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SHORT COMMUNICATION

CHANGES IN FUNCTIONAL CONNECTIVITY FOLLOWING INTENSIVE ATTENTION TRAINING IN PATIENTS WITH TRAUMATIC BRAIN INJURY. A PILOT STUDY

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Objective: **To explore functional connectivity after intensive attention training in the chronic phase after traumatic brain injury as clinical evidence indicates that intensive attention training improves attention dysfunction in persons with traumatic brain injury.**
Design and subjects: **A case series study. Two young adults, 13- and 18-months post traumatic brain injury, with traumatic brain injury induced attention deficits were assigned to 20 h of intensive attention training and neuroimaging.**
Methods: **Functional magnetic resonance imaging during a psychomotor vigilance test was conducted pre- and post-intervention.**
Results: **The neuroimaging indicated both increased and decreased connectivity density in frontal, posterior and subcortical brain regions, for some regions with separate change patterns for left and right hemisphere respectively, and an overall reduction in variability in functional connectivity.**
Conclusion: **The changed and decreased variability of functional connectivity in various brain regions, captured by fMRI during a psychomotor vigilance test after direct attention training in a small sample of persons with traumatic brain injury, suggests further studies of functional connectivity changes in neural networks.**

Key words: attention process training; traumatic brain injury; fMRI; functional connectivity metrics.

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LAY ABSTRACT

In our study, we wanted to know how the brain changes after intensive attention training. Two young adults with traumatic brain injury (car accident and fall from height) were administered intensive attention training for 20 h. To measure the intervention effect, the patients underwent a brain scan in an MRI-camera, while performing a test of vigilance. The vigilance test requires that you use your attention. The brain imaging showed that the brain activity was more stable and with less variability after the attention training. These findings suggest the potential benefit of attention training in regulating neural networks. More studies are needed to better illustrate the linkage between changes in the brain and intervention effect.

Attention deficit is common after traumatic brain injury (TBI). Since attention supports other cognitive functions, remediation of impaired attention should have a high priority early in the rehabilitation process (1). To better understand the recovery process, studies concerning brain mechanisms underlying different remediation techniques are also highlighted (2). A series of neuroimaging studies has shown that different aspects of attention including monitoring skills are dependent on functional connectivity networks of the prefrontal cortex, anterior cingulate cortex, and parietal cortex (3–8).

Attention training in patients with TBI has resulted in reduced frontoparietal activity suggesting a reduced demand for attentional processes post-training (9). Attention Process Training-II (APT-II) (10–13) is recommended as a standard practice for attention dysfunctions

post TBI (14–16). The APT-II is a direct, process-based attention training (10), promoting awareness and generalization through metacognitive strategy training. It is psychometrically validated (1, 17–20) with emerging radiological evidence suggesting reorganization of attention networks post training (21). Our objective is to explore functional connectivity after intensive attention training in the chronic phase after TBI exploring the potential impact of attention training on the frontoparietal attention network.

METHOD

The current pilot study is exploratory with a pre- and post-design of APT-II in 2 patients with TBI in the chronic phase. Twenty hours of APT-II was administered (1-h sessions, 3–5 times weekly). The inclusion criteria derive from a larger study (20): 18–40 years, >12 months post TBI, >7 scaled score (SS) in Matrices (logical reasoning) in Wechsler Adult Intelligence Scale-IV (WAIS-IV) (22), mild to moderate attention deficit as indicated by the APT-test (indicative test for severity and nature of attention deficit within the APT-II) defined as <70% accuracy on 2 out of 5 sublevels of attention in the APT-test (10). Exclusion criteria: signs of dementia (history or CT-scan) (22); contraindications for functional magnetic resonance imaging (fMRI). Written information about the study was delivered and consent was obtained. The Glasgow Outcome Scale – Extended (GOSE) (23) was used to evaluate functional outcome and overall recovery. Pre- and post fMRI including inclusion assessment was conducted within a week adjacent to the treatment period.

Neuroimaging protocol

Magnetic resonance imaging (MRI) data were acquired in a whole-body 3T clinical MRI scanner (Magnetom Prisma, Siemens Medical Solutions) equipped with a 64-channel phased-array receiving head coil. The protocol included: (*i*) Conventional clinical 3D MRI scans of T_1-weighted MPRAGE, T_2 and FLAIR; (*ii*) Diffusion tensor imaging of the whole brain; (*iii*) Perfusion mapping with PCASL; (*iv*) The longer session of 20 min of BOLD fMRI during a continuous psychomotor vigilance task (PVT) that requires sustained attention (24, 25) was used to avoid a learning effect in PVT (26). The main acquisition parameters for the BOLD fMRI included: TE/TR = 33.1/720 ms, flip angle = 52°, 72 slices of 2 mm thick, FOV = 208×180 mm, matrix size = 104×90. The data acquisition was accelerated twice with in-plane GRAPPA parallel imaging and further accelerated with a multiple band factor of 8 in the slice direction. A total of 1655 dynamic timeframes were acquired.

Functional connectivity (FC) metrics from the BOLD fMRI during the PVT reflect statistical associations between brain activity time series, like those derived from resting-state fMRI data (27). To remove first-order effect of task-evoked activations that can inflate FC estimates, we used a standard approach that flexibly fits and removes task-evoked responses. The fMRI datasets underwent a preprocessing pipeline (28, 29) based on programs from the AFNI software package (http://afni.nimh.nih.gov/afni), followed by a quantitative data-driven analysis framework (QDA) (30, 31). A sliding window approach was used to estimate FC between brain regions within shorter time segments. For each time segment, we used the QDA framework to compute the local (a given voxel in the brain) functional connectivity strength index (CSI) and connectivity density index (CDI) with the rest of the brain. The window length affects the temporal resolution of the analysis, and different window lengths are typically used to capture changes over different timescales (32, 33). To investigate the dynamic nature of CDI and CSI metrics during PVT, for each metric, we computed systematically 6 time series from each fMRI dataset by using 2 different window lengths (3 and 4 min) in combination with 3 different levels of overlapping (0.50 and 75%).

The means of the time series for CDI and CSI datasets for the participants underwent a paired t-test to assess the FC change pre- vs post-APT-II intervention. The statistical significance was evaluated by a voxel-wise threshold $p < 0.001$ ($t > 4.2$) to form initial cluster candidates, followed by a cluster-size limit of $n \geq 54$ to warrant a family-wise error rate (FWER) $p \leq 0.01$ as determined by permutation simulations. The number of permutations was set to 5×10^4. As discussed in previous studies (34, 35), a QDA framework can derive the connectivity metrics for each local voxel with the rest of the other voxels in the brain and can be used to assess overall how well the local voxel is connected with the rest of brain. As the QDA metrics do not provide information on where and how well specific brain regions are connected, a seed-based analysis using the AAL3 atlas (36) was performed. Using the average time courses of the preprocessed fMRI signals for the AAL3 Region of Interest (ROI), the Pearson correlation coefficients (CC) between different pairs of ROIs defined in AAL3 were computed to form a symmetric cross correlation matrix. The ROI-based analysis of FC is typically measured using static metrics, which uses the entire time series for more accurate and stable estimates of long-term FC.

Case presentations

Case 1. A 20-year-old male (left-handed, 11.5 years of education) suffered a TBI after a fall accident, Glasgow Coma Scale (GCS) = 5 (37, 38). Early MRI showed diffuse axonal injury (DAI) of grade III with a subdural haematoma on the left, contusion bleeding in the left frontal lobe and minor bleeding in the internal capsule. Two weeks post-injury at the Intensive Care Unit, he followed an extensive rehabilitation programme (6 weeks inpatient, 5 months home-based, and 4.5 months outpatient rehabilitation). He then resumed studies with an adjusted education curriculum while being admitted to the outpatient brain injury rehabilitation programme for young adults. He reported retrograde amnesia for 2 years before the incident, flat affect, difficulty finding words, difficulty concentrating during reading, and social isolation. He presented an average level of abstract thinking (Matrices, WAIS-IV: raw score [RS] = 19 points, SS = 11 points). The APT test indicated mild attention deficit (sustained attention: 67% and selective attention: 63%). APT-II was administered 18 months post-injury at the age of 21 years and 9 months. When discharged from the rehabilitation team at the age of 25, GOSE was 6 (23).

Case 2. A 21-year-old female (right-handed, 12 years of education) sustained a TBI in a car accident. Medical records reported a short post traumatic amnesia (<24 h) and only a few seconds of loss of consciousness (<30 min), corresponding to GCS = 15. MRI showed a minor tissue loss in the left fronto-basal anterior area, nonspecific supratentorial bilateral white matter changes, and minor extra-axial bleeding residuals on the left side of the surgery area. When medically stable (2 weeks post injury), she received additional inpatient care for 4 weeks. After a planned skull reconstruction, she was referred to home-based rehabilitation (4 weeks). Four months post-injury, she started an adjusted education programme at the

university while being admitted to the outpatient brain injury rehabilitation programme for young adults. She reported reduced social interaction, concentration difficulties, distractibility, mnemonic problems, difficulties in word-finding and theory of mind, headache, fatigue, tinnitus, and sensitivity to stress. She attained above average on abstract thinking (Matrices, WAIS-IV: RS = 22 points, SS = 13 points). The APT test indicated moderate to severe attention deficit (complex sustained attention: 50%, selective attention: 40% and alternating attention: 37.5%). APT-II was administered 13 months post-injury, at the age of 22 years and 7 months. When discharged from the rehabilitation team at the age of 25, GOSE was 8.

RESULTS

FC during the psychomotor vigilance test

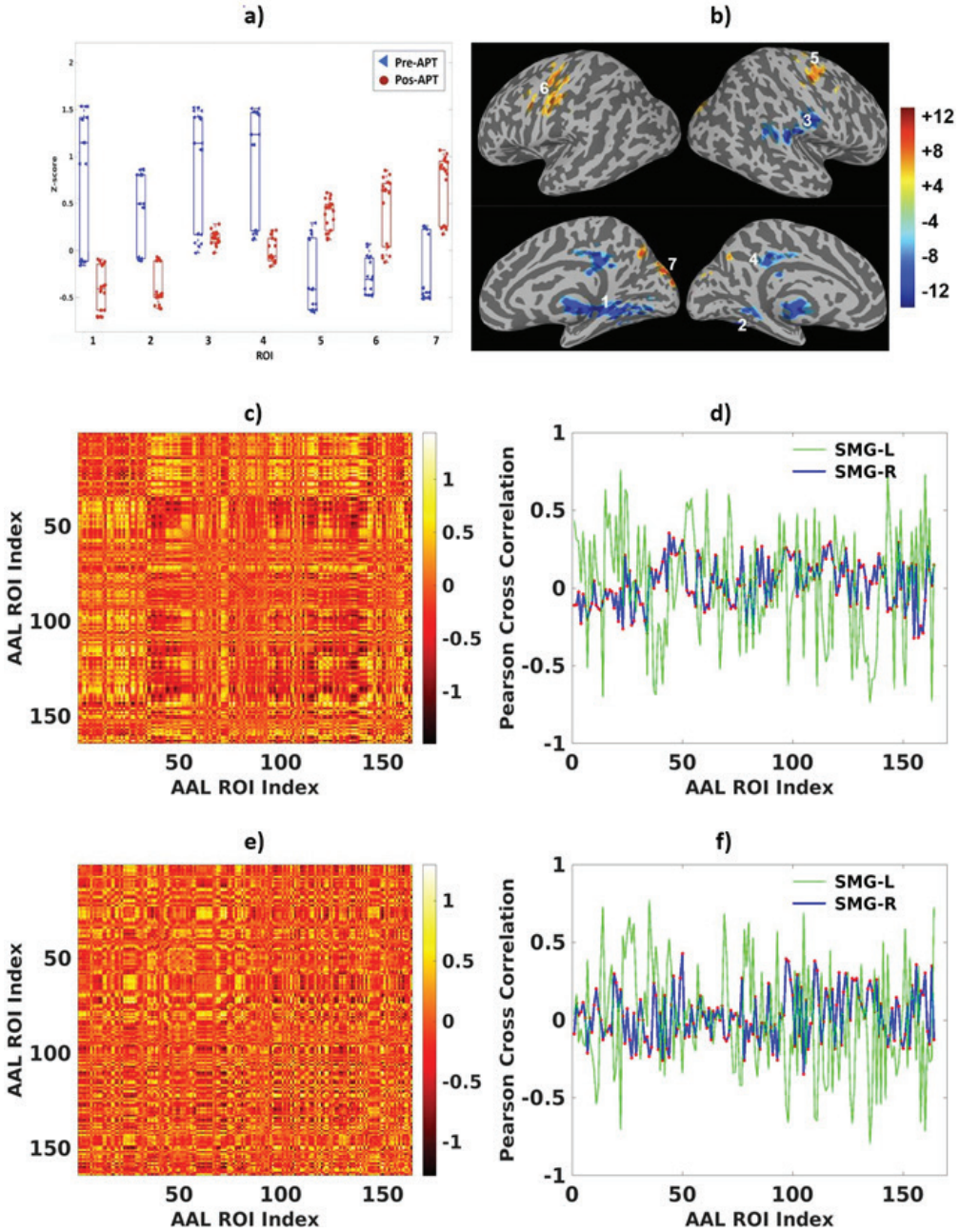

Fig. 1. Summary of task-state functional connectivity (FC). (A) The average connectivity density index (CDI) metrics for case 1 and 2 pre- vs post-APT-II for the ROIs listed in Table I. The main anatomical areas for ROIs 1–7 are thalamus, fusiform gyrus, R-supramarginal gyrus, MCC, R-precentral gyrus, L-postcentral gyrus, and R-Cuneus, respectively, (B) The paired t-test results for the CDI data pre- vs post-APT II. The colour bar indicates the t-score scales, and the numerical annotations indicate the locations of the ROIs shown in figure 1a and Table 1, (C) Pearson CC matrix differences based on the entire fMRI time course of 20 min long PVT (post-APT – pre-APT-II) for AAL3 ROIs in case 2, (D) Pearson CC for SMG-L and SMG-R with the rest of the AAL3 ROIs in case 2. (E) Pearson CC matrix differences based on the entire fMRI time course of 20 min long PVT (post-APT – pre-APT-II) for AAL3 ROIs in case 1. (F) Pearson CC for SMG-L and SMG-R with the rest of the AAL3 ROIs in case 1.

Table I. Differences in the connectivity density index metrics post-APT-II intervention between specific brain regions, with results for case 1 and 2, including the cluster size, centre of mass coordinates in MNI-template space (CM_x, CM_y, and CM_z), mean t-score ± the standard error of the mean (SEM) for the ROIs, and their anatomical overlaps with the brain atlas CA_ML_18_MNI

Nr	Volume (ml)	CM_x (mm)	CM_y (mm)	CM_z (mm)	t-score (± SEM)	R/L	Overlap with brain atlas template (CA_ML_18_MNI)
1	11,021	−7.1	389	−7.5	−4.37±0.15	B	50.4% Thalamus, 12.3% Fusiform gyrus, 5.3% Parahippocampal Gyrus
2	6993	−9.3	60.7	−45.9	−4.39±0.19	B	41.2% Fusiform gyrus, 30.6% Cerebellum, 11.1% Cerebellar Vermis
3	4644	−55.8	32.9	23.8	−4.42±0.22	R	50% Supramarginal Gyrus, 42.2% R-Superior Temporal Gyrus
4	2835	−1.1	32.4	35.7	−4.38±0.25	B	74.8% MCC, 19.8% PCC,
5	2349	−37.6	13.3	61.3	4.41±0.28	R	80.3% Precentral Gyrus, 19.6% Superior and Middle Frontal Gyri
6	2160	46.0	18.8	52.2	4.42±0.27	L	78.0% Postcentral Gyrus, 20.2% Precentral Gyrus
7	1809	−13.7	88.8	27.6	4.44±0.33	R	59.1% Cuneus, 33.8% Superior Occipital Gyrus

R: right, L: left, B: Bilateral. The ROIs are numbered in descending order of the cluster size.

As shown in Fig. 1 and Table I, differences in the CDI metrics after the APT-II were significant (FWER, $p \leq 0.01$) for both participants, with reduced variability post-intervention. The CDI was significantly enhanced in the right frontal eye field (R-FEF), and middle R-superior frontal gyri, R-cuneus and superior occipital gyrus, and bilateral motor-sensory cortex. In contrast, a significant reduction was detected in the following brain regions: thalamus, fusiform gyrus, para-hippocampal gyrus (PHC), cerebellum, middle and posterior cingulate (MCC, PCC), R-supramarginal gyrus (SMG), R-superior temporal gyrus (STG). The CSI metrics showed a similar trend.

The Pearson CC matrix indicated somewhat reduced connectivity among the brain regions in the frontal lobe (AAL3 ROI indexed 1–34) for case 2 (Fig. 1C). In contrast, the connectivity with posterior brain regions was enhanced post-APT-II. Similarly, the occipital gyri (ROI index 49–54) exhibited reduced connectivity with the frontal lobe but enhanced connectivity with other visual areas and the rest of the brain. Please note, the region-specific connectivity in parietal, SMG, and angular gyri (ROI indexed 63–70) exhibited different change patterns for the left and right hemispheres (Fig. 1D and F).

The measured reaction time in PVT during fMRI showed mixed results post-APT-II (see Table II). Decreased reaction time was accompanied by relatively high error rates.

DISCUSSION

A local connectivity density increase was detected in the right hemisphere in middle R-superior frontal gyri, R-cuneus and superior occipital gyrus, and also in the FEF, which is a vital part of the dorsal frontoparietal attention system that engages in an orienting process to prioritize visual input (7).

A local connectivity density decrease was found in thalamus, fusiform gyrus, PHC, MCC, PCC, SMG, R-superior temporal gyrus (STG). PCC plays a pivotal role in regulating the focus of attention (42) and is reported to be a part of the default mode network (DMN), the task negative network (3, 4).

The FC variability was reduced for both participants. Prior work (43) has shown reduced variability in psychometric tests, the Paced Auditory Serial Attention Test (PASAT) (44) after APT-II. Our findings provide cautious insight in the recovery process post-training.

The separate change patterns for the left and right hemispheres in parietal, SMG, and angular gyri may support findings saying that right hemisphere is connected to executive attention systems (7). The current results, that is, changed connectivity and reduced variability during PVT, are in line with changes in FC found after attention training (22) and are substantiated by the theory of balance between integrated and segregated networks for a healthy functioning brain (45).

This exploratory pilot study is limited by the small sample size. The connectivity changes might thus be the result of the natural course in the brain after a traumatic lesion since the brain is continuously changing, also in the chronic phase. Nevertheless, the changes in connectivity observed provide a result that justifies further investigations into how the relationship between connectivity and response to attention training can be

Table II. Summary of PVT data for the subjects pre- and post-APT-II. The results are provided in raw scale unless specified. Available reference values for healthy controls are provided

	Case1		Case 2		Control reference	
Assessment	Pre	Post	Pre	Post	Male	Female
PVT[a] RT, ms	305 (105)	320 (131)	250 (262)	113 (40)	418 (57)	406 (65)
PVT Error, %	8.2	6.0	12.1	14.5	5.1	4.0
Time for MRI[e]	18	19	13	14		

[a]Psychomotor Vigilance Test (PVT)(24, 25) was used for assessment of sustained attention during functional magnetic resonance imaging (fMRI); scoring was based on reaction-time (RT) and error-rate (Error). Intervals between stimuli range from 2 to 10 s, with the entire 20-min task administered in a pseudo-random fashion. [e]The time for MRI is given in months after the traumatic incident. The reaction time for case 2 is very short compared even to results for healthy volunteers, which are typically above 400 ms (24, 25). This result could be due to an artefact or reduced inhibition often connected to TBI. The error rate in PVT increased in the same participant, probably due to the reduced reaction time. In previous studies, a high error rate is linked to reduced alertness, slower problem-solving, and poorer psychomotor skills (39–41). "*" denotes items with statistically significant differences in performance pre- vs post-intervention ($p < 0.05$ uncorrected for multiple comparison).

captured during a psychomotor vigilance test by fMRI. For clinical translation, it is recommended to disclose psychometric data as a supplement to the neuroimaging protocol.

In conclusion, the results showed both an increase and a decrease in connectivity density in frontal, posterior and subcortical brain regions, for some regions with separate change patterns for left and right hemisphere respectively, and an overall reduction in variability in FC (indicating a more robust connectivity) after intensive APT-II in 2 patients with TBI. Whether these FC findings are related to intervention effects cannot be concluded due to a small sample. In future studies, the neuroimaging protocol would benefit from disclosing psychometric data on sustained attention and inhibition.

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The raw data supporting the conclusions of this article will be made available by the authors without undue reservation if the participants' privacy is guaranteed.

The local Regional Ethical Committee approved the study; registration number was 2017/1810-31. Written informed consent was obtained from participants to publish any potentially identifiable images or data included in this article.

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