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Cortical activity and network organization underlying physical and cognitive exertion in active young adult athletes: Implications for concussion

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ABSTRACT

Objectives: To examine the neurophysiological correlates and brain network organization underlying physical and cognitive exertion in active young adults.
Design: Repeated measures.
Methods: Thirteen healthy adults completed three exertion tasks in a counterbalanced order: a graded working memory task (anti-saccade and serial addition task (ASAT)), a graded exercise task (cycling on a stationary bicycle) (EX) and a combined graded working memory and exercise task (ASAT + EX). All three tasks were performed under five levels of increasing difficulty. Continuous EEG was recorded in each session. Heart rate, perceived exertion and accuracy on the working memory task were recorded throughout. Power spectrum analysis and graph theoretical analysis was applied to the EEG data.
Results: Heart rate and perceived exertion increased with exercise load and in both the EX only and ASAT + EX tasks. Overall accuracy was equally high for the ASAT and ASAT + EX tasks. Analysis of EEG data showed there was an increase in theta power associated with the ASAT + EX task and increase in functional connectivity in the frontal regions of the brain compared with ASAT only task. Accuracy decreased in the last two blocks when the task was most difficult. This decrease in accuracy was associated with a decrease in theta power and a decrease in functional connectivity.
Conclusions: Combined physical and mental exertion results in significant changes in perceived exertion, EEG theta power and network organization in healthy adults and will be valuable in revealing residual neurocognitive deficits after sports related concussion.

1. Introduction

Canadians between the ages of 15 and 34 years have the highest participation in sports and are at a greater risk of sport-related concussion.[1] After an initial concussion, there is an increased risk for repeat concussions, with prolonged recovery.[2] To prevent premature return to play, current expert consensus guidelines advise that athletes who sustain a concussion should gradually progress through a stepwise return to sport, beginning with light aerobic exercise.[3] Athletes who experience re-emergence of symptoms are returned to the previous stage until their symptoms subside again. This focus on subjective symptom reporting can be problematic as athletes can be asymptomatic at rest but have a re-emergence of symptoms following both physical and mental exertion. Microstructural and functional brain abnormalities persist after an athlete is asymptomatic.[4]

In order to help inform return to play decisions, standardized provocative exercise protocols have been developed for children[5] and adults.[6] They involve asking the athlete about worsening symptoms during a graded physical exertion. There are several fundamental problems with this approach. Foremost, it relies on subjective symptoms despite strong evidence that symptom reporting is affected by factors such as mood and motivation,[7] and can normalize before objective biomarkers such as electroencephalography (EEG). Second, using provocative aerobic exercise to determine whether an athlete is recovered is based on the

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assumption that cardiovascular challenge is the sole mechanism for exertion intolerance. Mental exertion (e.g., sustained concentration) can also elicit post concussion symptoms.[8] However, simple cognitive tasks have repeatedly demonstrated an inability to detect impairment beyond the acute phase of recovery from concussion.[9] We therefore chose the Anti-Saccade and Serial Addition Task (ASAT) to probe mental exertion. The ASAT is a more complex cognitive task that blends two behavioural tasks, the Paced Serial Auditory Test (PASAT)[10] and antisaccade test.[11] Each individual task shows relative sensitivity to the lingering effects of concussion[12,13] and we hypothesized that using the combined task would improve the sensitivity of either task used alone. Our aim was to combine physical and mental exertion into a more appropriate provocation test that closely resembles sport participation[14,15] and is capable of exposing residual neurobehavioral deficits after sports related concussion. In addition to traditional measures of performance and EEG metrics, we used a network perspective to understand how the underlying organization of the brain is altered under these different tasks.

In recent years graph theory has emerged as promising tool for understanding the brain using a network perspective.[16,17] Brain networks consist of spatially distributed brain regions that are functionally connected and the functional interactions between both local and distant brain regions can be evaluated using functional connectivity. Functional connectivity refers to the statistical interdependencies between time series recorded from different brain regions.[18] Using this approach, the brain is characterized as a network that contains nodes and edges. Nodes represent the different brain regions and edges represent the connecting pathways between those regions.[19] The relationship between nodes and edges provides information about the functional organization and efficiency of the network.[19] Information processing is proposed to be optimal in "small-world" networks that achieve a balance local specialization and global integration.[20]

The objective of this paper is to examine the association between EEG power and brain network organization and the relationship with performance during the following conditions: cognitive loading only (ASAT only), physical loading only (EX only) and combined physical and cognitive loading (ASAT + EX) in healthy athletes. Given the increased demands involved in the ASAT + EX task we hypothesize that: (a) overall accuracy will be lowest for the combined ASAT + EX task, (b) increased cognitive load will result in increased EEG power in both ASAT only and ASAT + EX tasks and (c) only the ASAT + EX task will be associated with changes in local functional connectivity measures (i.e. degree, clustering coefficient, betweenness) within the frontal regions of the brain.

2. Methods

Thirteen healthy right-handed volunteers participated in this study (22.5 ± 0.65 years/5 females). All denied a history of prior concussion or head injury, history of drug or alcohol abuse and diagnosis of learning disability or other neurological disorders. The Godin Leisure Questionnaire was used to ensure all individuals were moderately active with a score of greater than 14, as familiarity with exercise and fitness level is known to influence the effect of exercise on cortical activity.[21] The study was approved by the University of British Columbia's Clinical Research Ethics Board (H15-02714). All participants independently provided written and verbal informed consent, in accordance with the principles outlined by the Declaration of Helsinki.

In a repeated measures design, participants were asked to come to the laboratory on three (3) different days within a 7-day period, at the same time of day, in order to account for the effect of circadian rhythm on cognition. On the testing days the participants performed one of the three tasks: Anti-Saccade and Serial Addition Task (ASAT), EX or ASAT + EX task. The order in which the participants performed each of the three tasks was randomized to account for order effects.

During the first visit, physical activity level was quantified using the Recent Physical Activity Questionnaire (RPAQ).[22] The participant then completed the ASAT task training. The total learning period took 30 min. Following the task training, the EEG cap was placed on the participants' head, after which they were instructed to sit still with eyes closed while 5 min of baseline EEG was recorded.

The study procedure was composed of the three testing conditions. After the EEG cap was placed on the head, each participant was instructed to sit on a stationary bicycle (Zhejiang Everbright Industry, Inc, Taichung City, Taiwan). The participants were then instructed to complete one of the three (3) task conditions.

The ASAT began with a fixation point in the middle of the screen, followed by a distractor stimulus (red dot) shown for 100 ms at a fixed distance to the left or right of the center (in random sequence). In the opposite direction to the distractor stimulus, the target stimulus (single digit) was presented for 200 ms (Fig. 1-top).

The task required the participant to mentally track and verbally add the sequentially presented digits. The participants also had to ignore the distractor stimulus, or else they would miss the target stimulus as a result of the time cost attributed to the erroneous pro-saccade. The ASAT was presented with E-Prime (E-Prime 2.0, Psychology Software Tools). The task consisted of 5 blocks. "Block" refers to a discrete portion of the task (time epoch) in which the task difficulty was held constant. The blocks increased in difficulty from Block 1 to Block 5. Difficulty was changed by increasing the stimulus offset on the horizontal plane (making saccadic errors more costly) and shortening the inter-stimulus interval (enhancing processing speed demands). Participants were instructed to respond verbally following each stimulus.

A Polar Heart rate monitor band (Polar Electro, Oy, Kempele, Finland) was used to measure heart rate. The participant was asked to sit quietly for 5 min to record their resting HR. Using age, the max HR was calculated using Eq. (1). Their target HR was then calculated using Eq. (2).

$$HR_{Max} = 208 - 0.7 \times Age \tag{1}$$

$$TR_{HR} = (HR_{Max} - HR_{Rest}) \times \% + HR_{Rest} \tag{2}$$

The exercise task was divided into 5 separate blocks of increasing intensity. Participants were asked to begin biking at 30% of their heart rate reserve. The research coordinator monitored the participant's heart rate and modulated the intensity of the exercise appropriately by increasing or decreasing the resistance. The participant was asked to maintain a steady RPM of 60 throughout the task. Once a steady state HR was obtained, the participant continued for 5 min. After 5 min the experimenter increased the resistance on the bike to increase the participant's heart rate — first to 40% and then to 50%, 60% and finally 70%. Steady state HR was defined as within ±5 beats per minute and was constantly monitored by the research administrator to ensure compliance and adjust the necessary settings.

During the last 30 s of each exercise block the participants were shown a Borg intensity scale and asked to rate their perceived exertion using the scale. Following the final exercise block, the participants were instructed to cool down for 5 min.

For the combined physical and cognitive exertion (ASAT + EX) task participants followed the same procedure as described in the conditions above. ASAT difficulty and exercise intensity were increased simultaneously. Participants were not explicitly instructed to prioritize one task over the other; however, participants were instructed to maintain their pedaling cadence during

Fig.1

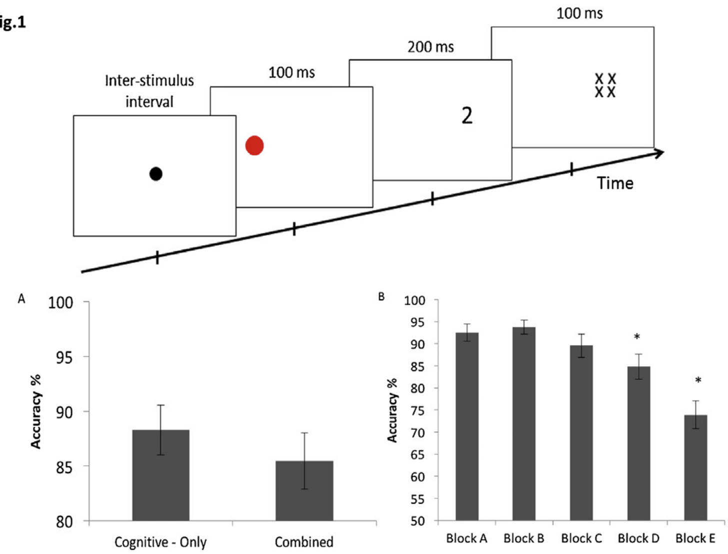


Fig.2

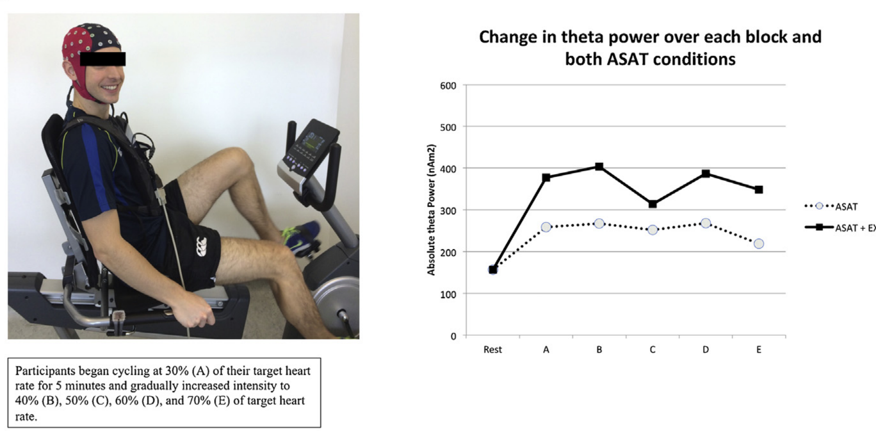
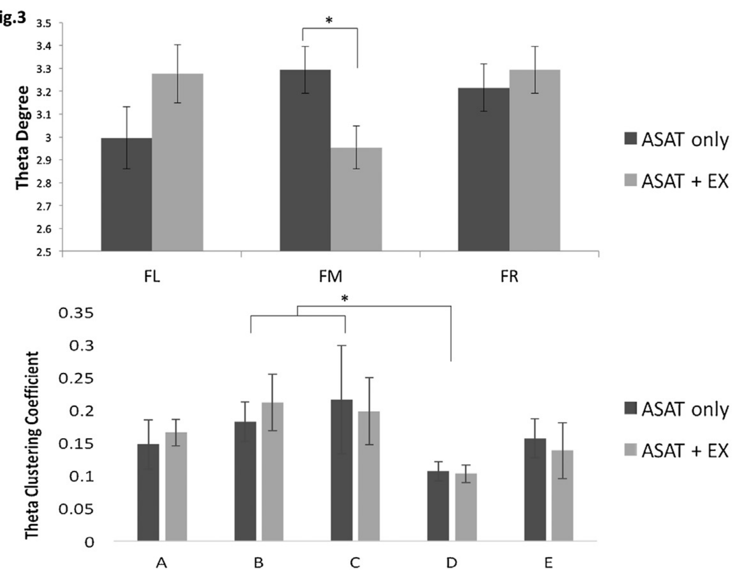


Fig.3



Figs. 1–3. Anti-Saccade and Serial Addition Task (ASAT) display example (Top) and task accuracy (Bottom).

the physical exertion task. The specific instructions to the participants were: "*try to do your best on the mental math task while maintaining your pedaling speed*." No minimum performance criterion was set for the ASAT.

EEG data was recorded using a 32 channels EEG ASAlab system with Waveguard Technology cap (Advanced Neuro Technology, Enschede, Netherlands). EEG data was continuously recorded using a 500 Hz sampling frequency. The ground electrode (AFz) and common average reference was positioned between Fpz and Fz to ensure low impedance values (<5 kΩ). The 32 electrodes were distributed along the scalp according to the 10/5 system.[23] The cap was fixed with a chinstrap to prevent shifting during the exercise trials and was permeable to air in order to prevent an increase in heat during exercise. Each electrode was filled with OneStep EEG-Gel (H + H Medizinprodukte GbR, Münster, Germany) for improved signal transduction. To ensure consistent cap placement, the vertex (Cz) electrode was placed midway between ears, and midway between the nasion and inion.

The EEG data was imported into Brain Electrical Source Analysis® Research (BESA) for analysis (Version 6.1 MEGIS Software GmbH, Graefelfing, Germany). The EEG signals were first filtered using a band-pass filter (4–50 Hz) and a notch filter (60 Hz) to remove signal drift, line noise and motion artifacts. Independent Component Analysis (ICA) was used to decompose the signal and identify eye blinks, which were removed from analysis, as were channels with excessive noise. An automated artifact scan was performed to check signal for noise. Trials in which the participant responded incorrectly were removed from further analysis (n = 131.1, % = 32.5). The data from the accurate trials for each task and block were averaged using 1.24 s epoch (−0.24–1000 ms). A 10–10 average virtual montage was applied to the data, resulting in 27 channels. This data was then exported into MATLAB (Version R2013b, The Mathworks, Inc., Natick, MA, USA).

Fast Fourier Transforms (FFT) was then applied to EEG signal, which transforms the data from the time domain to the frequency domain. Power was calculated at the following frequency bands: theta (4–8 Hz), low alpha (8–10 Hz), high alpha (10–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz).

We used the Brain Connectivity Toolbox[17] in Matlab (Natick, MA) to carry out the graph theoretical based analysis. We used traditional global graph theoretical calculations to characterize different features of the network of interest such as density, global efficiency, clustering coefficient, and modularity. Density (cost) is determined by the ratio of the present connections to all possible connections. Modularity of the network is used to measure the degree to which the network tends to divide into modules or subunit within the network and reflects the stability of sub-networks within the global network.[16] Clustering coefficient is used to measure the overall clustering levels in the network.[16]

We constructed the brain functional connectivity networks using the EEG signals and an error-rate controlled network learning algorithm. This was used to perform the graph theoretical analysis. Surface EEG signals that were transformed into 27 channels were used to construct the brain connectivity networks with each channel representing one brain region in the network. The connectivity network graphs were then computed for each individual subject using false discovery rate controlled PC (PCFDR) algorithm, which is a statistical model that tests the conditional dependence/independence between any two regions based on all other brain regions.[24] We used partial correlation to evaluate the conditional independence, which estimates the directed interactions between any two brain regions after removing the effects of all other brain areas. The PC algorithm starts from a complete graph and tests for conditional independence in an efficient way. The PCFDR algorithm enables to asymptotically control the false discovery rate (FDR) below the predefined levels which evaluates the proportion between the connections that are falsely detected to all those detected. Compared to the traditional Type-1 and Type-2 error rates, FDR has more conservative error rate criteria for modeling brain connectivity due to its direct relation to the uncertainty of the networks of interest.[25] The FDR threshold was set at the 5% level. The learned connectivity networks are binary undirected graph with the inferred functional connections at the 5% significance level. The binary undirected networks were computed for each individual for all frequencies, task conditions and blocks independently.

All statistical tests were performed using IBM SPSS Statistics (Version 23.0.0.0, IBM Corporation, Armonk, New York, USA). The dependent variables included accuracy, absolute power, and the connectivity measures. A linear mixed model (LMM) was used to model the effect of task condition, levels, regions, and interactions on the task accuracy and the EEG measures.

For the EEG data, the model included Task, Level and Region as fixed effects. Participant and Task type were used as random effects. Task type was considered a random effect as participants performed each task on a separate day. Day to day differences within each of the participants was thereby accounted for within the model.

In this model, Y is the dependent variable, either power amplitude or graph theory measure of the EEG signal. α represents the average dependent variable baseline value. $\beta_1 Task$, $\beta_2 Level$, and $\beta_3 Region$ represents the average task, level, and region effects on the slope of the model. a_i, $b_i Task$, *and* $b_i Participant$ represents the random variation in the intercept and slope of the model. $\in$ represents the residuals of the model. Residuals from the model were tested for symmetry. A reference for substantial departure from normality was suggested to be an absolute skew of 2.[26] If the residuals surpassed the skew threshold the data underwent a logarithmic transformation and re-run through the model. Only significant main effects and interactions present in both models are reported. Significance was set at 0.05 and all significant pairwise comparisons were corrected for multiple comparisons through a Bonferroni correction.

3. Results

The average total leisure activity score for all participants was 48.0 (5.6) from the Godin Leisure-Time Exercise Questionnaire, indicating the group was very active.[27] The participants' physical activity level was confirmed by the RPAQ, which revealed a mean of 1.38 h (0.22) of moderate to vigorous active per day.

Both HR and RPE showed no significant effect of task condition. There was a significant effect for Level for both HR and RPE, $F(17.9, 107) = 1143.5$, $p = <0.001$, $F(52.7, 95.05) = 165.88$, $p = <0.001$. Post hoc analyses using Bonferroni correction for multiple comparisons revealed significant increase in HR and RPE between each level ($p < 0.001$) as both values gradually increased from Block A to Block E.

Overall, there was no statistical difference in accuracy between the ASAT+EX and ASAT only tasks ($F(30.5, 55.35) = 3.71$, $p = 0.078$) (Fig. 1A). Both task conditions were then combined to assess changes by level of difficulty (Fig. 1B). There was a significant main effect of Level, $F(30.5, 95.3) = 63.7$, $p < 0.001$. Post hoc analysis revealed accuracy was stable during Blocks A–C but showed a significant decrease in the final two blocks.

The power spectrum showed that the theta frequency band was singularly impacted by task condition with a significant Main Effect, $F(268.2, 359.7) = 10.68$, $p = 0.001$. Post hoc analysis revealed significantly higher power during the Exercise only ($p < 0.001$) and ASAT + EX ($p = 0.042$) task compared to the ASAT only task condition. For this paper we focus on results from the ASAT and ASAT + EX conditions only.

Of all frequency bands, only theta power showed a significant difference between conditions reflected in an increase in theta power during the ASAT+EX task. Fig. 2 shows the change in theta power as a function of condition and level. Theta power increased from rest during the ASAT only condition and remained stable across conditions with a slight decrease in the last level. Theta power was significantly higher in the ASAT + EX task and remained high as the combined load increased, followed by a slight decrease in the last, most difficult block.

No significant differences were found in any of the global connectivity measures. The local connectivity analysis was therefore focused entirely on the frontal brain regions: frontal left (FL), frontal midline (FM) and frontal right (FR), as these areas are known to be involved in the ASAT. Theta degree showed a significant region by task interaction, ($F(12, 348) = 4.18$, $p = 0.016$), with higher values of degree in FL and FR in the ASAT + EX task. Post-hoc analysis showed a significantly higher value in the ASAT only task ($p = 0.014$) in the frontal midline region.

Clustering coefficient in theta showed a step wise increase in the first three levels of both tasks and then a significant decrease in the last two levels as the tasks became more difficult. There was a significant effect in clustering coefficient between task level, when all tasks were considered together, (F $(12, 336) = 2.59$, $p = 0.037$. F $(12, 336) = 2.59$, $p = 0.037$). Post hoc analysis revealed Block D to be significantly lower than Blocks B ($p = 0.011$) and C ($p = 0.005$) (Fig. 3).

4. Discussion

To our knowledge, this is the first study to evaluate brain-behaviour relationships during graded cognitive and physical exertion in healthy, active adults. We studied EEG metrics, network connectivity and task performance with a focus on evaluating the differences in a graded cognitive task compared with a combined graded cognitive and exercise task. Although there were no differences in accuracy between the ASAT and ASAT + EX tasks, EEG analysis revealed that there were a number of significant changes in brain activity and connectivity in the frontal regions. First, overall theta power was higher in the frontal regions during the ASAT+EX task suggesting increased neural activation associated with performing the combined task in comparison with the cognitive task alone. Importantly, we observed a significant decrease in accuracy in the last two most difficult levels for the cognitive task; this decrease was associated with a decrease in theta power. Increase in EEG power in the frontal regions during high intensity cycling was reported by Enders et al.,[28] however they did not examine changes during a graded cycling. Recently, Zhao et al.[29] showed that during an n-back working memory task with two different load conditions, theta power in the frontal regions decreased as memory load increased. Taken together, our results expand on this previous work showing that the combined task was associated with greater neural activation in the frontal regions and this was reflected in high accuracy scores; as the task became more difficult, accuracy decreased and there was a decrease in theta power.

The connectivity analysis adds further insights into how the network organization shifted as a result of increased load. During the first three blocks, we observed an increase in theta degree for the ASAT + EX task in the right and left frontal regions combined with a significant decrease in the mid frontal regions. Degree is a measure of network connectedness and nodal importance to the network. The higher the value of degree of a particular node, the more central and important the node is to the network as a whole. The observed changes in overall theta degree during the ASAT + EX task suggests that with the addition of exercise, the frontal network becomes more connected/central or important during performance of the tasks. This increased connectivity was also reflected in the measure of clustering coefficient, which also increased during the first three blocks. Interestingly, in the last two blocks both theta degree and theta clustering coefficient decreased as the task became more difficult. It should be noted that we computed graph theory analysis only in the frontal regions. This provides a limited window, as we do not know the effects on other brain regions. Further work should examine changes in functional connectivity over the whole brain.

Given that asymptomatic athletes continue to show persistent alterations in functional brain activity as measured by EEG (see Conley et al. for a recent review),[30] exertion testing combined with EEG may can provide a sensitive measure of assessing recovery from brain injury.

5. Conclusion

Combined physical and mental exertion results in significant changes in perceived exertion, EEG theta power and network organization in healthy adults. This preliminary work will be valuable in revealing residual neurocognitive deficits after sports related concussion.

Practical implications

- Combined physical and mental exertion was associated with increased neural activation and changes in brain network organization in the frontal regions.
- Combined physical and mental exertion more closely resembles sport participation.
- Comparing the brain responses and network organization to combined physical and mental exertion in individuals with concussion in future research could clarify the potential of EEG during exertion as a concussion biomarker.

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