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Bridging the bench to bedside gap: validation of a reverse-translated rodent continuous performance test using functional magnetic resonance imaging

Benjamin S. McKenna^{a,b,*}, Jared W. Young^b, Sharron E. Dawes^c, Gregory L. Asgaard^d, Lisa T. Eyler^{a,b}

^a Mental Illness Research, Education, and Clinical Center, Veterans Affairs San Diego Healthcare System, San Diego, CA 92161, USA

^b Department of Psychiatry, University of California, San Diego, CA 92161, USA

^c Research Department, Sharp Mesa Vista Hospital, San Diego, CA 92123, USA

^d USS Abraham Lincoln, CVN-72 aircraft carrier, United States Navy, USA

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ABSTRACT

Vigilance, which requires attending to relevant while ignoring irrelevant stimuli, is a cognitive domain impacted by schizophrenia and bipolar disorder. Various continuous performance tests (CPT) have been used to examine neural correlates of vigilance within people with and without severe mental illness, though there are limited cross-species paradigms available. The 5-choice CPT (5C-CPT) was designed for use in rodents as a cross-species translational paradigm. Here, we evaluate construct validity of a reverse-translated human analog of the 5C-CPT in assessing the neural correlates of vigilance. Functional magnetic resonance imaging during the 5C-CPT was used to examine activation of healthy individuals during target and non-target trials separately. We found activation in brain regions implicated in sustained attention processes including premotor cortex, inferior parietal lobe, basal ganglia, and thalamus during target trials. For non-target trials, we found expected activation in inferior frontal cortex, premotor cortex, presupplementary motor area, and inferior parietal lobe. Results support the construct validity of the 5C-CPT in measuring attentional and inhibitory systems within a single task paradigm enabling the assessment of vigilance across species. This task can be used for powerful parallel human and animal investigations of the biological basis of vigilance deficits in populations with severe mental illness.

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1. Introduction

Within severe mental illnesses such as schizophrenia and bipolar disorder, the link between cognitive deficits and functional outcome has been well established (Bearden et al., 2010; Green, 2006; Green et al., 2000). However, current interventions focus mainly on reduction of mood and psychotic symptoms and are less effective in altering cognitive performance (Carter and Barch, 2007). Efforts towards development of pro-cognitive interventions for use in schizophrenia and bipolar disorder are underway, but are in early stages (Kern et al., 2008; Nuechterlein et al., 2008). One important pathway to develop treatments for cognitive deficits in these disorders is a more complete understanding of the neurophysiological underpinnings of cognitive performance in domains that are of functional significance.

One common functional ability that is impaired in both schizophrenia and bipolar disorder is vigilance, which involves both

maintaining focus over time in responding to target stimuli while inhibiting responses to infrequent non-target distracter stimuli. There is a growing body of research assessing levels of impairment during vigilance in an attempt to identify core mechanisms of cognitive vulnerability within these disorders (Alloy et al., 2006; Clark and Goodwin, 2004). In bipolar disorder, a number of studies have found that euthymic patients demonstrate impaired attentional performance on continuous performance tests (CPTs) compared to healthy individuals while inhibitory processing deficits, when measured or observed, are found to be dependent on manic mood (Bora et al., 2006; Harmer et al., 2002; Swann et al., 2003). Patients with schizophrenia exhibit deficits on CPTs in both sustained attention and response inhibition (Birkett et al., 2007; Liu et al., 2006), which remain relatively unchanged despite fluctuations in clinical symptoms (Liu et al., 2002). The importance of impaired vigilance in patients with schizophrenia has been highlighted by the correlation of impairment on the CPT and the cost of caregiving in these patients (Ko et al., 2003). Additionally, CPT performance deficits are similar between patients with bipolar disorder and those with schizophrenia, except for a psychomotor processing speed component, which is relatively more impaired in schizophrenia (Fleck et al., 2001).

* Correspondence to: 3350 La Jolla Village Drive, Mail Code: 151B, San Diego, CA 92161, USA. Tel.: +1 858 552 8585x6992; fax: +1 858 642 3962.

E-mail address: bmckenna@ucsd.edu (B.S. McKenna).

Various types of CPT paradigms have been used to assess sustained attention processes and, to a lesser extent, inhibitory functioning behaviorally. CPT paradigms vary in design, but are similar in that they require responses to target stimuli and inhibition of responses to non-target stimuli (Borgaro et al., 2003). There is a relatively large literature describing the neural processes underlying vigilance in individuals without mental illness using a variety of CPT-like paradigms, the most popular of which are generally stop signal tasks and go/no-go paradigms. Within a stop signal paradigm, participants are asked to inhibit a motor response when a stop-cue is presented after already initiating the motor response. Alternatively, in the go/no-go paradigm participants are asked to inhibit a prepotent response when a non-target appears. This body of research has generally found that response to target stimuli over time requiring sustained attention generally activates a bilateral, but more predominantly right hemispheric, network involving frontal and parietal cortices, bilateral occipital cortex when using visual stimuli, and subcortical structures such as the thalamus and basal ganglia (Coull, 1998; Riccio et al., 2002). Alternatively, inhibitory processes are thought to be mediated by right hemispheric anterior cingulate, bilateral supplementary motor area, inferior frontal and parietal cortices (Aron, 2011; Rubia et al., 2001). However, findings are not always consistent and this may be due to the wide variety of tasks that have been used to examine these processes, each tapping into different underlying mechanisms of response inhibition (Riccio et al., 2002). Variations in the proportion of target compared to non-target trials, use of verbal versus non-verbal stimuli, and analyses of correct versus all trials can have effects on results within the normative population. These same variations between CPT paradigms are likely to have an even greater impact in studies of severe mental illness where deficits in cognition and abnormalities of mood affect the ability to perform the task for reasons beyond attentional/inhibitory deficits alone (e.g., altered motivation, poor verbal skills).

The existing neuroimaging paradigms that assess vigilance have not been specifically designed with the goal of integrating human imaging findings with those from model systems such as rodents. This failing is unfortunate given that drug development requires translational paradigms that offer the ability to isolate and manipulate certain neural networks by lesion investigations, pharmacological, and genetic manipulations. A recent review of animal cognition paradigms found that assessment of vigilance was a potential area for cross-species research in severe mental illness (Young et al., 2009b). Existing behavioral paradigms with animal and human analog versions include the human 5-choice serial reaction-time task in the Cambridge Neuropsychological Test Automated Battery (Morris et al., 1987), distract sustained attention task (Demeter et al., 2008), and 5-choice CPT (5C-CPT; Young et al., 2009a). Of these, only the 5C-CPT assesses both sustained attention and response inhibition processes within a single task paradigm (Young et al., 2009a). Work with the 5C-CPT in rodents has demonstrated that task outcome measures can be related to psychometric parameters commonly used in human CPTs based on signal detection theory. Such work has demonstrated that mice can exhibit a vigilance decrement on the task and subchronic phencyclidine impairs rat performance (Young et al., 2009a; Barnes et al., 2012). Further, hits, false alarms, and premature responses may be mediated by distinct mechanisms in rodents in this task (Barnes et al., 2011, 2012; Young et al., 2009a; Young et al., 2011).

The human analog version of the 5C-CPT closely matches the rodent version in task parameters and has been administered to patients with schizophrenia and healthy comparison subjects in a recent behavioral study (Young et al., submitted for publication). Schizophrenia patients exhibited significantly impaired vigilance characterized by reduced target detection and increased impulsive

responding. It is not yet known, however, whether this CPT task will reliably activate brain systems known to be important for human attention and inhibition. The aim of the present study, therefore, was to validate the human analog 5C-CPT within functional magnetic resonance imaging (fMRI) by examining the underlying neural correlates of vigilance during target and non-target trials within a sample of healthy individuals. It is important to first establish the validity of the 5C-CPT in measuring the neural systems underlying vigilance within a healthy population before neuronal inferences can be made in bipolar and schizophrenia patient groups. Based upon results of existing studies using CPT and CPT-like tasks, we predicted that while maintaining adequate attention to task demands during target trials (i.e., during the period preceding initiation of correct responses), healthy individuals would display bilateral, but predominantly right hemisphere activation of dorsal and ventral prefrontal, inferior parietal, and occipital cortices; and subcortical regions including the basal ganglia and thalamus. We expected that during correct inhibitory processing of a motor response while ignoring irrelevant stimuli during non-target trials, healthy individuals would show activation of predominantly right hemispheric anterior cingulate, supplementary motor area, inferior frontal, dorsomedial and dorsolateral prefrontal, and inferior parietal cortices.

2. Methods

2.1. Participants

Ten healthy participants (5 females) were studied with a mean age of 34.9 ± 11.4 years (range: 22–53 years) and a mean education of 15.7 ± 1.2 years (range: 14–18 years). All participants were right-handed, did not have a lifetime history of DSM IV Axis I psychopathology or an immediate family history of mood or psychotic disorders, a personal history of significant head injury, neurological illness, non-correctable vision impairment, or any contraindication to completing MRI. Participants were recruited from the general San Diego community and from the University of California, San Diego (UCSD) campus and gave informed, written consent before beginning the experiment, which was approved by the local Human Research Protections Program.

2.2. Experimental paradigm

In the scanner, participants completed a version of the rodent 5C-CPT (Young et al., 2009a) reverse-translated into a human paradigm. The goal of this translation is to maintain the highest degree of continuity between versions of the task, while making only minimal modifications to the animal-based parameters so as to promote task engagement in human participants. The target stimuli are five white circles, with black centers, displayed on a black background in a semi-circular array with stimuli separated by equal distance. Participants initiate a trial themselves by pressing a button on an MRI-compatible joystick from a common starting location, indicated on the screen by a white square with a black center. During most trials, the black center of one of the circles becomes white for 250 milliseconds (ms) followed by a variable inter-trial (ITI) interval (500, 1000, or 1500 ms) presented in a pseudo-random order so that no more than three of a specific ITI appear consecutively. Participants were asked to identify the targets as quickly as possible during the ITI by moving a cursor with an MRI-compatible joystick from the starting location until breaking the perimeter of the target circle. During a minority of trials, all five circles became solid white and participants were asked to withhold responding by not breaking the plane of the perimeter of the square in the starting position with the joystick. Correct responses are followed by the word “correct” displayed on the screen after each trial, while incorrect responses are followed by a totally white screen with the word “incorrect” displayed in red for 4000 ms. Performance feedback was included to mirror the rodent version where food pellets are used as a reward for correct responses. However, there is not parallel reward between the human and rodent versions of the 5C-CPT. There is a ratio of 5 to 1 target versus non-target trials with a total of 120 target trials and 24 non-target trials across four runs of the task. Blocks of fixation trials (where the participant looks at a crosshair in the center of the screen) of 30 s duration are interspersed between 30 s blocks of the task trials where participants begin a trial by clicking the button on the joystick when in the starting position. Each run consisted of 11 blocks and lasted for 5 min and 10 s. A total of four runs were collected for each participant (see Fig. 1 for trial examples).

2.3. Image acquisition

Participants were scanned at the UCSD Keck Center for Functional Magnetic Resonance Imaging using a GE Signa EXCITE 3.0 T whole-body imaging system.

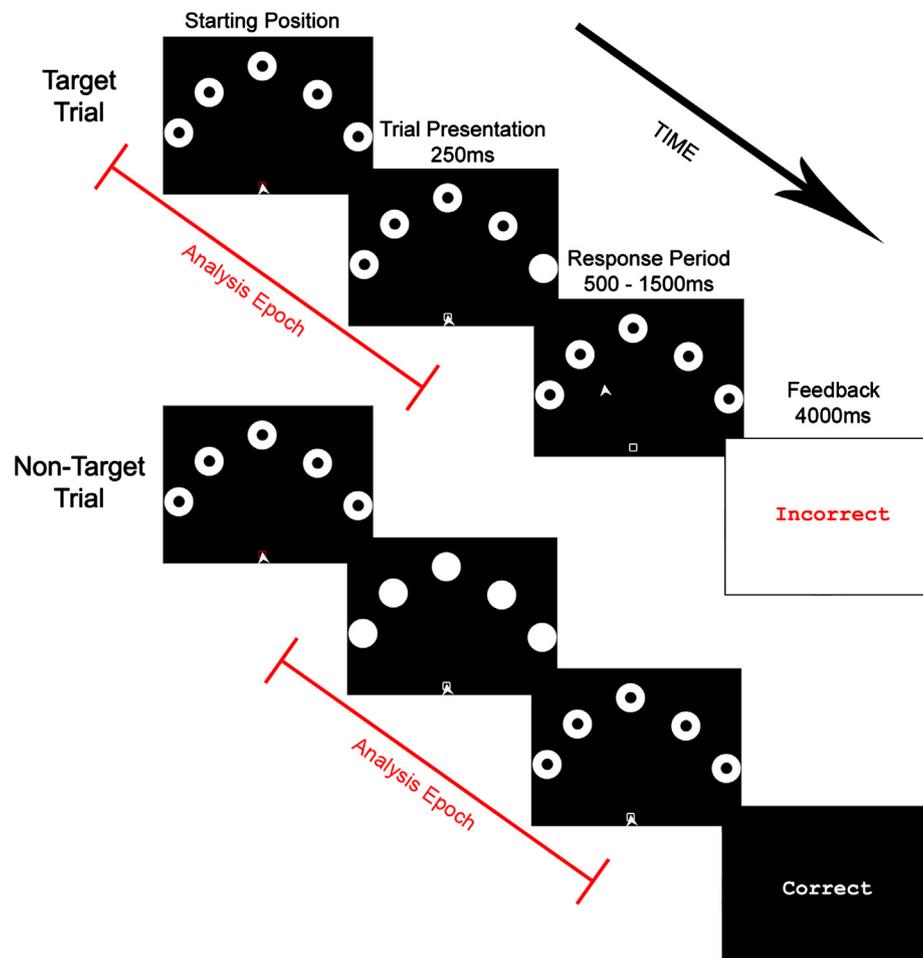


Fig. 1. Example of two trials from the human 5 choice continuous performance test. The top presents an incorrect target trial and the bottom presents a correct non-target trial. In both conditions participants press a button to initiate a trial (indicated by a red starting box). In a target trial one circle becomes solid white indicating the participant should move the cursor to that circle. In a non-target trial all five circles become solid white indicating the participant should not move the cursor outside the starting box. The red analysis epoch encompasses periods that were used for analyses. For target trials we measure the BOLD response from the button press to when the cursor crosses the plane of the starting box for correct trials only. For non-target trials we measure the BOLD response from presentation of 5 solid white circles to the end of the trial for correct trials only. ms: milliseconds. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Anatomical scans utilized a T1-weighted fast spoiled gradient echo pulse sequence (TE=4 ms, flip angle=90°, 1 mm³ resolution). The functional scans were sensitive to the T2*-weighted blood-oxygenation-level-dependent (BOLD) signal. Thirty echoplanar 4-mm axial slices covering the whole brain (TR=2000 ms, TE=30 ms, image matrix=64 × 64, 4 mm × 4 mm resolution) were acquired in an interleaved manner using a gradient echo pulse sequence for each task over 155 repetitions. Field maps were collected and applied to the functional data in order to unwarp the echo-planar images to mitigate inhomogeneities in the magnetic field.

2.4. Image processing

We used local software, FSL (Smith et al., 2004), and the Analysis of Functional NeuroImages (AFNI; Cox, 1996) library to analyze images. To improve structural to functional image correspondence, we used a specialized cost function optimized for T2*- to T1-weighted image alignment that uses a weighted local Pearson coefficient (Saad et al., 2009). Echo planar slices were aligned to have the same temporal origin and were then corrected for motion artifact by co-registering to a base image. A general linear model (GLM) was applied to each participant's time series data, which contained parameters for the constant, linear, quadratic, and cubic drift, six motion parameters derived from the motion correction, and the reference functions. The reference functions are vectors representing the behavioral paradigm convolved with the estimation of the hemodynamic response curve using a gamma function. We estimated BOLD signal response to correct target and correct non-target trials separately. Target trials were defined as the period between a button press and crossing the plane of the target for correct trials only, whereas non-target trials were defined as the period between onset of the five-circle no-go signal and the end of the trial for correct trials only (where participants do not move the joystick outside the starting box; see Fig. 1).

For target trials, 95 percent of all trials were correct and used in analyses. For non-target trials, 91 percent of all trials were correctly inhibited. Further, the average time period modeled in the GLMs for target and non-target trials was 1.48 and 1.02 s per correct trial, respectively. Each participant's behavioral data were thus used to create individual reference functions for correct target and non-target trials. Finally, raw BOLD signal data were transformed into percent signal change from baseline, spatially smoothed using a Gaussian filter in an iterative fashion to result in an overall smoothness of FWHM=6 mm, and normalized into standard Talairach atlas space (Talairach and Tournoux, 1988).

2.5. Data analyses

Analyses followed standard statistical procedures. We chose a whole-brain approach (as opposed to a region of interest approach) in order to establish validity of the task paradigm within fMRI such that only those brain areas related to sustained attention and response inhibition were predicted to be activated and other regions within the whole brain predicted to not show a response. For analyses, the fMRI dependent measure was percent signal change from the baseline condition for each participant during the target and non-target task intervals (see Fig. 1). Voxel-wise two-tailed single-sample *t*-tests were employed to create statistical parametric maps for target and non-target trials separately. A two-tailed paired-samples *t*-test comparing target to non-target BOLD response was also conducted to examine the differential effects of each condition. Thus, we conducted a total of three primary contrasts across the whole brain. We applied a cluster threshold method in all analyses to control Type I error (Forman et al., 1995). This method utilizes a Monte Carlo simulation to determine the probability that a single significantly activated voxel is also part of a contiguous cluster of *N* voxels that are all individually significantly activated in the analysis at $P \leq 0.01$. That is, we only considered an area

of activation as reliable if it contained at least 32 contiguous voxels, each of which is individually activated at the $P \leq 0.01$ level providing a Bonferroni-corrected p -value of 0.03 (for the three total contrasts) for each cluster in all fMRI analyses. Within significant regions found during target and non-target trials, we then regressed each individual's sensitivity index from the 5C-CPT onto the BOLD signal for each condition separately to examine the relationship between behavioral performance and brain activation using a threshold of $P=0.01$. Regression analyses utilized the same statistical thresholds as in the main analyses, except with the cluster threshold adjusted to 11 contiguous voxels to account for the smaller volume of significantly activated task-related regions. The sensitivity index provides a non-parametric assessment of appropriate responding and is employed with single choice procedures within signal detection theory (Marston, 1996). We calculated the sensitivity index with the following formula where HR is the hit rate, or the proportion of inappropriate responses to target stimuli, and FAR is the false alarm rate, or the proportion inappropriate responses to non-target stimuli:

$$\text{Sensitivity Index} = \frac{\text{HR} - \text{FAR}}{2[(\text{HR} + \text{FAR}) - (\text{HR} + \text{FAR})^2]}$$

3. Results

3.1. Behavioral performance

As a sample, participants had a mean reaction time of 1.48 ± 0.03 s, hit rate of 95.2 ± 4.8 percent, and a false alarm rate of

1.8 ± 1.2 percent. There were no significant differences between males and females on any measure. The target and non-target responses yielded a sensitivity index of 0.936 ± 0.052 . The index ranges from -1 to $+1$, with 0 indicating chance responding and $+1$ indicating all signal events were responded to, while non-signal events were inhibited (Frey and Colliver, 1973). Further, these responses yielded a responsivity index of -0.162 ± 0.322 . The responsivity index is an estimate of response bias with lower numbers indicating a conservative response strategy, while higher numbers equate to liberal responding (Frey and Colliver, 1973).

3.2. Functional MRI results

The BOLD response from the human analog 5C-CPT task provided robust results with conservative statistical thresholds (correct $P \leq 0.01$ per contrast). Further, both the target and non-target trials provided overlapping and distinct neuronal regions related to sustained attention and inhibitory processes. Table 1 presents the significant clusters of activation found during the target trials using a one-sample t -test (two-tailed, $n=10$, $d.f.=9$) where participants correctly responded to target stimuli including the

Table 1
Brain regions demonstrating a significant BOLD response during target trials in the 5C-CPT.

Target trials						
Brain region	Volume	Center mass			Brodmann areas	
		Talairach coordinates				
		X	Y	Z		
Activations—Positive BOLD response						
B Cerebellum/Primary visual and visual association cortex/Cuneus	76,416 mm ³	1.9 R	64.9 P	7.6 I	17, 18, 19	
R Precuneus	5760 mm ³	19.7 R	62.7 P	48.2 S	7	
R Supramarginal gyrus	2560 mm ³	36.9 R	35.5 P	36.7 S	40	
L Supramarginal gyrus/Precuneus primary motor cortex/B Premotor cortex and supplementary motor area	57,024 mm ³	19.1 L	24.3 P	52.5 S	4, 6, 7, 40	
B Basal ganglia/Thalamus	36,032 mm ³	1.9 L	12.9 P	13.9 S	n/a	
Deactivations—Negative BOLD response						
L Superior frontal gyrus	2304 mm ³	1.0 L	30.3 A	56.1 S	8	

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral; A: anterior; P: posterior; I: inferior; S: superior. Clusters were found from a one-sample t -test. The magnitude of the BOLD response from each cluster was significant at a minimum t -value of ± 3.25 (two-tailed, $n=10$, $d.f.=9$). Positive responses reflect increased BOLD relative to baseline, whereas negative responses reflect decreased BOLD relative to baseline.

Table 2
Brain regions demonstrating a significant BOLD response during non-target trials in the 5C-CPT.

Non-target trials						
Brain region	Volume	Center mass			Brodmann areas	
		Talairach coordinates				
		X	Y	Z		
Activations—Positive BOLD response						
B Primary visual and visual association cortex/Cuneus/R Supramarginal gyrus	73,024 mm ³	11.8 R	65.9 P	7.6 S	17, 18, 19, 40	
L Supramarginal gyrus	10,048 mm ³	41.6 L	51.7 P	40.2 S	40	
L Premotor cortex	2880 mm ³	41.5 L	1.9 P	33.5 S	6	
L Dorsolateral prefrontal CORTEX	3392 mm ³	37.9 L	27.8 A	31.3 S	9, 46	
R Dorsolateral prefrontal and inferior frontal cortices/Premotor cortex and presupplementary motor area/Insular cortex	30,784 mm ³	34.5 R	15.3 A	32.0 S	6, 9, 13, 45, 46	
Deactivations—Negative BOLD response						
L Postcentral gyrus	7680 mm ³	34.8 L	31.5 P	54.5 S	1, 2, 3	

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral; A: anterior; P: posterior; I: inferior; S: superior. Clusters were found from a one-sample t -test. The magnitude of the BOLD response from each cluster was significant at a minimum t -value of ± 3.25 (two-tailed, $n=10$, $d.f.=9$). Positive responses reflect increased BOLD relative to baseline, whereas negative responses reflect decreased BOLD relative to baseline.

inferior parietal, premotor, and occipital cortices, basal ganglia, and thalamus. All clusters, except for the left superior frontal gyrus, followed the same pattern such that subjects exhibited greater activity when maintaining attention relative to baseline; whereas the left superior frontal gyrus demonstrated decreased activation relative to baseline. Table 2 presents those significant clusters of activation found during the non-target trials using a one-sample *t*-test (two-tailed, $n=10$, $d.f.=9$) including the prefrontal, premotor, insular, inferior parietal, and occipital cortices, and the postcentral gyri. Similar to the target trials, all clusters, except for the left postcentral gyrus, followed the same pattern

such that subjects exhibited greater activity when inhibiting a motor response relative to baseline; whereas the left postcentral gyrus demonstrated decreased activation relative to baseline. Table 3 presents the significant clusters found from directly comparing target to non-target trials using a paired-samples *t*-test (two-tailed, $n=10$, $d.f.=9$, $P \leq 0.01$). Fig. 2 illustrates the statistical parametric maps associated with the significant clusters from this analysis. Results include the regions reported in Tables 1 and 2, such that target trials elicited greater BOLD signal compared to non-target trials in bilateral primary motor cortices, bilateral cerebellum, left thalamus, and left basal ganglia regions.

Table 3

Brain regions demonstrating a significant BOLD difference between non-target and target trials in the 5C-CPT.

Non-target–target trials					
Brain region	Volume	Center mass			Brodmann areas
		Talairach coordinates			
		X	Y	Z	
Non-target > Target					
L Supramarginal gyrus/Angular gyrus	5888 mm ³	43.2 L	57.8 P	35.8 S	39, 40
R Supramarginal gyrus/Angular gyrus	5440 mm ³	44.2 R	52.0 P	41.4 S	39, 40
B Superior frontal gyri	2880 mm ³	1.1 R	30.1 A	47.1 S	8
R Dorsolateral prefrontal cortex	11,712 mm ³	41.3 R	24.9 A	28.4 S	9, 46
L Dorsolateral prefrontal cortex	4992 mm ³	39.5 L	24.2 A	30.9 S	9, 46
Target > Non-target					
L Supramarginal gyrus/Precuneus/Primary motor cortex/Premotor cortex/Postcentral gyrus	28,480 mm ³	31.7 L	29.3 P	54.8 S	1, 2, 3, 4, 6, 7, 40
R Primary motor cortex/Premotor cortex	4736 mm ³	25.3 R	11.8 P	50.1 S	4, 6
B Cerebellum	19,456 mm ³	5.2 R	52.5 P	15.6 I	n/a
L Basal ganglia/Thalamus	4096 mm ³	16.9 L	18.2 P	12.1 S	n/a

Each entry represents a significant cluster of activation. L: left hemisphere; R: right hemisphere; B: bilateral; A: anterior; P: posterior; I: inferior; S: superior. Clusters were found from a paired-sample *t*-test comparing non-target to target trials. The magnitude of the BOLD response from each cluster was significant at a minimum *t*-value of ± 3.25 (two-tailed, $n=10$, $d.f.=9$).

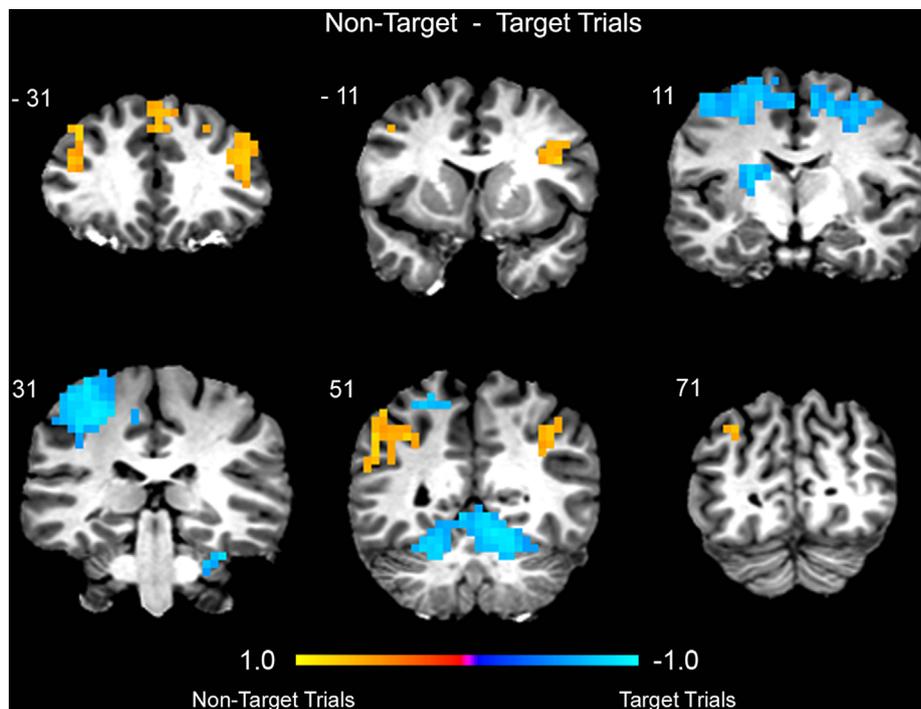


Fig. 2. Clusters of significant BOLD response comparing non-target to target trials. All MRI images are in the coronal plane and in neurological orientation. Numbers correspond to Talairach coordinates in the Y-direction. Statistical parametric maps reflect the effects size η^2 . Warm colors indicate a greater effect in the BOLD signal in non-target relative to target trials whereas cool colors indicate greater effect in the BOLD response in target relative to non-target trials. A negative sign was applied to η^2 values that demonstrated a greater target trial response.

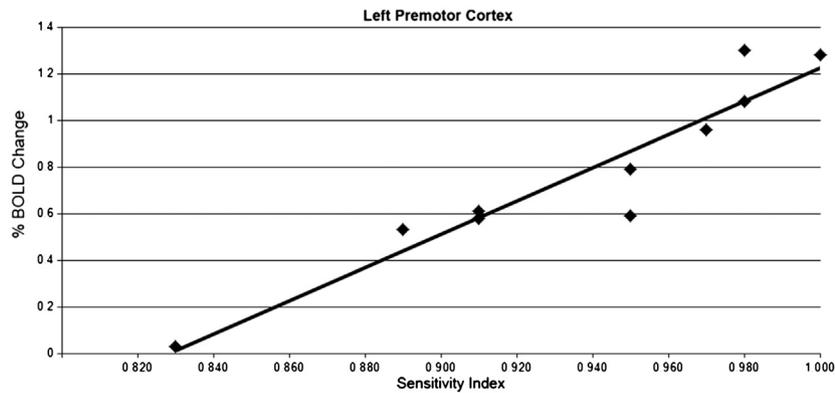


Fig. 3. The relationship between sensitivity index and BOLD signal in the left premotor cortex. Data were derived by correlating participants' sensitivity indices with the BOLD signal within each voxel in a search region and taking the mean signal from the significant cluster of brain response–performance correlation for each participant.

Alternatively, non-target trials elicited greater BOLD signal compared to target trials in bilateral dorsolateral prefrontal, superior frontal, and inferior parietal cortices.

Regression analyses ($n=10$, $d.f.=8$, $P \leq 0.01$) within the significant clusters found from the target trials revealed sub-regions that demonstrated a positive association with the sensitivity index such that those individuals with higher sensitivity indices had a greater BOLD response in bilateral cuneus (left: volume=1344 mm³; peak voxel coordinates= 2L, 69P, 8S; $r^2=0.712$; right: volume=2880 mm³; peak voxel coordinates=10R, 77P, 4S; $r^2=0.787$), right cerebellum (volume=1408 mm³; peak voxel coordinates=6R, 61P, 8I; $r^2=0.760$), and left premotor gyrus (volume=4224 mm³; peak voxel coordinates=32L, 21P, 60S; $r^2=0.865$; see Fig. 3). Within the significant clusters found from non-target trials, a positive association with sensitivity was found in right supramarginal gyrus (volume=704 mm³; peak voxel coordinates=38R, 57P, 48S; $r^2=0.729$).

4. Discussion

Development of analog human and rodent versions of tasks that measure cognitive domains impacted by serious mental illness provides an opportunity to: (1) use multiple tools to investigate the neuroanatomy underlying cognitive deficits in clinical populations including schizophrenia and bipolar disorder; (2) develop sensitive and valid animal models of cognitive impairments in clinical populations; (3) investigate the effects of genetic manipulation on task performance; and (4) improve cross-species translational testing for drug development. However, for such research endeavors to have cross-species translational power, the reliability and validity of the analog tasks must first be established. Since attention and inhibition deficits are frequently observed in serious mental illness and have been linked with everyday impairments of function, we focused on the vigilance domain and developed analog human and rodent versions of a spatial continuous performance task, the 5C-CPT. Within the rodent literature, the 5C-CPT reliably measures vigilance (Barnes et al., 2011, 2012; Young et al., 2009a; Young et al., 2011). Recently, reverse-translational work has demonstrated the validity of the 5C-CPT for measuring behavioral differences between schizophrenia and healthy comparison populations, suggesting this task accurately captures sustained attention and response inhibition deficits within this clinical population (Young et al., submitted for publication). Here, we built upon the validity of the human 5C-CPT by examining the neural correlates of sustained attention and response inhibition within vigilance as measured by this task in healthy individuals. Validation of the 5C-CPT in healthy individuals is important in understanding the

vigilance brain response measured by the task before use in clinical samples.

As predicted, activation patterns during target and non-target trials were highly consistent with previous literature using other types of CPTs and demonstrated differential patterns of brain response. In addition, subregions within these networks were positively correlated with task performance, as measured by the sensitivity index. Sustained attention requires the ability to maintain attention to a particular stimulus or location for prolonged periods of time while ignoring irrelevant stimuli, relying on both attention and arousal neural networks (Coull, 1998; Parasuraman, 1998). Functional neuroimaging studies have identified an amodal attention system in the brain including right dorsal and ventral frontal cortex and inferior parietal lobe (Coull, 1998; Pardo et al., 1991; Paus et al., 1997). These attentional regions are hypothesized to be modulated by arousal regions (predominantly a subcortical network) comprising thalamus, striatum, and anterior cingulate. Maintaining arousal over time is an integral part of maintaining vigilance, and the thalamus in particular is thought to be associated with arousal within attentional tasks (Langner and Eickhoff, 2012). For example, Wu and colleagues found reduced metabolism using positron emission tomography in the thalamus and decreases in vigilance following sleep loss (Wu et al., 1991). As predicted, the 5C-CPT activated the majority of these regions in target trials when compared to baseline trials including the premotor cortex, inferior parietal lobe, and subcortical regions encompassing the basal ganglia and thalamus. The subcortical regions in particular demonstrated a greater effect when directly compared to non-target trials, highlighting a prominent role of these regions in sustained attention processes of the 5C-CPT. Further, bilateral activation was observed within parietal and subcortical regions, as well as activation within the left motor cortex and cerebellum. The latter two are most likely related to hand/arm movements of the joystick during target trials relative to baseline fixation and non-target trials in this CPT. Interestingly, greater activation in the superior frontal lobe during the baseline trials relative to target trials was observed in the present study, which may be accounted for by greater eye movements and/or saccades during baseline, as this region is part of the supplementary eye fields which, along with the frontal and parietal eye fields, control eye movements (Grosbras et al., 1999). Eye movements may play an especially important role in the spatial demands of the 5C-CPT, which requires eye saccades to numerous spatial locations throughout the task. Further investigation into eye movements during the 5C-CPT is warranted.

Response inhibition as measured by the 5C-CPT reflects reactive stopping (cf. proactive stopping) where participants must

inhibit a motor response when instructed by an external signal (Aron, 2011). Studies using stop signal paradigms suggest that sensory information about the stop signal is relayed to the prefrontal cortex (Chambers et al., 2009). Specifically, broadly distributed activity within the right inferior frontal cortex and the dorsomedial frontal cortex (especially the presupplementary motor area within the prefrontal cortex) is critical for response inhibition, though other regions including the premotor cortex and right insular cortex play a role (Hampshire et al., 2010). This “inhibitory network” is likely highly integrated with valuational and mnemonic functions in other areas of the prefrontal cortex including left and right hemisphere orbitofrontal and dorsolateral regions (Aron, 2011), and with inhibitory functions relying upon the inferior parietal cortex (Rubia et al., 2001). Within the correct non-target trials of the 5C-CPT, we observed a similar network of activation where predominantly right hemisphere inferior frontal cortex, insula, premotor cortex, and presupplementary motor area; and bilateral dorsolateral prefrontal and supramarginal gyri were activated when correctly inhibiting a motor response. Specifically, the dorsolateral prefrontal cortex seemed to play a prominent role in inhibiting a response when directly comparing target to non-target trials on the 5C-CPT. Contrary to our hypotheses, we did not observe activation within the anterior cingulate. Considering the relatively short time of each task run (i.e., 5 min), there may not have been enough change in the arousal system to elicit a response from this region. Alternatively, our analyses focused on correct responding in short temporal windows, and so may not have revealed anterior cingulate involvement due to this structure’s role in error processing (Erickson et al., 2004). Interestingly, we observed deactivations within the left postcentral gyrus that may reflect inhibition of the motor response with the right hand in maintaining arm and hand position on the joystick. This observation is consistent with previous studies that have implicated the postcentral gyrus in processing of kinesthetic information in the contralateral hand (Naito and Ehrsson, 2001; Naito et al., 2005).

We did not observe any activation within the occipital lobes when comparing non-target to target trials, suggesting that the visual processing demands are similar between conditions. Indeed, both conditions elicited bilateral occipital region activation when compared to baseline likely related to the visuospatial demands of task trials relative to baseline fixation trials in this CPT with spatially distributed stimuli (given that stimuli in other CPTs appear in a fixed location). Lastly, the inferior parietal lobe was predicted to respond to both conditions as this region is involved in a multitude of cognitive operations. Specifically, the parietal cortex is thought to be important for the disengagement and reengagement of attentional focus (Posner et al., 1984; Robinson et al., 1995; Sarter et al., 2001) and involved in matching to stimulus function (Robinson et al., 1995; Bunge et al., 2002; Broussard et al., 2006). Indeed, activation in the supramarginal gyri was observed in both target and non-target trials supporting the matching role of this region in response to stimulus type. Further, non-target trials elicited significantly greater activation within the supramarginal and angular gyri than target trials. This suggests that, within the 5C-CPT, inferior parietal regions are more involved with sustained attention and inhibiting a prepotent response in non-target trials, perhaps due to a greater cognitive load compared to target trials (which only involve sustained attention processes).

The neural correlates of vigilance observed with the human analog 5C-CPT correspond to the same regions that have been reported in the literature for other types of CPT paradigms, demonstrating construct validity of the task. An advantage to this task is the use of varying locations of stimulus presentations that can improve the ability to localize the source of attentional

networks because of accounting for hemisphere asymmetry when compared with methods using fixed positions (Sylvester et al., 2007), perhaps resulting in bilateral regional activation. Given that the 5C-CPT demonstrates predictable patterns of activation in the neural systems underlying vigilance in healthy humans, future translation studies could examine the neuronal abnormalities in patients with severe mental illness and test pro-cognitive treatments. For example, putative pharmaceutical interventions can be tested in rodent models of psychiatric disorders and in patients using near identical rodent and human 5C-CPT tasks. Indeed, patients with schizophrenia exhibit a heightened vigilance decrement in the 5C-CPT (Young et al., submitted for publication) and vigilance decrements are observed in rodent models of schizophrenia in this task (Barnes et al., 2011, 2012). Current rodent models of schizophrenia have relied on pharmaceutical manipulations (e.g., NMDA receptor antagonists). However, rodent models using transgenic mice with allelic variants of genes implicated in vigilance impairment in mental illness (e.g. COMT gene) could further enable modeling psychiatric disorders. Lastly, manipulations of 5C-CPT parameters, such as time of task or number of target to non-target trials, could facilitate cross-species translational work to examine whether increased task demands have similar effects between species.

A limitation of the present study was the sample size of 10 participants and lack of anterior cingulate activation during the response inhibition condition. Such a small sample may reduce the reliability of the results and possibly obscure activation in task-related brain regions because of low statistical power. Future studies utilizing the 5C-CPT with a longer time on task, analyses comparing correct to incorrect trials, and larger sample sizes would prove beneficial in examining the role of the anterior cingulate in the 5C-CPT. However, despite the relatively small sample size, the neural correlates observed in the present study corresponded with expectations from numerous other CPT studies and suggest that the attentional/inhibitory networks can be robustly measured by the 5C-CPT. Further, we conducted a whole-brain analysis with a conservative threshold to protect Type I error and did not find regions implicated in additional cognitive functions outside those of the task demands, further strengthening the evidence for the use of the 5C-CPT to measure sustained attention and response inhibition separately. Behaviorally, participants performed very well on the task, but not at ceiling levels (e.g., 100 percent). However, ceiling effects cannot be ruled out on the 5C-CPT in normal healthy populations. Nonetheless, the 5C-CPT provides a useful task for use in severe mental illness where poorer behavioral performance would be expected, but floor effects should be avoided. Indeed, no floor effects were found in a behavioral study of patients with schizophrenia (Young et al., submitted for publication). Additionally, even in light of a small sample size and limited variance in behavioral performance, we found that the individuals with better performance on the sensitivity index exhibited greater activation within subregions of those found in the main analyses, providing additional construct validity.

In summary, results from human and animal studies using nearly identical tasks will be able to inform each other, leading to more powerful investigations of the biological basis of deficits in vigilance processes involving sustained attention and inhibitory processing. Such investigations can generate novel treatment targets for patient populations with deficits in these cognitive domains. Here, we demonstrate that a reverse-translated human analog of the rodent 5C-CPT measures sustained attention and response inhibition separately within a single task paradigm of vigilance by measuring the neural correlates of these functions with fMRI. Future work is needed to further establish the validity and reliability of the 5C-CPT in both human and rodent populations.

Preliminary evidence supports this paradigm as providing a powerful methodology to conduct cross-species work in drug discovery for pro-cognitive treatments of patient populations, such as schizophrenia and bipolar disorder.

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References

- Alloy, L.B., Abramson, L.Y., Walshaw, P.D., Keyser, J., Gerstein, R.K., 2006. A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Development and Psychopathology* 18, 1055–1103.
- Aron, A.R., 2011. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biological Psychiatry* 69, e55–e68.
- Barnes, S.A., Young, J.W., Neill, J.C., 2011. D(1) receptor activation improves vigilance in rats as measured by the 5-choice continuous performance test. *Psychopharmacology (Berl)* 220, 129–141.
- Barnes, S.A., Young, J.W., Neill, J.C., 2012. Rats tested after a washout period from sub-chronic PCP administration exhibited impaired performance in the 5-Choice Continuous Performance Test (5C-CPT) when the attentional load was increased. *Neuropharmacology* 62, 1431–1441.
- Bearden, C.E., Woogen, M., Glahn, D.C., 2010. Neurocognitive and neuroimaging predictors of clinical outcome in bipolar disorder. *Current Psychiatry Reports* 12, 499–504.
- Birkett, P., Sigmundsson, T., Sharma, T., Touloupoulou, T., Griffiths, T., Reveley, A., 2007. Reaction time and sustained attention in schizophrenia and its genetic predisposition. *Schizophrenia Research* 95, 76–85.
- Bora, E., Vahip, S., Akdeniz, F., 2006. Sustained attention deficits in manic and euthymic patients with bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 30, 1097–1102.
- Borgaro, S., Pogge, D.L., DeLuca, V.A., Bilginer, L., Stokes, J., Harvey, P.D., 2003. Convergence of different versions of the continuous performance test: clinical and scientific implications. *Journal of Clinical and Experimental Neuropsychology* 25, 283–292.
- Broussard, J., Sarter, M., Givens, B., 2006. Neuronal correlates of signal detection in the posterior parietal cortex of rats performing a sustained attention task. *Neuroscience* 143, 407–417.
- Bunge, S.A., Hazeltine, E., Scanlon, M.D., Rosen, A.C., Gabrieli, J.D., 2002. Dissociable contributions of prefrontal and parietal cortices to response selection. *Neuroimage* 17, 1562–1571.
- Carter, C.S., Barch, D.M., 2007. Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophrenia Bulletin* 33, 1131–1137.
- Chambers, C.D., Garavan, H., Bellgrove, M.A., 2009. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience and Biobehavioral Reviews* 33, 631–646.
- Clark, L., Goodwin, G.M., 2004. State- and trait-related deficits in sustained attention in bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience* 254, 61–68.
- Coull, J.T., 1998. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging, and psychopharmacology. *Progress in Neurobiology* 55, 343–361.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research* 29, 162–173.
- Demeter, E., Sarter, M., Lustig, C., 2008. Rats and humans paying attention: cross-species task development for translational research. *Neuropsychology* 22, 787–799.
- Erickson, K.I., Milham, M.P., Colcombe, S.J., Kramer, A.F., Banich, M.T., Webb, A., Cohen, N.J., 2004. Behavioral conflict, anterior cingulate cortex, and experiment duration: implications of diverging data. *Human Brain Mapping* 21, 98–107.
- Fleck, D.E., Sax, K.W., Strakowski, S.M., 2001. Reaction time measures of sustained attention differentiate bipolar disorders from schizophrenia. *Schizophrenia Research* 52, 251–259.
- Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., Noll, D.C., 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine* 33, 636–647.
- Frey, P.W., Colliver, J.A., 1973. Sensitivity and responsibility measures for discrimination learning. *Learning and Motivation* 4, 327–342.
- Green, M.F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry* 67, e12.
- Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophrenia Bulletin* 26, 119–136.
- Grosbras, M.H., Lobel, E., Van de Moortele, P.F., LeBihan, D., Berthoz, A., 1999. An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cerebral Cortex* 9, 705–711.
- Hampshire, A., Chamberlain, S.R., Monti, M.M., Duncan, J., Owen, A.M., 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* 50, 1313–1319.
- Harmer, C.J., Clark, L., Grayson, L., Goodwin, G.M., 2002. Sustained attention deficit in bipolar disorder is not a working memory impairment in disguise. *Neuropsychologia* 40, 1586–1590.
- Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S.E., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 2: co-norming and standardization. *American Journal of Psychiatry* 165, 214–220.
- Ko, S.Y., Chen, P.S., Yang, Y.K., Liao, Y.C., Lee, Y.D., Yeh, T.L., Yang, M.J., 2003. Correlation between performance on the continuous performance test and economic costs in patients with schizophrenia. *Psychiatry and Clinical Neurosciences* 57, 373–377.
- Langner, R., Eickhoff, S.B., 2012. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*. Electronic publication, 19 November; <http://dx.doi.org/10.1037/a0030694>.
- Liu, S.K., Chiu, C.H., Chang, C.J., Hwang, T.J., Hwu, H.G., Chen, W.J., 2002. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state dependent markers. *American Journal of Psychiatry* 159, 975–982.
- Liu, S., Hsieh, M., Hwang, T., Hwu, H., Liao, S., Lin, S., 2006. Re-examining sustained attention deficits as vulnerability indicators for schizophrenia: stability in the long term course. *Journal of Psychiatric Research* 40, 613–621.
- Marston, H.M., 1996. Analysis of cognitive function in animals, the value of SDT. *Cognitive Brain Research* 3, 269–277.
- Morris, R., Evenden, J., Sahakian, B., Robbins, T., 1987. Computer aided assessment of dementia: comparative studies of neuropsychological deficits in Alzheimer's type dementia and Parkinson's disease. In: Stahl, S., Iversen, S., Goodman, E. (Eds.), *Cognitive Neurochemistry*. Oxford University Press, Oxford.
- Naito, E., Ehrsson, H.H., 2001. Kinesthetic illusion of wrist movement activates motor-related areas. *Neuroreport* 12, 3805–3809.
- Naito, E., Roland, P.E., Grefkes, C., Choi, H.J., Eickhoff, S., Geyer, S., Zilles, K., Ehrsson, H.H., 2005. Dominance of the right hemisphere and role of area 2 in human kinesthesia. *Journal of Neurophysiology* 93, 1020–1034.
- Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D., Cohen, J., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *American Journal of Psychiatry* 165, 203–213.
- Parasuraman, R., 1998. *The Attentive Brain*. MIT Press, Cambridge, MA.
- Pardo, J.V., Fox, P.T., Raichle, M.E., 1991. Localization of a human system for sustained attention by positron emission tomography. *Nature* 349, 61–64.
- Paus, T., Zatorre, R.J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., Evans, A.C., 1997. Time-related changes in neural systems underlying attention and arousal during performance of an auditory vigilance task. *Journal of Cognitive Neuroscience* 9, 392–408.
- Posner, M.I., Walker, J.A., Friedrich, F.J., Rafal, R.D., 1984. Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience* 4, 1863–1874.
- Riccio, C.A., Reynolds, C.R., Lowe, P., Moore, J.J., 2002. The continuous performance test: a window on the neural substrates for attention. *Archives of Clinical Neuropsychology* 17, 235–272.
- Robinson, D.L., Bowman, E.M., Kertzman, C., 1995. Covert orienting of attention in macaques II. Contributions of parietal cortex. *Journal of Neurophysiology* 74, 698–712.
- Rubia, K., Russell, T., Overmeyer, S., Brammer, M.J., Bullmore, E.T., Sharma, T., Simmons, A., Williams, S.C.R., Giampietro, V., Andrew, C., Taylor, E., 2001.

- Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage* 13, 250–261.
- Saad, Z.S., Glen, D.R., Chen, G., Beauchamp, M.S., Desai, R., Cox, R.W., 2009. A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage* 44, 839–848.
- Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Research Reviews* 35, 146–160.
- Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23 (S1), 208–219.
- Swann, A.C., Pazzaglia, P., Nicholls, A., Dougherty, D.M., Moeller, F.G., 2003. Impulsivity and phase of illness in bipolar disorder. *Journal of Affective Disorders* 73, 105–111.
- Sylvester, C.M., Shulman, G.L., Jack, A.I., Corbetta, M., 2007. Asymmetry of anticipatory activity in visual cortex predicts the locus of attention and perception. *Journal of Neuroscience* 26, 14424–14433.
- Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain. Thieme Medical, New York.
- Wu, J.C., Gillin, J.C., Buchsbaum, M.S., Hershey, T., Hazlett, E., Sicotte, N., Bunney Jr., W.E., 1991. The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep* 14, 155–162.
- Young, J.W., Light, G.A., Marston, H.M., Sharp, R., Geyer, M.A., 2009a. The 5-choice continuous performance test: evidence for a translational test of vigilance for mice. *PLoS One* 4, e4227.
- Young, J.W., Powell, S.B., Risbrough, V., Marston, H.M., Geyer, M.A., 2009b. Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. *Pharmacology and Therapeutics* 122, 150–202.
- Young, J.W., Geyer, M.A., Rissling, A.J., Eyster, L.T., Asgaard, G.L., Light, G.A., Impaired vigilance but not accuracy of patients with schizophrenia in a human version of the rodent 5-choice continuous performance test. Submitted for publication.
- Young, J.W., Powell, S.B., Scott, C.N., Zhou, X., Geyer, M.A., 2011. The effect of reduced dopamine D4 receptor expression in the 5-choice continuous performance task: separating response inhibition from premature responding. *Behavioural Brain Research* 222, 183–192.