Prefrontal cortex activation mediates cognitive reserve, alertness and attention in the Virtual Classroom: preliminary fMRI findings and clinical implications

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Abstract- **The Virtual Classroom is an interactive virtual reality simulation of a classroom-learning task, allowing continuous performance assessment in the context of sleep and attention research. Audiovisual distractions can be incrementally manipulated to assess cognitive workload and performance vigilance. In this feasibility study, we sought to establish a neuroimaging correlate of previous pilot work using the Virtual Classroom paradigm to study performance decrements in alertness and sustained attention. We hypothesized a thalamocortical (TLC) network subserving alertness, primarily mediated by activation of prefrontal cortex under differing distraction levels. In a block design of alternating 1-minute blocks of high and low visual distraction during the Go-No-Go task embedded in the Virtual Classroom program we studied a single healthy adult subject, with whole brain analysis used to assess regional activations.**

Differential activation between low and high distraction load conditions was noted while performing the task. Specific regions displaying increased activation during high distraction included bilateral frontal polar cortex and prefrontal cortex (PFC). Differential bilateral Area-V5 activation was also noted during "high distraction" condition due to increased visual monitoring of distracters. The implies a probable neural mechanism of action for this and other "virtual" tasks requiring effortful cognition and vigilance which involves prefrontal cortex activation. Given the numerous CNS psychopathologies involving PFC dysregulation, this implies that the Virtual Classroom task may be useful as a "broad-spectrum" assessment tool of frontal lobe function.

Manuscript received April 15, 2007. Revised manuscript received June 23, 2007

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I. Introduction

A. *Alertness and attention: Clinical relevance and related neural networks*

The concept of cognitive reserve while engaging in task performance is of broad-spectrum relevance to treatment of neuropsychiatric disease [1], and of probable relevance to virtual reality (VR)- based rehabilitation. Alertness and attention as markers of neurocognitive dysfunction have been researched intensively in a number of neuropsychiatric paradigms involving functional MRI (fMRI) [2-4]. Alertness can be separated into two categories: tonic/intrinsic alertness and phasic alertness [5-10]. While both of these relate to task-specific response capacity, the former describes the monitoring of a task, while the latter relates to the preparation to appropriatel y and selectively respond to a cue embedded in the task [5]. The phenomenon of "alertness" has also been described as "vigilance" and "sustained attention", and has been linked to more general mental phenomena such as working memory and cognitive processing/ performance [11;12].

As with other biological systems, attention has a distinct anatomy that carries out basic psychological functions. Disparate attentional networks correlate with discrete neural circuitry and can be influenced by specific brain injuries, states, and drugs. Dysregulation of frontal and prefrontal lobe function have been described as anatomical models for cognitive dysfunction in narcolepsy [13], stroke [14], dementia [15;16], mood disorders [17;18] and schizophrenia [4;17;19] as well as attention deficit hyperactivity disorder (ADHD)[2;20]. A clinical commonality of many of these disorders includes chronic sleep disturbance; thus it is noteworthy that in both experimental models of sleep deprivation [21;22] and clinical studies of subjects with chronic sleep disturbances such as obstructive sleep apnea [23;24] or even chronic insomnia [25], a "relative hypofrontality" during effortful cognition has been noted. Executive functions such as sustained attention [11;26], set-shifting [27;28], working memory [29-31] and response inhibition [20;32-37] have also been attributed to frontal lobe function, (particularly prefrontal cortex (PFC)) and to a lesser degree, anterior cingulate cortex (ACC) and striatum [38-40].

Impairment in alertness and selective attention has been associated with a PFC deficit in behavioural and fMRI models [32;41;42] and is a well-known clinical entity in stroke neglect syndrome involving the right hemisphere (RH) [43;44]. Executive functions such as sustained attention [45], working memory [29;46] and inhibition [47] have also been attributed to the RH TLC, particularly RH PFC and ACC [32;38-41;48-51]. Thus it is believed that intact RH frontal cortex, in particular PFC is necessary for phasic alertness as well as selective attention, but additional homologous LH structures appear to be co-involved, particularly as task demand/complexity is increased [46].

In summary, fMRI research to date points towards a distinct neural network subserving alertness, consisting of tonic and phasic components. Tonic alertness appears primarily associated with a RH thalamo-frontal network that widens and expands to homologous LH structures in phasic states relating to cued stimulus response. The study of alertness networks in an fMRI model using interactive tasks of varying complexity that relate to "real-world" function would increase clinical relevance of these theoretical constructs of alertness, and allow for an integrated model of cognitive reserve.

B. *Simulation development background and related studies*

In order to investigate the feasibility of activating neural networks relating to alertness and attention in a combined fMRI/VR paradigm, the Virtual Classroom (Digital Media Works, Kanata, Ont, Canada, see Figure 1) was employed [52]. This program evolved from research at University of Southern California in 1999 intended to evaluate and potentially rehabilitate deficits in the human attention process via more naturalistic and ecologically valid paradigm than standard "pencil-and paper" checklists and neuropsychological testing procedures. As originally described [32], the classroom is a modified continuous performance assessment within a virtual environment simulating an interactive classroom-learning task. Visual and auditory distracting events affecting attentional focus (e.g. ambient classroom noise, student in next seat moving, fidgeting or coughing, car driving by window, PA system, etc.) can be introduced from a list of available distractions. Rizzo et al performed a pilot study [32] of eight age-matched male pediatric ADHD patients with ten healthy controls in the Virtual Classroom under two conditions: one with standardized audiovisual distractions, and one without distractions. ADHD patients showed a slower reaction time (distraction condition), higher reaction time variability (both conditions) and higher errors of omission and commission (both conditions).

As it is known that sleep disturbance can significantly affect alertness [23;53], our group recently examined the effect of sleep deprivation on performance of the Virtual Classroom in a small comparative study of 12 healthy young adults [54]: four with total sleep deprivation, four with partial sleep deprivation, and four with eight hours of sleep.

Figure 1: Screenshot of Virtual Classroom simulation

In this study, no significant reaction time differences were noted, although a trend was noted of shorter reaction time in the "total sleep deprivation" group. This group was noted to have a significantly higher rate of errors of commission, but not omission (p-.059). This was interpreted to imply an "overarousal" state in the sleep deprivation group: subjects were more prone to inappropriately and impulsively react to non-target stimuli. In this model of cognitive performance related to sleep pathology, processing speed (RT) is traded off at the expense of response accuracy.

One emerging pathophysiologic model of deficits in attention and alertness consists of disturbances in restorative sleep which would normally facilitate processes such as learning and filtering of sensory inputs. This is consistent with current conceptualization of insomnia as a "24-hour" syndrome, which includes the feature of inappropriate nocturnal hyperactivation of frontal regions, and consequent hypofrontality during daytime function [25;55]. Disruptions in neural networks connecting midbrain and thalamic structures to top-down control from frontal cortex have been reported as a consequence of chronic sleep disturbance [33, 34], although most fMRI tasks do not show significant "real-world" relevance to patient-related activities of daily living.

II. NETWORK ACTIVATION PATTERN UNDER DIFFERING LEVELS OF VISUAL DISTRACTION

A. *Experimental design & methodology*

In the present feasibility study, we sought to establish a fMRI neuroimaging correlate of the performance decrements in alertness and attention described above, using the Virtual Classroom. We hypothesized a thalamocortical network subserving alertness and sustained attention, primarily mediated by activation of prefrontal cortex under differing visual distraction levels. Due to scanner noise inherent to the fMRI environment (up to 100 dB), auditory distractions contained in the program were not included in the experimental design.

The study was conducted on a 3Tesla fMRI system (parallel imaging, 8-channel head coil, EPI gradient echopulse sequence, 128x128 matrix, ~ 30x 4mm thick contiguous slices.) at Toronto Western Hospital, University of University Health Network. The VR simulation was run off a Dell Inspiron 8200 Laptop, with clone-monitor display showing the classroom scene on a 2-dimensional LCD screen placed at the head of the fMRI coil and viewed through a mirror placed directly in front of the subject's eyes.

A single healthy subject (F, 40) performed the task in the fMRI scanner, with alternating 1-minute blocks of high- and low-distraction (see Figure 2). Distracters consisted of "naturalistic" events such as a paper airplane flying past the field of view, a student in an adjacent seat moving, a car driving by the window, etc., and were increased in frequency and intensity by the experimenter during "high-distraction" blocks. Stimuli presented to the subject consisted of a letter sequence requiring selective response accuracy and speed; stimulus duration was 150 ms, and interstimulus duration was 1350 ms. The letter sequence consisting of a "K" following an "A" was used as the "Go" task, with all other sequences, including other letters following "A" used as "No-Go" tasks, requiring the subject to inhibit a response. General linear model (GLM) whole brain analysis was performed using AFNI for the "high distraction" versus "low distraction" conditions.

Correlations were drawn on a voxel per voxel basis of MRI signal and block waveform. For the purpose of this feasibility study, data differentiating "high" versus "low" distraction states was thresholded with an r-value of 0.3 and 10-voxel cluster (p=0.05).

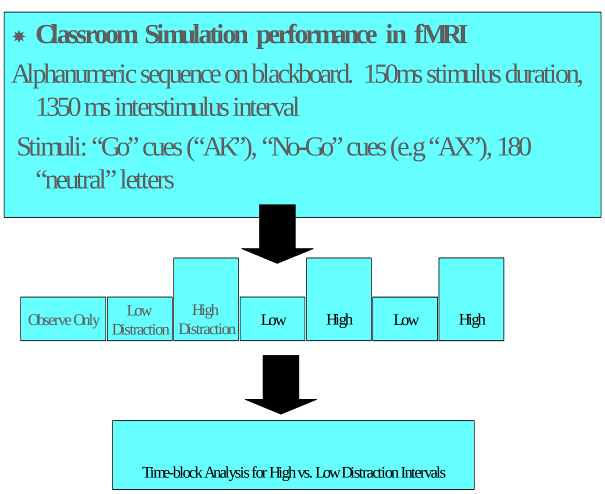

Figure 2: Effect of visual distracters on alertness and effortful cognition: fMRI protocol for "High" vs. "Low" distraction conditions in virtual classroom

B. Results

As shown in Figure 3, we noted differential neural network activation between "low" and "high" distraction load conditions while performing the classroom task. Specific regions displaying increased activation during high distraction included bilateral frontal polar cortex and medial prefrontal cortex. Differential bilateral Area-V5 activation was also noted during "high distraction" condition; this was presumably due to increased visual monitoring of motion of distracting stimuli [56] and demonstrates the ability of the simulation to activate stimulus-relevant networks.

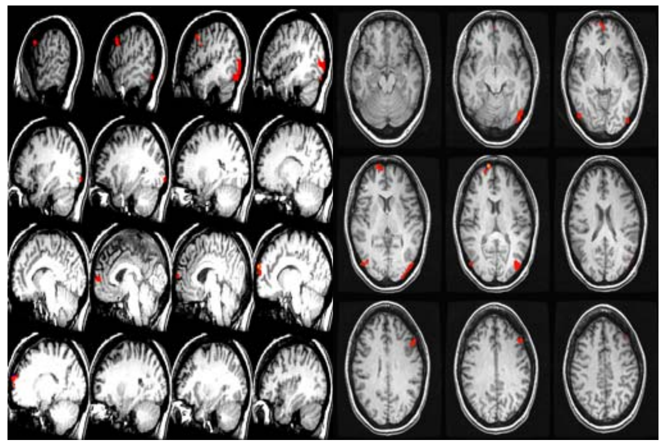

Figure 3: Differential neural network activation during Virtual Classroom task under differing distraction loads (AFNI, whole brain analysis, 10 voxel cluster threshold, r = .3) Increased activation of bilateralArea V5/MT, frontal polar and medial PFC during "high distraction" condition.

III- DISCUSSION

The Virtual Classroom shows promise as a measure of cognitive reserve for protocols related to sleep and vigilance in a wide array of neuropsychiatric disorders, affecting frontal lobe function. While our findings are preliminary and based on a single subject, this paper describes proof of concept of a specific simulation/imaging protocol using this program. Based on demonstrated feasibility of hypothesized network activation, further fMRI studies in clinical groups with disorders of alertness and attention are planned.

We are looking to replicate this work on groups of clinically homogeneous subject groups, with implementation of Bonferroni or other correction methods. Demonstrating PFC activation using an immersive VR task is significant within the context of potential for assessment, and ultimately rehabilitation of cognitive deficits involving the frontal cortex. A limitation of using an fMRI paradigm to assess the neural network activation is the ambient noise of the scanner environment, as this makes the assessment of auditory attention and alertness tasks embedded in a VR task methodologically difficult. For further studies, we will employ shielded goggles allowing for expanded field of view; as discussed by Hoffman et al [57;58], an image delivery system optimized for immersive simulation significantly enhance presence, although system cost remains prohibitive at present for most centres.

Functional imaging in combination with selected virtual neurocognitive testing offers an elegant methodology to study the cerebral blood flow associated with tasks challenging cognitive workload. Beyond the study of healthy subjects under different levels of distraction and effortful cognition, we now seek to examine clinical groups with structural lesions in circuits affecting prefrontal function (e.g. acquired brain injury due to stroke) and functional lesions (chronic sleep disturbance), each mediating disturbances in alertness and attention. Future studies will also aim to obtain a multimodal measure of cognitive reserve (i.e. fMRI-measured network activation, with corresponding real-time simulation performance) as this will also allow for inferences to be made about regional brain activations in relation to impulsive errors and/or omissions. The attractiveness of this VR as a cognitive rehabilitation strategy lies in its potential to enact adaptive neuroplasticity [59;60]. In this model, by allowing alternative "corrective" neural network activation early in a disease process, appropriate circuits may be activated more selectively than through pharmacotherapy, which does not take into account human-environment interaction, or standard cognitive exercises which are difficult to standardize, make salient to the patient, and track in terms of effectiveness.

While this simulation appears to demonstrate ideal ecological validity for a pediatric population, where school performance is a primary endpoint of clinical interest, for older age-groups, other ergonomic environments specific to work-related environments are desirable, although the final common pathway of target neural network activation remains frontal lobe function. Other populations with demonstrated functional hypofrontality such a patients with schizophrenia, major depression or dementia may also be target populations for a simulation task geared at activation of thalamocortical network circuits. However, as with the design of the Virtual Classroom task, thought must be put into the design of ecologically relevant environments that are relevant to instrumental actitvities of daily living, such as management tasks related to work, personal finance, self-care or social competency.

ACKNOWLEDGEMENT

The authors acknowledge Digital Media Works (Kanata, Ontario, Canada) for software development of the Virtual Classroom program and Keri Taylor (PhD candidate, University of Toronto) for assistance with data analysis.

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