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Abstract: Background: Hyperthymic temperament has been generally accepted as one of premorbid temperament of bipolar disorders. Although several studies indicate that subjects with hyperthymic temperament receive more illuminance, our recent study suggests that the threshold of brightness and darkness judgment is not different between more and less hyperthymic subjects, and that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which has been reported to be associated with bipolar disorder. Therefore, at the next stage, it can be hypothesized that hyperthymic subjects may prefer brightness (i.e., heliotropism) and thereby seek illuminance, and that percent signal changes of left inferior orbitofrontal cortex during the preference task may be associated with hyperthymic temperament scores.
Methods: We compared brightness preference and un-preference between more hyperthymic subjects and less hyperthymic subjects, and investigated percent signal changes of left inferior orbitofrontal cortex during brightness preference judgment, brightness un-preference judgment, and control task by using functional Magnetic Resonance Imaging (fMRI).
Results: There were significant differences in brightness preference judgment and un-preference judgment, showing that more hyperthymic subjects preferred brighter illuminace levels and un-preferred darker illuminance levels than less hyperthymic subjects. Moreover, fMRI signal changes of left inferior orbitofrontal cortex was significantly and negatively associated with hyperthymic temperament scores.
Limitations: It is unknown why left but not right inferior orbitofrontal cortex was associated with hyperthymic temperament scores.
Conclusions: The present findings suggest that more hyperthymic subjects may prefer brightness and un-prefer darkness than less hyperthymic subjects (i.e., heliotropism), and reconfirm that hyperthymic temperament

may be associated with left inferior orbitofrontal cortex, which have been reported to be associated with bipolar disorders.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Authors Harada, Terao, Hatano and Kohno designed the study and wrote the protocol. Authors Harada, Hoaki, Hatano, Kohno, Araki, Mizokami, Kodama, Arasaki, Shimomura, and Fujiki collected the data of the study and managed the literature searches and analyses. Authors Harada, Terao, Shimomura, Fujiki, and Kochiyama discussed the results and draw a conclusion. Author Harada wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

*Cover Letter

June 1, 2013

Dear Professor Akiskal

We are submitting herewith a manuscript entitled "**Hyperthymic Temperament and Brightness Preference in Healthy Subjects: Further Evidence for Involvement of Left Inferior Orbitofrontal Cortex in Hyperthymic Temepramen**t**"** for possible publication in Journal of Affective Disorders.

This manuscript is a sequel to the manuscript entitled ""Hyperthymic Temperament and Brightness Judgment in Healthy Subjects: Involvement of Left Inferior Orbitofrontal Cortex" which has been accepted by you in this Journal.

As you see, the present findings are very interesting and suggest that more hyperthymic subjects may prefer brightness and un-prefer darkness than less hyperthymic subjects (i.e., heliotropism), and reconfirm that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which have been reported to be associated with bipolar disorders.

We believe that this manuscript will also much contribute to the research of affective temperament and hope that this manuscript will be suitable for publication in your Journal.

Sincerely yours
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A Manuscript for Journal of Affective Disorders

Hyperthymic Temperament and Brightness Preference in Healthy Subjects: Further Evidence for Involvement of Left Inferior Orbitofrontal Cortex in Hyperthymic Temepramentplane

(running title) Hyperthymic Temperament and Brightness Preference

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ABSTRACT

Background: Hyperthymic temperament has been generally accepted as one of premorbid temperament of bipolar disorders. Although several studies indicate that subjects with hyperthymic temperament receive more illuminance, our recent study suggests that the threshold of brightness and darkness judgment is not different between more and less hyperthymic subjects, and that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which has been reported to be associated with bipolar disorder. Therefore, at the next stage, it can be hypothesized that hyperthymic subjects may prefer brightness (i.e., heliotropism) and thereby seek illuminance, and that percent signal changes of left inferior orbitofrontal cortex during the preference task may be associated with hyperthymic temperament scores.

Methods: We compared brightness preference and un-preference between more hyperthymic subjects and less hyperthymic subjects, and investigated percent signal changes of left inferior orbitofrontal cortex during brightness preference judgment, brightness un-preference judgment, and control task by using functional Magnetic Resonance Imaging (fMRI).

Results: There were significant differences in brightness preference judgment and un-preference judgment, showing that more hyperthymic subjects preferred brighter illuminace levels and un-preferred darker illuminance levels than less hyperthymic subjects. Moreover, fMRI signal changes of left inferior orbitofrontal cortex was significantly and negatively associated with hyperthymic temperament scores.

Limitations: It is unknown why left but not right inferior orbitofrontal cortex was associated with hyperthymic temperament scores.

Conclusions: The present findings suggest that more hyperthymic subjects may prefer brightness and un-prefer darkness than less hyperthymic subjects (i.e., heliotropism), and reconfirm that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which have been reported to be associated with bipolar disorders.

1. INTRODUCTION

With regard to the association between hyperthymic temperament and light, Hoaki et al. (2011) and Araki et al. (2012) showed that illuminance of daytime was significantly and positively associated with hyperthymic temperament scores. This positive association between hyperthymic temperament and illuminance may suggest several possibilities. One possibility is that high illuminance may maintain and enhance hyperthymic temperament such as light therapy for depression. To examine this possibility, Kohno et al. (2012) reported that healthy residents at higher latitude (43°, Sapporo city in Japan) with lower illuminance had lower hyperthymic temperament scores than another healthy residents at lower latitude (33°, Oita city in Japan) with more illuminance, supporting the possibility.

Another possibility is that hyperthymic temperament may involve heliotropism and thereby seek brightness as a sunflower. Before examining heliotropism, we hypothesized that brightness and darkness judgment are different between healthy subjects with more and less hyperthymic temperament (i.e., more hyperthymic temperament subjects feel darker than less hyperthymic subjects at the same illuminance and thereby seek brightness) and investigated this hypothesis (Harada et al, in press). Consequently, there was no significant difference in the threshold of brightness or darkness judgment between more and less hyperthymic subjects. Nonetheless, there was a significant difference in activations of left inferior orbitofrontal cortex during control task, indicating that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which has been reported to be associated with bipolar disorder (Bermpohl et al., 2010; Hulvershorn et al., 2012; Nusslock et al., 2012). At the next stage, in the present study, it can be hypothesized that hyperthymic subjects may prefer brightness (i.e., heliotropism) and thereby seek illuminance, and that percent signal changes of left inferior orbitofrontal cortex during the preference task may be associated with hyperthymic temperament scores.

2. METHODS

2.1. Subjects

Thirty-four (16 women and 18 men , 26.1±4.7 of a mean age with range 21-41 years) healthy subjects participated in this experiment. The duration between this experiment and the previous one (Harada et al, in press) was at least 3 months and there were overlapping 13 subjects. All subjects were right-handed and had normal or corrected to normal vision. None of the subjects had any current or lifetime history of psychiatric disorders, which were determined by Mini-International Neuropsychiatric Interview. They gave written informed consent to participate in this study according to procedures approved by the ethical committee at Oita University Faculty of Medicine.

2.2. Hyperthymic temperament identification

The Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A) has been developed by Akiskal et al. (2005). This scale has 110 questions to measure 5 temperaments (depressive, hyperthymic, cyclothymic, irritable and anxious) and has been verified in 32 language versions and widely used in a number of epidemiological and clinical studies with psychiatric patients and healthy subjects. Also in Japan, the scale has been validated and widely used to identify affective temperaments (Akiyama et., 2005; Matsumoto et al., 2005), where it was decided that the cut-off point is 6 points (i.e., subjects with equal to or more than 6 points are considered to have more hyperthymic temperament whereas subjects with less than 6 points have less hyperthymic temperament). The present subjects were divided into subjects with more hyperthymic temperament (more hyperthymic subjects) and subjects with less hyperthymic temperament (less hyperthymic subjects) using this cut-off point.

2.3 Functional Magnetic Resonance Imaging (fMRI) stimuli

Similar to the previous study (Harada et al, in press), all blocks consisted of a sequence of 11 blank screens (with 11 levels of indirect illuminance in the absence of any figure) screens adjusted by tristimulus value (Red, Green, and Blue: 0~250), each blank screen graduating from white to black by 25 tristimulus value (Figure 1). The graduated blank screens were randomly assigned in each block. From the white to black screen, the illuminance at the location of the subject's head was measured as 700, 589, 481, 396, 324, 263, 220, 185, 164, 152, and 146 lux (Figure 1).

2.4.Experiment

The same 3 different experimental conditions/blocks as the previous one (Harada et al, in press) were presented to the subjects in randomly allocated pattern of two balanced-order patterns which consisted of 9 blocks of "A" pattern or reverse "B" pattern. In a different way from the previous study (Harada et al, in press), at this experiment, subjects were instructed as follows; "Please judge if the screen is preferable or not preferable by pressing the corresponding button" in preference judgment, and; "Please judge if the screen is un-preferable or not un-preferable by pressing the corresponding button" in un-preference judgment, and; "Please press the button when the screen changes without making a judgment of preference or un-preference" in control task.

2.5.Analysis of performance data

As performance data, the rate of preference judgment at 11 illuminance levels were compared between more hyperthymic subjects and less hyperthymic subjects while the rate of un-preference judgment at 11 illuminance levels were also compared between more hyperthymic subjects and less hyperthymic subjects. For statistical analysis, Fisher's exact probability test was used for the rates of each preference or un-preference judgment at 11 illuminance levels between more hyperthymic subjects and less hyperthymic subjects without multiple comparison correction.

2.6.fMRI image acquisition

fMRI images were collected using Siemens magnetom verio 3T MRI system. A time course series of 174 volumes was acquired with a T2-weighted single shot gradient echo planar imaging (EPI) sequence. Each volume consisted of 36 slices, with a slice thickness of 3 mm and a gap of 0.75mm, and covered the almost the whole brain. Images were acquired in the axial plane (TR = 3,000 ms; TE = 30 ms; FOV = 210 mm; voxel size = 3 x 3 x 3 mm). The total acquisition time was 8 min 50 sec, including periods for signal equilibration. T1-weighted structural images were acquired with 3-D magnetization prepared rapid gradient echo (MPRAGE) in the sagittal plane (TR=2040 ms; TE = 2.53 ms; TI = 900 ms; the flip angle was 9°; FOV = 192 mm; voxel size = 1 x 1 x 1 mm).

2.7.fMRI Image analysis

All fMRI analysis was performed in SPM8 (Statistical Parametric Mapping software, University College of London, London, UK; available at: http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing (movement correction, normalization 6 to the MNI EPI template, smoothing with an isotropic 8 mm FWHM kernel, and resampling to 2 mm cubic voxels) were performed firstly. Each individual data set was carefully screened for data quality via inspection for image artifacts and excessive head motion (>3 mm head motion or 2° head rotation).

2.8.Region-of-interest (ROI) analyses of BOLD signal change

We conducted region-of-interest (ROI) analyses using marsbar toolbox (marsbar.sourceforge.net). Before that, conventional individual analyses were performed on SPM8 to estimate the task-related activation for later use in ROI analyses. We defined three conditions: preference judgment, un-preference judgment and control task. Each condition were modeled with a boxcar function and convoluted with a canonical hemodynamic response function. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 128 s. Serial autocorrelation was also corrected using AR (1) model.

Following the hypothesis that percent signal changes of left inferior orbitofrontal cortex during the preference task may be associated with hyperthymic temperament scores, the region of interest (ROI) was set at left inferior orbitofrontal cortex using automated anatomical labeling (Figure 2), and percent signal change (relative to the low-level baseline activity observed during viewing of the fixation cross during the individual task) in the ROI was measured by marsbar toolbox. Moreover, the association between percent signal changes of the ROI and hyperthymic scores were investigated during brightness preference judgment, darkness preference judgment, and control task by Spearman's rank correlation coefficient.

3. Results

3.1. Performance data

There were several significant differences in preference judgment task where more hyperthymic subjects had significantly higher rate of preference judgment than less hyperthymic subjects at 589 lux and more hyperthymic subjects had significantly lower rate of preference judgment than less hyperthymic subjects at 185 lux (Figure 3A), and in un-preference judgment task where more hyperthymic subjects had significantly higher rate of un-preference judgment than less hyperthymic subjects at 146, 152, 164, 185, and 220 lux (Figure 3B), showing that more hyperthymic temperament subjects preferred brighter illuminace levels and un-preferred darker illuminance levels than less hyperthymic temperament subjects.

3.2. fMRI results

As shown in Figure 4, there was a significantly negative association between percent signal changes of left inferior orbitofrontal cortex during control task and hyperthymic temperament scores (ρ=-0.347, $p<0.05$), but not during preference judgment or un-preference judgment.

4. Discussion

In the present study, more hyperthymic subjects preferred brighter illuminace levels and un-preferred darker illuminance levels than less hyperthymic subjects. Considering the previous findings that there was no significant difference in any rates of brightness judgment or darkness judgment at 11 illuminace levels between more hyperthymic and less hyperthymic subjects (Harada et al, in press), these findings suggest that more hyperthymic subjects may prefer brightness and un-prefer darkness than less hyperthymic subjects (i.e., heliotropism) without the difference in brightness or darkness perception between more and less hyperthymic subjects.

There was a significantly negative association between percent signal changes of left inferior orbitofrontal cortex during control task and hyperthymic temperament scores. Also in the previous study (Harada et al, in press), there was a significantly positive association between a cluster containing left inferior orbitofrontal cortex during control task and hyperthymic temperament scores, although the associations lie in opposite directions. In any case, the present findings reconfirm that hyperthymic temperament may be associated with left inferior orbitofrontal cortex. It is unknown why these significant activations were observed during control task but not during brightness preference judgment or darkness preference judgment. Nonetheless, it cannot be denied that the present control task might have been affected by brightness preference judgment and/or darkness preference judgment which were located just before or just after the present control task. Such modest stimulation as control task could have induced activations in association with hyperthymic scores in the opposite way to the activations induced by the previous control task between brightness judgment and darkness judgment (Harada et al, in press), which are different from brightness preference judgment and darkness preference judgment in the present study.

With regard to bipolar disorder, manic patients have been reported to show increasing activations in left lateral orbitofrontal cortex (BA11 and BA47) during expectation of increasing gain and decreasing responses during expectation of increasing loss (Bermpohl et al., 2010) while another group of manic patients have been reported to exhibit decreased left lateral orbitofrontal cortex activation during facial emotion processing (Hulvershorn et al., 2012). Also, euthymic patients with bipolar I disorder have been reported to display elevated left lateral orbitofrontal cortex (BA 47) activity during reward anticipation (Nusslock et al., 2012). Depressive patients with bipolar I disorder have been reported to show attenuation in bilateral orbitofrontal cortex (BA 47) and increased activation in left lateral orbitofrontal cortex (BA 10) during face matching paradigm (Altshuler et al., 2008). Also, depressive patients with bipolar II disorder have been reported to show reduction in activation in bilateral ventrolateral prefrontal cortex (BA 47) during emotional face-matching task (Vizueta et al., 2012). These findings suggest that left orbitofrontal cortex may be associated with bipolar disorder. Therefore, hyperthymic temperament may have the neural correlates close to those of bipolar disorder, suggesting hyperthymic temperament as a biologically prodromal trait of bipolar disorder.

As a limitation, it is unknown why the left but not right inferior orbitofrontal cortex was associated with hyperthymic temperament scores.

In conclusion, the present findings suggest that more hyperthymic subjects may prefer brightness and un-prefer darkness than less hyperthymic subjects (i.e., heliotropism), and reconfirm that hyperthymic temperament may be associated with left inferior orbitofrontal cortex, which have been reported to be associated with bipolar disorders.

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Figure legends

Figure 1. Experiment Protocol

All blocks consisted of a sequence of 11 blank screens adjusted by tristimulus value, each blank screen graduating from white to black by 25 tristimulus value. These kinds of blocks graduated blank screens were randomly arranged in each block. Three kinds of blocks were presented to the subjects in randomly allocated pattern of two balanced-order patterns which consisted of 9 blocks (A or B). Prior to each block, an instruction screen was presented for 5 sec with fixation cross for 20 sec. These visual stimuli were presented using Presentation (version 14.1) and projected via a forward projection system onto a translucent screen placed at the end of the magnet's gurney. Subjects viewed the screen through a mirror attached to the head coil. Prior to each block, an instruction screen was presented for 5 sec with fixation cross for 20 sec. Subjects were instructed as follows; "Please judge if the screen is preferable or not preferable by pressing the corresponding button" in preference judgment, and; "Please judge if the screen is un-preferable or not un-preferable by pressing the corresponding button" in un-preference judgment, and; "Please press the button when the screen changes without making a judgment of preference or un-preference" in control task.

Figure 2. Axial Images of Left Inferior Orbitofrontal Cortex

We conducted region-of-interest (ROI) analyses using marsbar toolbox (marsbar.sourceforge.net). Following the hypothesis that percent signal changes of left inferior orbitofrontal cortex during the preference task may be associated with hyperthymic temperament scores, the region of interest (ROI) was set at left inferior orbitofrontal cortex using automated anatomical labeling, and percent signal change (relative to the low-level baseline activity observed during viewing of the fixation cross during the individual task) in the ROI was measured by marsbar toolbox. Left inferior orbitofrontal cortex was depicted in red.

Figure 3. Performance Data

The rate of brightness preference judgment at 11 illuminance levels (A) were compared between more hyperthymic subjects and less hyperthymic subjects while the rate of darkness preference judgment at 11 illuminance levels (B) were also compared between more hyperthymic subjects and less hyperthymic subjects. There were several significant differences in preference judgment task where more hyperthymic subjects had significantly higher rate of preference judgment than less hyperthymic subjects at 589 lux and more hyperthymic subjects had significantly lower rate of preference judgment than less hyperthymic subjects at 185 lux (Figure 3A), and in un-preference judgment task where more hyperthymic subjects had significantly higher rate of un-preference judgment than less hyperthymic subjects at 146, 152, 164, 185, and 220 lux (Figure 3B). *: $p<0.05$

Figure 4. The Association Between Hyperthymic Temperament Scores and Percent Signal Changes of Left Inferior Orbitofrontal Cortex during Control Task

There was a significantly negative association between percent signal changes of left inferior orbitofrontal cortex during control task and hyperthymic temperament scores ($\rho=-0.347$, $p<0.05$), but not during preference judgment or un-preference judgment.

Figure(s)

Figure 1

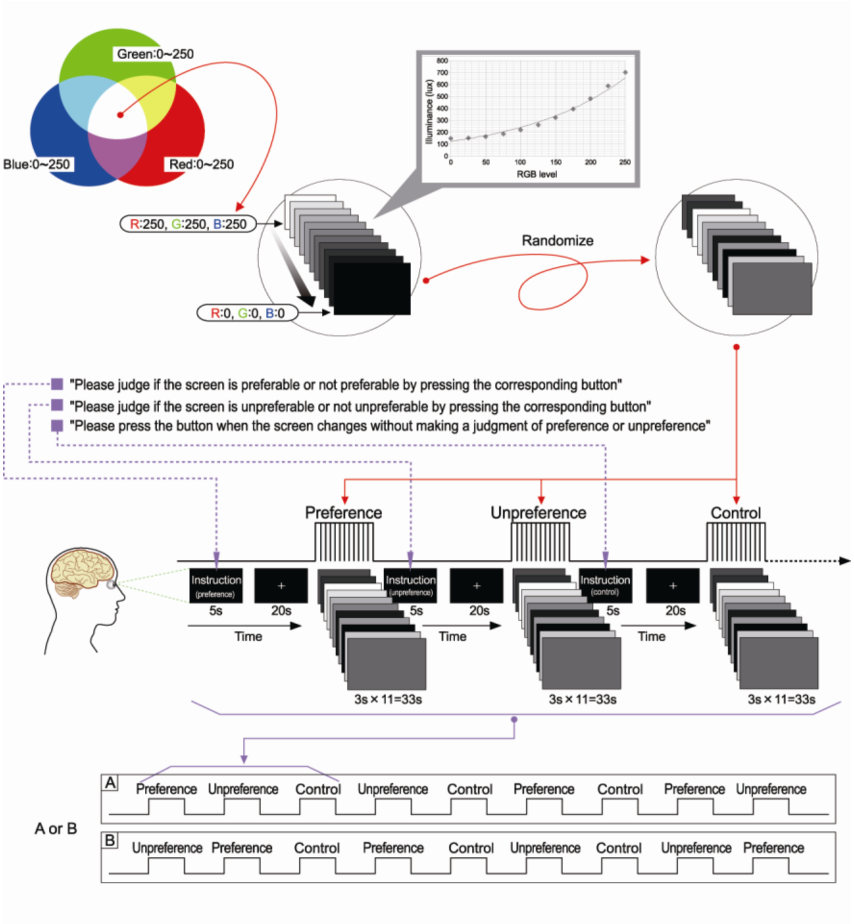

Figure 2

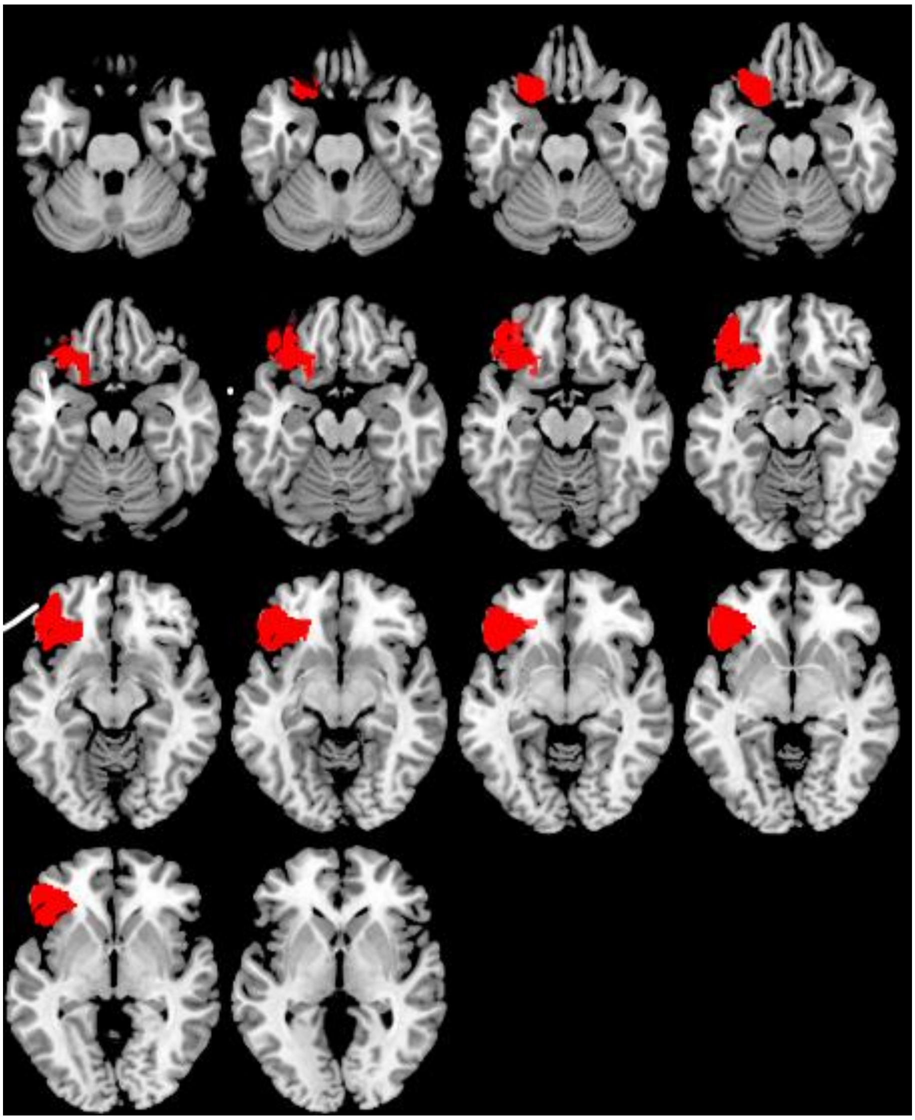

Figure 3

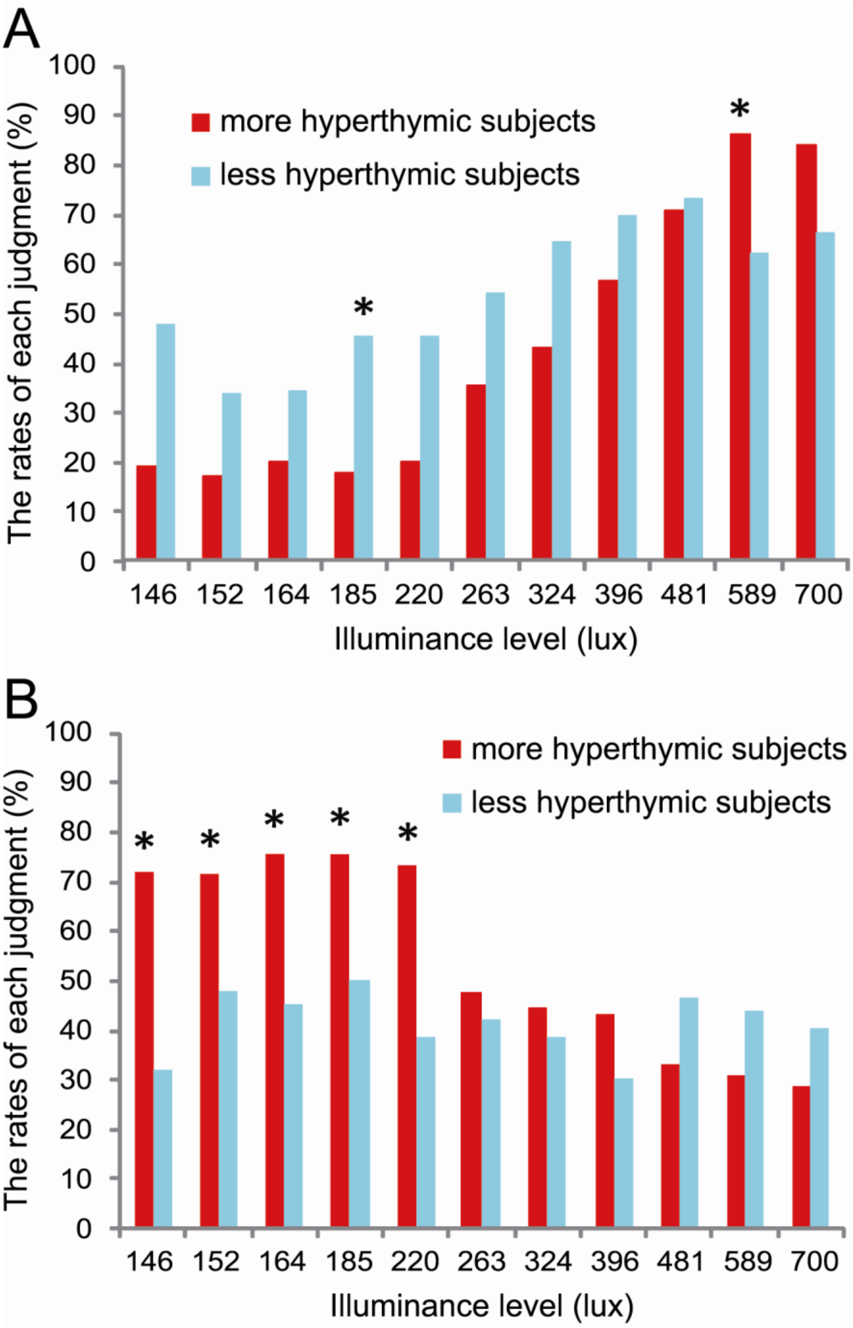
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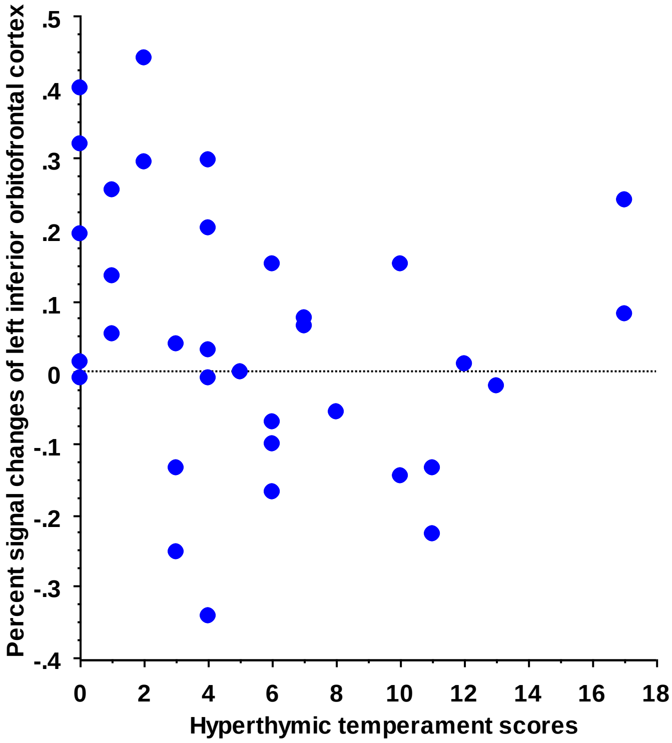
Figure 4



Percent signal changes of left inferior orbitofrontal cortex
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Hyperthymic temperament scores