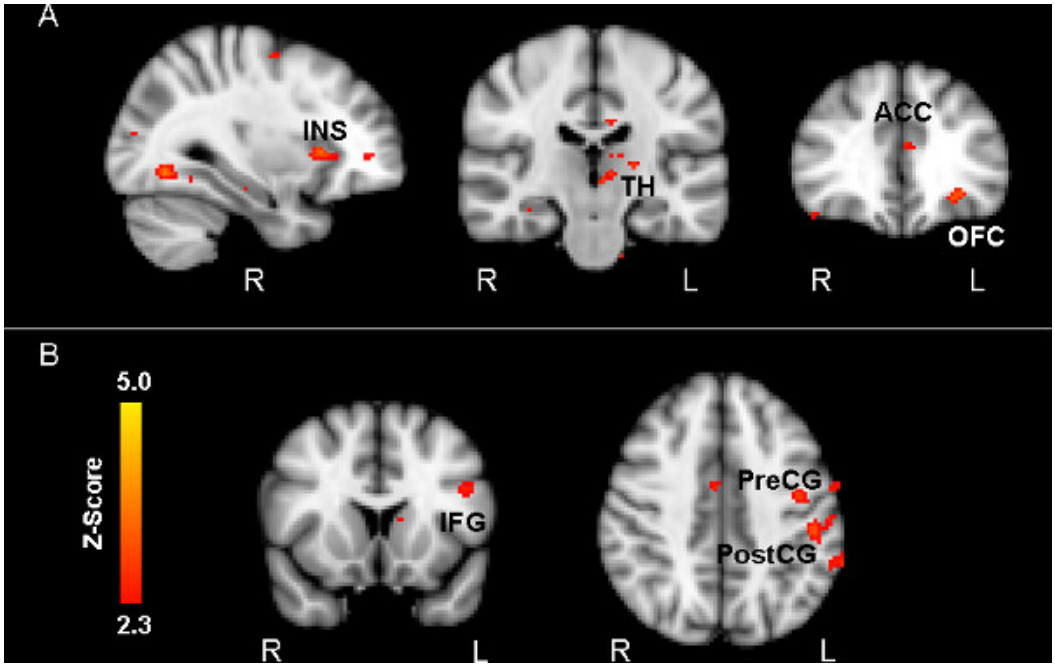

Figure 3. Activation Maps of Age-Related Group Differences. (**A**) Areas with a greater positive correlation with age in the familial high risk group than in controls during target processing. ACC = Anterior cingulate cortex; INS = Insula; OFC = Orbitofrontal cortex; TH = Thalamus. (**B**) Areas with a greater positive correlation with age in controls than in the familial high risk group during the Aversive > Neutral contrast. IFG = Inferior frontal gyrus; PostCG = Postcentral gyrus; PreCG = Precentral gyrus. This figure has been modified from Hart et al.[20], with permission. Please click here to view a larger version of this figure.

ST1. Within-Group Activation Foci in Controls (n = 21)						
		MNI coordinates				
Region	Hemisphere	x	y	z	Max Z-value	Max p-value[1]
Target activation (p<0.05, false discovery rate corrected)						
Middle frontal gyrus / Frontal pole	B	-30	-2	50	5.57	<0.0000001
Inferior frontal gyrus	B	46	12	32	5.41	<0.0000001
Insula	B	-32	24	0	5.4	<0.0000001
Precentral gyrus	B	-40	-22	48	5.53	<0.0000001
Thalamus	B	-12	-16	12	5.03	<0.0000001
Caudate	B	-12	12	4	4.07	0.000003
Putamen	B	18	8	2	4.27	0.00009
Anterior cingulate / Paracingulate gyrus	B	0	12	46	5.6	<0.0000001
Posterior cingulate gyrus	B	8	-16	28	5.2	<0.0000001
Superior / Middle temporal gyrus	B	48	-46	10	5.88	<0.0000001
Fusiform / inferior temporal gyrus	B	-30	-50	-12	5.64	<0.0000001
Superior parietal lobule /	B	30	-44	44	6	<0.0000001

Supramarginal gyrus / Postcentral gyrus						
Lateral occipital cortex	B	48	-62	12	6.12	<0.0000001
Aversive > Neutral activation (p<0.05, false discovery rate corrected)						
Inferior frontal gyrus	L	-44	14	14	3.16	0.0004
Frontal pole / Medial frontal cortex	B	-2	64	0	3.42	0.0005
Postcentral gyrus	L	-62	-22	34	3.12	0.0004
Anterior cingulate cortex	B	-4	34	8	3.27	0.0002
Posterior cingulate gyrus	B	0	-44	28	3.26	0.0002
Inferior temporal / Fusiform gyrus	B	-44	-44	-14	3.03	0.0006
Angular gyrus	B	46	-64	8	3.42	0.0001
Supramarginal gyrus	L	-40	-56	20	3.59	0.00005
Aversive activation (p<0.05, false discovery rate corrected)						
Amygdala	R	22	-4	-18	2.86	0.001
Orbitofrontal cortex / Insula	B	36	22	-4	4.93	<0.0000001
Middle frontal gyrus	B	32	4	40	4.7	<0.0000001
Frontal pole	B	-38	36	10	4.95	<0.0000001
Anterior cingulate / paracingulate gyrus	B	6	16	50	4.85	<0.0000001
Posterior cingulate gyrus	B	2	-28	24	5.88	<0.0000001
Thalamus	B	18	-26	2	5.44	<0.0000001
Precentral gyrus	B	-44	8	34	4.54	<0.0000001
Superior parietal lobule	B	-20	-56	54	6.05	<0.0000001
Lateral occipital cortex	B	-36	-82	4	6.05	<0.0000001
Occipital pole	B	-16	-90	18	5.18	<0.0000001
B, Bilateral						
[1] Reported p-values are uncorrected, significant at FDR-corrected value of <0.05						

Table 1. Within-Group Activation Foci in Controls (n=21). This table has been modified from Hart et al.[20], with permission.

Table 2. Between-Group Differences in Activation						
		MNI coordinates				
	Hemisphere	x	y	z	Max Z-value	Max p-value[1]
Targets						
Familial High risk > Controls (p<0.05, false discovery rate corrected)						
Frontal pole	B	16	76	6	3.52	0.00007
Inferior frontal gyrus	L	-58	16	18	3.37	0.0001
Caudate	B	-14	20	10	3.2	0.0003
Inferior temporal gyrus	L	-52	-44	-20	2.94	0.0009
Controls > Familial High Risk (p<0.05, false discovery rate corrected)						
Middle frontal gyrus / Precentral gyrus	R	48	8	34	3	0.0007
Frontal operculum cortex	L	-46	16	-4	2.94	0.0009
Supplementary motor area	R	18	-16	40	3.02	0.0007
Insula	L	-34	-18	4	2.94	0.0009
Precentral gyrus	B	10	-26	60	3.29	0.0002
Postcentral gyrus	B	14	-38	54	3.57	0.0001
Superior temporal gyrus	R	54	-6	-4	3.18	0.0003
Middle temporal gyrus	R	48	-46	8	3.65	0.00004
Precuneus	R	2	-40	46	2.89	0.001
Lateral occipital cortex	B	-20	-74	36	3.36	0.0002
Aversive - Neutral						
Familial High Risk > Controls (p<0.05, false discovery rate corrected)						
Central opercular cortex	R	50	-2	6	3.01	0.0007
Controls > Familial High Risk (p<0.05, false discovery rate corrected)						
Anterior cingulate cortex	L	-6	38	8	2.68	0.002
Precuneus	L	-10	-54	36	2.7	0.002
B, Bilateral						

[1] Reported p-values are uncorrected, significant at FDR-corrected value of <0.05						

Table 2. Between-Group Differences in Activation Foci. This table has been modified from Hart et al.[20], with permission.

Discussion

The modified emotional oddball paradigm in the current study has been shown to elicit differences in neural recruitment during selective attention and emotional processing in children and adolescents at risk for schizophrenia. While existing paradigms using the emotional oddball task have been used to investigate neural changes in adult populations with psychiatric illness[8], the current paradigm may be particularly useful for measurement of vulnerability markers in younger age groups.

There are several challenges inherent in performing fMRI studies with children and adolescents, including ensuring that the task is appropriate in terms of difficulty and content and in minimizing motion artifacts. Critical steps in the protocol include step 2.2, which requires that participants have a mock scan and practice session prior to the fMRI session. This step is particularly helpful for improving participants' comfort and data quality. Additionally, the design of the behavioral task is critical to ensure that the task has an appropriate level of difficulty and that the selection of aversive images is appropriate for younger age groups. The current task design was successful in eliciting significant behavioral differences between the aversive and neutral conditions and had a moderate difficulty level for both high-risk and control groups.

A limitation of this protocol was that the task did not elicit a significant difference in amygdala activation between the aversive and neutral conditions. There was significant amygdala activation during the aversive condition, but the difference was not significant when contrasted with neutral stimuli. This finding is likely due to the selection of children-appropriate stimuli. Future modifications of the task could examine effects of emotional facial expressions, which may produce more robust differences in amygdala activation between emotional and neutral conditions[21].

Other future applications of this technique include applying it to populations of children and adolescents who may be at risk for other psychiatric illnesses that may similarly affect executive and emotional processing. Several other psychiatric conditions, such as bipolar disorder and mood disorders, have been found to be associated with alterations in brain structure and function that reflect endophenotypes, or heritable markers associated with a disease[22,23]. This suggests the possibility that these intermediate changes in brain structure or function may potentially precede the onset of pathological symptoms in at-risk individuals. The use of the described paradigm in longitudinal studies and with children and adolescents may help to identify relevant endophenotypes for a particular condition to help to refine risk estimates.

Disclosures

Dr. Perkins is currently receiving grant support from Janssen, and is a consultant to Dainippon. In the past, Dr. Perkins is or has been on speaker's bureau for Eli Lilly and AstraZeneca. Dr. Perkins has previously received grants from AstraZeneca, Bristol-Myers Squibb, Otsuka, Eli Lilly, Janssen and Pfizer; and consulting and educational fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, Glaxo Smith Kline, Forest Labs, Pfizer and Shire. All other authors declare no biomedical financial interests or potential conflict of interest.

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