The Functional and Structural Neural Correlates of Dynamic Balance Impairment and Recovery in Persons with Acquired Brain Injury

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Research Article

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Abstract

Dynamic balance depends on the interaction between multiple brain networks and is impaired following Acquired Brain Injury (ABI). This study aims to characterize the brain functional and structural correlates of ABI-induced dynamic balance impairment and recovery at the chronic-phase following a rehabilitation treatment. 31 participants participated in a novel rehabilitation treatment composed of 22 sessions of perturbation training. Dynamic balance was assessed using the Community Balance and Mobility scale (CB&M) and the 10-Meter Walking Test (10MWT). Brain function was assessed based on resting-state fMRI scans which were analysed using independent component analysis (ICA), and regions of interest analyses. Brain volume was assessed using structural MRI and compared to age-matched and elderly participants.

ICA revealed a reduction in component-related activation within the sensorimotor and cerebellar networks post-intervention ($p < 0.035$). Improvement in CB&M scale was associated with a reduction in FC within the cerebellar network ($p = 0.023$) and with baseline FC within the cerebellar-putamen ($p = 0.002$) and cerebellar-thalamic networks ($p = 0.026$). Improvement in 10MWT was associated with baseline FC within the cerebellar-putamen ($p = 0.012$) and cerebellar-cortical networks ($p = 0.017$, $p = 0.004$, $p < 0.001$ and $p = 0.005$). A global brain volume reduction was found in the ABI-group when compared to the age-matched controls ($p < 0.001$), which was negatively associated with ABI chronicity, but not associated with CB&M scale.

Our results show that dynamic balance recovery is associated with FC changes within and between the cerebellar and sensorimotor networks that are consistent with the contribution of modularity to balance control and recovery. The diffused atrophy post-ABI indicates that ABI led to a degenerative process.

Introduction

Acquired Brain Injury (ABI) is defined as a damage to the brain that occur after birth. Two common ABI conditions are Traumatic Brain Injury (TBI) and stroke.^[1] Both etiologies are characterized by neuronal losses, and local and remote neurophysiological changes in structural and functional networks, that are associated with the sensorimotor impairments and with the recovery process^[2, 3]. Furthermore, both etiologies trigger brain atrophy and neurodegenerative conditions^[4, 5] that were shown to be associated with motor, cognitive and psychiatric decline^[4, 6]. Longitudinal studies indicated an association between brain atrophy post-stroke and gait control decline^[7, 8] and increased risk of motor-related neurodegenerative disorders such as Parkinson disease post-TBI^[9].

Subjects post-ABI at the chronic phase frequently suffer from a dynamic balance control impairment which restricts their mobility, limits their community integration and their locomotor abilities^[10–12]. Dynamic balance control is a complex function that is achieved by both feedback and feedforward control mechanisms and mediated by both central pattern generation at the spinal level and subcortical and cortical brain areas^[13–15]. Imaging studies indicate the involvement of the cerebellum, basal ganglia and the motor cortex in gait and postural control in healthy subjects^[16–19]. Lesions in the previously mentioned areas are associated with gait and balance impairments^[20–22].

Dynamic balance and mobility at the chronic phase of ABI have been shown to respond to rehabilitation treatments such as virtual reality training, multi-disciplinary rehabilitation and conventional balance training^[23–26]. Furthermore, facing unpredictable perturbations, coming from mechatronic shoes, has been recently shown to be associated with improvement in dynamic balance^[26]. Imaging studies from recent years showed that cognitive and motor training effects could be predicted by functional brain connectivity and are associated with changes in functional connectivity^[27–29]. Moreover, increased modularity in brain network organization was shown to be associated with a more flexible and adaptable behaviour that is needed for supporting cognitive functions and motor coordination^[30, 28]. In this study, we investigate the neural correlates of dynamic balance impairments and recovery by longitudinally examining resting state functional Magnetic Resonance Imaging connectivity (Rs-fMRI) in a group of ABI participants that improved their dynamic balance following a rehabilitation intervention^[26]. Further, in order to map the neural correlates of dynamic balance impairments in

ABI, we examine the correlation between the volume of pre-defined regions of interest in the cortex and sub-cortex with dynamic balance impairments [17–19,31].

Specifically, we hypothesize that: (1) dynamic balance impairment and recovery will be associated with functional connectivity within and between neural networks that play a role in balance control, including the sensorimotor cortical network, the cerebellar network, and the basal ganglia network. Furthermore, we expect that improvement in dynamic balance will be associated with reduction in connectivity between regions of interest (i.e., reflecting an increase in modularity). (2) we hypothesize that baseline functional and structural neural measures from networks that are involved in dynamic balance control will predict dynamic balance recovery. (3) Lastly, we hypothesize that dynamic balance impairments will be associated with reduction of brain volume in areas controlling posture and balance when compared to age-matched controls.

Methods

This study was approved by the Research Ethics Committee of the Reuth Rehabilitation Medical Center, Tel-Aviv, Israel and by the Research Ethics Committee of Soroka University Medical Center, Beer Sheva, Israel. All participants in this study signed an Informed Consent Form when they agreed to participate, and all methods were performed in accordance with the relevant guidelines and regulations.

The ClinicalTrials.gov identifier number is NCT02215590, 13/08/2014.

Subjects:

1. Participants post-ABI:

A total of 36 (7 females, 29 males; mean age 60.44 ± 12.07 years) were enrolled in the study. Participants were approached using a database of hospitalized patients in Reuth Rehabilitation Medical Center, Tel-Aviv, Israel and using an add that was published in a local newspaper. After signing an informed consent, participants went through a screening process that included detailed neurological assessment of muscle strength and tone, sensation, reflexes, balance and coordination assessments, in addition to a cognitive assessment and medical history review by a neurologist. Inclusion criteria were: within an age range of 18-80 years; Residual dynamic balance impairment due to ABI; At least a year post-ABI (TBI or ischemic stroke) before recruitment; Ability to walk at least 10 meters with or without an assistive device; Drug therapy unchanged for one month prior to trial and during the entire trial period. Lastly, with a score above 19 on the Montreal Cognitive Assessment test (MoCA) [32]. Exclusion criteria were: Presence of an acute progressive neurological; systemic, or musculoskeletal disorder affecting gait and balance; Severe visual or hearing impairment; Pulmonary or cardiac condition impairing exercise endurance; Psychiatric disorders; Alcoholism or drug use.

2. Structural MRI Control groups:

Data of 36 aged-matched healthy participants, and 35 elderly participants with no neurological or psychiatric disorders and no brain damage was obtained with permission from the Cambridge Centre for Ageing Neuroscience (Cambridge Centre for Ageing and Neuroscience, 2019).

Experimental procedure:

The study included behavioral and MRI assessments. Each assessment was conducted twice, pre- and post-intervention. Between the assessments, participants underwent a rehabilitation program using the Re-step™ technology (mechatronic

shoes)^[25, 26].

For the behavioral assessment we used the community balance and mobility scale (CB&M) in order to assess dynamic balance. This scale assesses difficulties in ambulation and balance skills which are needed for community integration in individuals with stroke and adults with TBI^[33, 34]. The scale includes 13 tasks requiring multitasking and complex motor tasks (e.g., Unilateral stance, forward to backward walking, descending stairs, crouch and walk). Higher scores indicate better balance and mobility skills (maximum possible score=96). Furthermore, we used the 10-Meter Walking Test (10MWT) for participants post-stroke in order to assess self-paced gait velocity^[35]. Participants were asked to walk a 14-meter track at a comfortable speed and then at a fast speed. The middle ten meters were timed. Time was measured by a handheld stopwatch. Velocity was computed based on the track length and time parameters. The 10MWT was added to the behavioral assessments after the begging of the experiment, and was therefore performed only on the stroke participants.

Outcome measures:

Resting-state functional connectivity, which is sensitive to brain network changes following brain injury^[36], and brain volume measure for detecting structural brain changes following brain injury^[37].

Interventional procedure:

22 sessions, given twice a week. Each session began with several warm-up exercises like mobilization and strengthening for 10 minutes, that were followed by training using the mechatronic shoes^[25], for up to 40 minutes and ended with 10 minutes of cool-down exercises of stretching and relaxation walking (see,^[26] for details about the task and the perturbation protocol).

MRI sessions and MRI acquisition:

Participants underwent two identical MRI sessions, pre- and post-intervention, each session included a 3D anatomical scan, a Rs-fMRI scan, fMRI-Localizer scan and a DTI scan (not reported here).

The time length of the 3D anatomy scan was four minutes and 50 seconds. This scan was acquired using a high resolution T1-weighted anatomical protocol with fast spoiled gradient-echo (FSPGR) sequence, with a voxel size of 1×1×1 mm, (Repetition Time (TR) = 8165 ms, Echo Time (TE) = 3.74 ms, 256×256 acquisition matrix). The field of view (FOV=192 mm) covered the entire cerebrum and the cerebellum.

The time length of the fMRI-Localizer scans was nine minutes and 50 seconds. The fMRI data was acquired using a gradient echo EPI with voxel size of 3×3×3 millimetres (mm), TR=2000 millisecond (ms), TE=35ms, flip angle=77°, 35 slices, with a 0.6 mm gap.

The fMRI-Localizer scan was a block design experiment containing six conditions (five movement blocks and one rest block); left or right limbs movement of dorsi/palmar flexion for palms and dorsi/plantar flexion for the ankles and bipedal ankle movements, (the limb moving frequency was equal to 1 hertz (Hz) as demonstrated by the experimenter before the scan). Movement blocks of 12 seconds were separated by resting periods of 10 seconds, which were cued by a fixation cross on a black screen. Visual cues for instructing hand and ankle movements were displayed on a screen during the experiment. Participants trained on the task before the scan using a dedicated apparatus located outside the scanner. The order of the blocks was random. In total, each localizer session included 25 movement blocks (five repetitions of each of the five movement conditions).

The time length of the Resting state scan was equal to seven minutes and 26 seconds. The resting state data acquisition parameters were similar to the fMRI-Localizer data scan. At the resting state session, a cross “+” was displayed in the middle

of the screen, and participants were instructed to fixate on it during the scan.

The magnetic resonance imaging and data acquisition were performed at the imaging center of Soroka Medical Center using a 3-Tesla Philips Ingenia whole-body MRI scanner (Philips Ingenia, Amsterdam, Holland).

MRI data acquisition-healthy control group:

The control group data was taken, with permission, from the Cambridge Centre for Ageing Neuroscience (CamCAN) dataset (Cambridge Centre for Ageing and Neuroscience, 10 January 2019, Cam-CAN Data Repository Cambridge, accessed 30 August 2019, <<http://www.camcan.org/index.php?content=dataset>>).

This data set was acquired on a 3T Siemens whole body MRI scanner (Siemens MAGNETOM TrioTim syngo MR B17). 3D anatomical scans were acquired using a high resolution T1-weighted anatomical protocol with a magnetization-prepared rapid acquisition with gradient echo (MPRAGE), (TR=2250 ms, TE=2.99 ms, FOV=256x249x192 mm, TI=900 ms, Flip angle (FA=9 deg); 1mm isotropic; GRAPPA=2; TA=4 min 32s).

Imaging analysis:

Functional, resting-state, and structural data were analysed by Brain Voyager 20.6 (Brain Innovation, Maastricht, The Netherlands).

Pre-processing of the localizer scan data:

Pre-processing included removal of the first two functional images of each run series to allow stabilization of the BOLD signal; correction of the slice scan time acquisition (ascending-interleaved; using a cubic-spline interpolation algorithm); head motion correction (using a trilinear/sinc interpolation) and a temporal high-pass filtering using a cut-off frequency of 2 sine/cosine cycles.

Pre-processing of the Resting-state scan data:

The pre-processing included removal of the first two functional images of each run series to allow stabilization of the BOLD signal; correction for slice scan time acquisition (ascending-interleaved; using a cubic-spline interpolation algorithm); a trilinear interpolation approach in order to remove head motions; a high-pass (GLM-Fourier) frequency filter with a cut-off value of 2 sine/cosine cycles and a low-pass Gaussian-Full Width at Half Maximum (FWHM) of 1.9 data points^[38]. Further, we used band pass filtering with an 8th order Butterworth filter with cut-off frequencies of $0.009 < f < 0.08\text{Hz}$ ^[38]. Lastly, we projected out averaged signals of the white matter, the cerebro-spinal fluid, and head motion parameters. This step was conducted by running a multiple GLM regression analysis. The residuals of this analysis were free from the unwanted components and were used as inputs in the resting state functional connectivity (FC) Region of interest (ROI) analysis. Functional connectivity was computed using a correlation analysis (Pearson correlation coefficient) between the time courses of pre-defined ROIs (M1, cerebellum, thalamus, putamen, superior frontal, and superior parietal).

Both the fMRI-task and fMRI-rest data sets of each participant were spatially aligned onto the corresponding anatomical scan (T1 weighted structural scan) by an automatic alignment procedure (implemented in Brain Voyager 20.6). The results of the automatic alignment were inspected during the processing and manually adjusted if needed. Subsequently, the co-aligned images were transformed into Talairach space^[39].

Regions of interest definition:

12 ROIs were examined: leg areas in M1 and cerebellum, thalamus, putamen, superior frontal, and superior parietal bilaterally. The M1 and the cerebellum were identified using the localizer scan (contralateral ankle movement vs baseline). The coordinates of each ROI were selected based on activation peaks of the above contrasts. The thalamus, putamen, superior frontal, and superior parietal were defined for each participant anatomically using FreeSurfer software V 5.0 (developed by the Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital in Charlestown in Boston, MA). The size of each ROI was defined as the number of functional voxels (3mm isovoxel). (Detailed characteristics (mean, SD, SEM) of each ROI are presented in Table 1).

Independent component analysis (ICA):

resting state data was analysed using the ICA method in Brain Voyager 20.6. This method allows the detection of a set of statistically independent spatial maps (networks) on a subject-by-subject basis during the resting-state scans and subsequently measures changes in the strength of these spatial maps after the intervention^[40]. The analysis was composed of two stages: In the first, 30 ICA components were defined for each participant based on the individual resting-state scans. In the second, consistent components across participants were selected. We compared the averaged related activation across the networks pre- and post-perturbation training at the voxel level using the “self-organizing groups” feature in Brain Voyager. We minimized detection of false positives (type I errors) by using cluster-corrected familywise error rate correction at $p < 0.05$. We decided to focus our analysis on the sensorimotor network and the cerebellar networks that were shown to be sensitive to balance training^[27].

Processing of the anatomical data for the volume analysis:

We analysed the 3D anatomical scan for each participant using Free-Surfer software 5.0^[41]. To quantify the differences in volumes, we computed the percent change with respect to the control group, according to the following formula:

$$PC = \frac{\text{patient} - \text{mean}(\text{control})}{\text{mean}(\text{control})} \cdot 100$$

Statistical analysis:

for statistical calculations, we used SPSS statistics (SPSS for Windows, Version 16.0; SPSS Inc., Chicago). The significance level was set to $p < 0.05$ for all statistical tests. Normality assumption was tested by using the Kolmogorov-Smirnov test ($p > 0.05$). Paired t -test was used for within-subject analyses of the behavioral data (pre-intervention vs. post-intervention). The ES (Cohen's d) for the within-subject design was calculated by dividing the mean difference between pre and post-intervention by the pooled SD.

For the resting state functional connectivity analysis, we used z-Fisher transformation in order to normalize the distribution of the correlation coefficients. To check for the significance of the correlations between functional connectivity measures, brain volume parameters and functional behavioral measures, we used multivariate linear regression models. Whole-brain multiple comparison concerns were addressed by a cluster-correction for family-wise error rate at $p < 0.05$. Lastly, for the brain volume analysis, we ran an independent t -test for data that did not deviate from a normal distribution and Mann-Whitney U test for data that deviated from a normal distribution.

Results

Data from five participants from the ABI-group were excluded from the analysis because of the following: 1) one participant refused to enter the MRI scanner. 2) four participants refused to continue participating in the study due to loss of interest and transportation difficulties. The total number of participants included in the imaging analysis was 31. Additionally, one participant out of the 31 did not undergo the behavioural assessment post-intervention due to loss of interest.

The average age of the participants that participated in the study (N=31) was 60.16 ± 12.85 years, the average time since injury was 92.74 ± 144.43 months and the time interval between pre-and post-assessments was equal to 117 ± 14.14 days (see Table 2 for additional information).

Recovery of dynamic balance and gait velocity following intervention:

Dynamic balance (measures by CB&M scale) in ABI subjects (N=30) was affected by the intervention. CB&M score changed from 37.73 ± 16.5 pre-intervention (T1) to 43.33 ± 17.01 post-intervention (higher scores indicate improvement) ($p < 0.001$) with a large effect size (ES=0.83).

The 10MWT score for stroke participants (N=21), changed from $0.88 \text{ m/sec} \pm 0.34$ pre-intervention (T1) to $0.95 \text{ m/sec} \pm 0.32$ post-intervention ($p = 0.02$) with a medium ES=0.6.

Recovery was associated with a signal reduction in sensorimotor and the cerebellar networks:

We first examined global changes in connectivity using an ICA approach. We focused our analysis on two resting-state spatial maps of interest that were shown to be involved in gait control [27]: the sensorimotor and the cerebellar spatial maps (Figure 1A). For each network, we examined the strength of these networks at the voxel's level using contrasts. This analysis revealed a reduced component-related activation in both networks ($p < 0.05$) (Figure 1B).

Recovery of dynamic balance was associated with reduced FC within the cerebellar network:

Next, we examined the association between FC between regions of interest and dynamic balance impairment and recovery. The first analysis focused on inter-hemispheric functional connectivity (IHFC) between cerebellar and sensorimotor networks. Out of the eight regression models that were examined (between the behavioral parameters baseline CB&M, Δ CB&M, baseline 10MWT, or Δ 10MWT and baseline FC or Δ FC of IHFC), only the association between Δ FC within the cerebellum and Δ CB&M was significant [$F(4, 25) = 3.41$; $\beta = -0.57$, $p = 0.02$ and $R^2 = 0.35$] (Table 3).

We did not find a significant change in the FC between ROIs at the IHFC level following the intervention ($p > 0.1$).

Baseline resting-state Intra-hemispheric FC (IntraHFC) at the cerebellar-cortical and cerebellar-subcortical networks predicts dynamic balance recovery

We next examined the intraH FC correlates of dynamic balance impairment and recovery. We examined the association between the cerebellar-cortical networks (including M1, superior parietal, and superior frontal lobes) and cerebellar-subcortical networks (putamen and thalamus).

Eight regression models were examined (baseline CB&M, Δ CB&M, baseline 10MWT, Δ 10MWT and baseline FC and Δ FC).

Out of all associations the following were statistically significant:

1) Baseline IntraHFC in the cerebellar-cortical and cerebellar-subcortical networks was associated with Δ CB&M [$F(10, 19) = 2.27$; $p = 0.02$ and $R^2 = 0.58$ (Table 4)]. Covariates contributing to the significant model were left cerebellar-right thalamic network ($\beta = -0.51$, $p = 0.02$) and left cerebellar-right putamen network ($\beta = 0.62$, $p = 0.002$).

2) Baseline IntraHFC in the cerebellar-cortical and cerebellar-subcortical networks was associated with Δ 10MWT [$F(10, 10) = 7.55$; $p = 0.002$ and $R^2 = 0.88$ (Table 5)]. Covariates contributing to the significant model were:

Left cerebellar-right putamen network ($\beta = 0.44$, $p = 0.01$),

Right cerebellar-left frontal network ($\beta = 0.47$, $p = 0.01$),

Right cerebellar-left superior parietal network ($\beta = 0.55$, $p = 0.004$),

Left cerebellar-right superior parietal network ($\beta = 0.69$, $p < 0.001$), and Left cerebellar-right M1 network ($\beta = -0.41$, $p = 0.005$).

We did not find a significant change in the FC between ROIs at the IntraHFC level following the intervention ($p > 0.1$).

Results of brain volume analysis

Motivated by the results showing sensorimotor and cerebellar functional correlates of dynamic balance, we were interested in studying the morphological changes that are associated with ABI. In order to study the effects of ABI on morphological properties and to

detect whether dynamic balance deficits were associated with the location and magnitude of the structural damage following the ABI, we compared structural data of the ABI participants with data of healthy age-matched ($N = 36$; age 57.78 ± 14.93 years) and elderly control subjects ($N = 35$; 17 females and 18 males; age 84.20 ± 1.69 years). In relation to age there was no significant difference between the ABI group and the age-matched group ($\Delta = 2.38 \pm 3.43$ years, $t(65) = -0.69$, $p = 0.49$). Further, the ABI group was younger than the elderly control group ($\Delta = 24.04 \pm 2.19$ years, $t(30.92) = -10.33$, $p < 0.001$).

Reduced brain volume post ABI:

The comparison between brain volume of both groups revealed a significant reduction of brain volume of the ABI group compared to the age-matched healthy control group. The reduced brain volume was global and statistically significant in 40 out of 42 examined regions (Table 6) (Figure 2). An additional feature of global brain atrophy is the enlarged right and left ventricles ($p < 0.001$, $p = 0.005$, respectively (Figure 3, Table 6)). Notably, the reduction in brain volume was also greater when compared to the group of healthy elderly participants (36 out of 44 ROIs) (table 7). Last, we examined if the brain atrophy was directly induced by the ABI at the time point of the initial injury or was a degenerative process that started following the initial brain injury and continued since then. Consistent with the degenerative prediction, there was a correlation between volume reduction of both total gray matter (Figure 4A) and cortical white matter (left and right hemispheres) (Figure 4B and 4C) and time since injury ($r = -0.4$ $p = 0.02$, $r = -0.54$ $p = 0.001$, $r = -0.46$ $p = 0.008$). The reduction indicates that atrophy in ABI is a degenerative process that continued since the injury.

The structural neural basis of dynamic balance

Lastly, we searched for association between atrophy and dynamic balance impairment and its recovery using a multivariate linear regression model which included the following independent variables: (1) Total gray matter volume, (2) Total cortical WM volume and (3) left and right cerebellar WM volume and baseline CB&M score as the dependent variable. The model revealed a non-significant association between brain volume and baseline CB&M score [$F(4,26) = 0.6, p = 0.66$]. Furthermore, we ran a multivariate linear regression model which was similar to the previous model, with the delta Δ CB&M as the dependent variable. This model was not significant as well [$F(4,25) = 0.55, p = 0.69$], suggesting that there is no linear dependency between the examined global brain volume variables and dynamic balance impairment and recovery.

Discussion

This study aimed to explore the neural substrates of dynamic balance by examining the association between dynamic balance impairments and recovery in chronic ABI participants and functional and structural brain measurements. The rationale for combining two subgroups of ABI (TBI and stroke) in the study was that both subgroups suffer from balance impairments due to a neuronal damage. Furthermore, both etiologies are characterized by initial neuronal loss, neurophysiological changes and disruptions of integration in structural and functional networks (diaschisis) [2], resulting in sensorimotor impairments and loss of motor functions [2]. Lastly, in both groups recovery is mediated by neural plasticity in intact cortical and sub-cortical regions [2].

We report that dynamic balance recovery was associated with a reduction in connectivity in the sensorimotor and cerebellar networks. Furthermore, dynamic balance recovery was negatively associated with baseline connectivity within the cerebellar-thalamic network and with baseline connectivity in the cerebellar-M1 network. Dynamic balance recovery was also positively associated with baseline connectivity within the cerebellar-putamen network and both the cerebellar-frontal and cerebellar-parietal networks. We also found that while morphological features were not correlated with dynamic balance impairment and recovery, brain atrophy was globally enhanced following the ABI at the chronic phase.

Network modularity as a biomarker of impairment post-ABI and of intervention-induced plasticity

Using the ICA approach, we found a reduction in component-related activation in the sensorimotor and cerebellar networks post-training. Furthermore, the results of the regression analysis showed that reduction in FC within the cerebellar network post-training and low baseline FC within the cerebellar-cortical and cerebellar-putamen were associated with better dynamic balance recovery.

We suggest that the reduced component-related activation and FC in sub-networks can be considered as a manifestation of increased network modularity (where the modules of the networks are the ROIs) [30]. Networks with high modularity have dense connections within modules and sparse connections between modules. High modularity was suggested to be associated with increased brain plasticity and enhanced motor and cognitive abilities [28]. This concept was previously adopted for describing the neural basis of complex behaviours in health [30, 28], and in disease [42, 43], suggesting that modular brain organization can be considered as a biomarker of efficiency, engagement and improved processing and adaptability to changing environments post-rehabilitation [43-45]. We propose that the reduced component-related activation in the sensorimotor and cerebellar networks post-training manifests increases in modularity which is related to better recovery in dynamic balance post-training [28, 45], and that the functional advantage of high baseline modularity is apparent in our cerebellar ROI analysis [29]. Following the previous results, we suggest that modularity within the cerebellar-cortical and cerebellar-subcortical networks can provide an insight into the neural substrates and mechanisms that support the recovery of dynamic balance.

The role of the cerebellar-cortical and cerebellar-subcortical in dynamic balance control

The resting state FC analysis revealed a correlation between the cerebellum, the putamen and thalamus and dynamic balance recovery. These inferred connections are consistent with the increasing evidence for the existence of subcortical loops that reciprocally connect cerebellum with the putamen through the thalamus ^[46,47], and functional interconnection between the cerebellum and the putamen ^[27].

The role of the putamen in gait and gait kinematics has been demonstrated in studies involving healthy adults ^[27,48], and in stroke ^[21,49]. Lastly, the resting state FC analysis revealed a correlation between cerebro-cortical areas and dynamic balance recovery (10MWT) which is also consistent with previous studies highlighting the involvement of the cerebellum and the cerebral cortices in gait and balance control in relation to healthy subjects ^[50,27], and post-brain injury ^[51,52]. Our results highlight the potential contribution of these cortical and subcortical brain areas to dynamic balance and gait related recovery following brain injury.

Global volume reduction post-ABI

The main finding from the brain volume analysis was a global volume reduction in the ABI group at cortical and subcortical brain regions when compared to healthy age-matched control group. Our results are consistent with previous studies that reported that ischemic brain lesion affects global white and gray matter morphology ^[53,54], and induces prolonged neuro inflammatory processes that continues to the chronic phase post-brain lesion ^[55,56], thereby expanding the effect of the initial lesion ^[57,58]. Furthermore, it should be taken into consideration that the restricted physical activity, mobility and lower rate of daily social interactions post-brain injury might be an additional factor that contribute to the atrophy ^[59,60]. Lastly, an additional feature of the global brain atrophy in our study was the ventricles enlargement in comparison to age-matched healthy control-group. Ventriculomegaly following brain parenchymal shrinkage is commonly observed in neurodegenerative disorders ^[61]. Further studies should attempt to differentiate between the direct contribution of the initial lesion to atrophy and its indirect effect on atrophy through behavioural modifications.

Chronicity of ABI and brain volume

Our findings exhibit a global brain volume reduction, indicating a diffused atrophy. These findings are consistent with previous studies which showed that the spatial pattern of TBI-related atrophy affects multiple grey and white matter areas ^[62,32]. Furthermore, we found that atrophy worsens with time since injury, consistently with a previous longitudinal study that exhibited enhanced volume reductions with time in total brain volume, reduced white matter integrity post-ABI ^[62]. Importantly, we did not find a direct association between brain atrophy and dynamic balance. The lack of association can be explained by the involvement of multiple brain areas in dynamic balance control and the variability between subjects in terms of damage and or recovery mechanisms. Thus, there might be an indirect association between brain atrophy and dynamic balance which is manifested by the alteration in functional networks, as has been reported previously in cognitive impairments post-stroke ^[63]. Furthermore, since atrophy is a process associated with time, conducting longitudinal assessments over time will provide a better understanding of the relationships between atrophy and dynamic balance.

The integration between the structural and functional brain measures (the multimodal approach)

Brain functional connectivity and structural morphology are clearly not independent. Two emerging perspectives in the neuroimaging literature attempt to explain the association between structural damage and network function. Firstly, a study indicated a negative association between the size of the brain damage (post-stroke/TBI/Tumours) and FC depicting a depression of neural activity in brain regions remote from the initial brain damage due to reduced FC (diaschisis) [3,64]. Secondly, studies report an increase in FC within brain regions that had reduced structural connectivity, which may represent the reorganization of the system following the brain damage [63, 65].

Future studies should adapt a multi-modal approach of brain network assessments post brain damage which can open new perspectives for the understanding of the consequences of brain damage and its impact on impairment and recovery.

Several limitations of this study should be acknowledged:

1) Resting state data was collected only for post-ABI with no control reference. This limitation limits the discussion about abnormal patterns of connectivity but does not affect the interpretation of the longitudinal data. 2) The absence of follow up assessments limits the estimation of the efficacy of the treatment and its long-term neural outcomes. 3) There is an increase in the risk of type-1 bias due to multiple comparisons, especially in the ROI FC analyses. We therefore suggest taking these results as preliminary exploratory evidence and call for their replication. 4) While all subjects suffered from dynamic balance impairment due to ABI, there was variability between subjects due to the causes of damage (TBI vs stroke) and locations of damage.

In conclusion, functional and structural mapping of brain networks allows the detection of widespread alterations of networks following brain injury and rehabilitation. We suggest that these alterations were more likely to be as a result of the training than the effect of the chronic time post-injury since spontaneous changes are less prominent at the chronic phase post-brain injury. Our study demonstrates functional connectivity changes in the cerebellar and sensorimotor networks following a rehabilitation treatment for post-ABI participants and suggests neural markers for the treatment's gains. The lack of inter-subject correlations with structural atrophy suggest that dynamic balance is an emergent feature of functional or composite networks. Our results contribute to the understanding of the neural correlates of dynamic balance and depict several markers of recovery that should be further investigated.

Abbreviations

ABI: Acquired Brain Injury.

CB&M: Community Balance and Mobility.

FC: Functional Connectivity.

IHFC: Inter-hemispheric functional connectivity.

IntraHFC: Intra-hemispheric functional connectivity.

MoCA: Montreal Cognitive Assessment.

ROI: Region of interest.

Rs-fMRI: Resting state functional Magnetic Resonance Imaging.

TBI: Traumatic Brain Injury.

TE: Echo Time.

TR: Repetition Time.

10MWT: 10 Meter Walking Test.

Declarations

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Conflicts of interest:

Dr Simona Bar-Haim holds equity positions in Step of Mind, the company that developed the Re-Step system.

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Tables

Table 1

ROI Characteristics Presented as Means, SD, and SEM of Number of functional Voxels (3mm isovoxel)

ROI	Mean	SD	SEM
Right M1	1228.9	98.4	17.6
Right Cerebellar	1158.4	106.7	19.1
Left M1	1189.8	120.5	21.6
Left Cerebellar	1176	132.7	23.8
Left Thalamus	6023.1	1159.6	208.2
Left Putamen	4325.3	1068.5	191.9
Right Thalamus	5353.03	1082.3	194.3
Right Putamen	4429.6	1164.6	209.1
Left Frontal superior	14275.8	1854.5	333.09
Left Parietal superior	4805.6	837.9	150.4
Right Frontal superior	13587.5	1904.5	342.06
Right Parietal superior	4002.5	652.6	117.2
Abbreviations: ROI=region of interest, M1=motor cortex, SD=standard deviation, SEM=standard error of the mean.			

Table 2

Baseline Characteristics of each participant.

Participants	Age (year)	Gender	weight	height	Stroke/ TBI	Time since injury, months (days)	Damaged hemisphere	MOCA score	Assistive device for walking (No/Yes)
S1	68	M	78	182	stroke	99 (7)	R	24	No
S2	61	M	72	175	stroke	31 (2)	L	26	No
S3	39	M	62	180	TBI	236 (2)	R	23	No
S4	63	F	57	155	stroke	52 (6)	L	29	No
S5	69	M	89	182	stroke	21 (28)	R	22	No
S6	69	M	73	172	stroke	90 (29)	R	26	Yes
S7	61	M	69	186	stroke	19 (2)	L	29	No
S8	68	M	62	161	stroke	80 (4)	R	23	Yes
S9	61	F	53	163	TBI	435 (27)	L	25	Yes
S10	36	F	56	158	stroke	20 (15)	L	28	No
S11	61	M	68	165	TBI	39 (11)	L	26	No
S12	69	M	81	169	TBI	563 (28)	R	25	No
S13	43	F	60	159	TBI	468 (5)	Bilateral	24	No
S14	69	M	88	175	stroke	11 (2)	R	28	No
S15	72	M	90	170	stroke	13 (2)	R	24	Yes
S16	47	M	100	172	stroke	10	L	21	No

						(21)			
S17	53	M	81	175	TBI	24 (24)	Bilateral	23	No
S18	68	F	84	164	stroke	14 (1)	L	30	No
S19	58	M	64	166	stroke	25 (2)	L	25	Yes
S20	57	M	68	163	stroke	14 (15)	L	21	No
S21	66	M	70	160	stroke	14 (15)	R	27	Yes
S22	60	M	99	180	stroke	14 (28)	R	22	No
S23	67	M	99	182	stroke	22 (2)	R	26	No
S24	66	M	69	170	stroke	25 (15)	R	24	No
S25	80	M	87	169	stroke	23 (24)	R	23	No
S26	69	M	75	185	stroke	226 (24)	R	21	Yes
S27	63	M	90	180	stroke	24 (6)	R	28	No
S28	78	M	77	172	stroke	12 (2)	R	23	Yes
S29	36	F	53	160	TBI	132 (5)	R	29	Yes
S30	63	F	68	157	TBI	43 (6)	R	25	No
S31	30	M	77	173	TBI	76 (14)	Bilateral	26	No
Abbreviations: F, female; M, male; TBI, traumatic brain injury; R, right; L, left.									

Table 3

Multi-variate regression model of the association between Δ IHFC and recovery of dynamic balance (Δ CB&M)

Predictor	B	Standard Error	Standardized β coefficients	t	p-value
(Constant)	6.45	1.15		5.58	0.001
Δ FC within the frontal superior lobes	3.18	3.15	0.17	1.01	0.32
Δ FC within the parietal superior lobes	1.38	2.49	0.1	0.55	0.58
Δ FC within the M1s	-1.69	3.05	-0.09	-0.55	0.58
Δ FC within the cerebellum	-11.20	3.46	-0.57	-3.23	0.003
Abbreviations: Δ FC, delta functional connectivity; M1, motor cortex.					

Table 4

Multi-variate regression model of baseline IntraHFC at the cerebellar-cortical and cerebellar-subcortical networks to predict recovery of dynamic balance (Δ CB&M)

Predictor	B	Standard Error	Standardized β coefficients	t	p-value
(Constant)	3.96	1.43		2.75	0.01
FC between right cerebellum & left thalamus_T1	10.57	5.71	0.45	1.85	0.08
FC between right cerebellum & left putamen_T1	1.08	6.8	0.03	0.16	0.87
FC between left cerebellum & right thalamus_T1	-12.03	4.97	-0.51	-2.41	0.02
FC between left cerebellum & right putamen_T1	13.64	3.69	0.62	3.68	0.002
FC between right cerebellum & left frontal superior_T1	-7.34	5.11	-0.26	-1.43	0.16
FC between right cerebellum & & left parietal superior_T1	3.01	6.85	0.09	0.43	0.66
FC between left cerebellum right frontal superior_T1	-4.61	3.03	-0.23	-1.52	0.14
FC between left cerebellum & right parietal superior_T1	-1.58	1.21	-0.20	-1.29	0.2
FC between left cerebellum & right M1_T1	6.97	3.46	0.38	2.01	0.05
FC between right cerebellum & left M1_T1	7.52	6.07	0.2	1.23	0.23
Abbreviations: FC, functional connectivity; T1, pre-intervention; M1, motor cortex					

Table 5

Multi-variate regression model of baseline IntraHFC at the cerebellar-cortical and cerebellar-subcortical networks to predict recovery of self-paced velocity (Δ 10MWT)

Predictor	B	Standard Error	Standardized β coefficients	t	p-value
(Constant)	0.06	0.01		3.74	0.004
FC between right cerebellum & left thalamus_T1	-0.09	0.07	-0.25	-1.34	0.2
FC between right cerebellum & left putamen_T1	-0.07	0.10	-0.10	-0.69	0.5
FC between left cerebellum & right thalamus_T1	-0.03	0.06	-0.09	-0.57	0.5
FC between left cerebellum & right putamen_T1	0.15	0.05	0.44	3.06	0.01
FC between right cerebellum & left frontal superior_T1	0.2	0.07	0.47	2.85	0.01
FC between right cerebellum & left parietal superior_T1	0.3	0.08	0.55	3.75	0.004
FC between left cerebellum right frontal superior_T1	-0.05	0.03	-0.18	-1.57	0.14
FC between left cerebellum & right parietal superior_T1	0.08	0.01	0.69	5.59	0.0001
FC between left cerebellum & right M1_T1	-0.02	0.05	-0.05	-0.39	0.69
FC between right cerebellum & left M1_T1	-0.25	0.07	-0.41	-3.52	0.005
Abbreviations: FC, functional connectivity; T1, pre-intervention; M1, motor cortex					

Table 6

volumes values of 45 ROI's for ABI-group and healthy control group, values are means $\pm$ STD and p-value.

	Regions	Mean-ABI	Mean-Control	P-value
1	Left Lateral Ventricle	20041±10868	13162±8007	p=0.005
2	Left cerebellar cortex	45447±4324	53742±5085	p<0.001
3	Left thalamus	6529±1411	8420±1212	p<0.001
4	Left Caudate	3513±1194	3816±560	p=0.1
5	Left Putamen	4592±1239	5037±813	p=0.6
6	Brain stem	18429±2368	21397±2508	p<0.001
7	Right Lateral Ventricle	20990±10246	11829±6881	p<0.001
8	Right cerebellar cortex	45469±4954	55851±5451	p<0.001
9	Right thalamus	5597±1024	7288±864	p<0.001
10	Right Caudate	3676±1193	3767±575	p=0.2
11	Right Putamen	4572±1193	4763±762	p=0.3
12	Brain Sagittal	1030492±113295	1169795±120367	p<0.001
13	Left Cortex	976483±107623	1136288±124364	p<0.001
14	Right Cortex	191155±22801	235582±27422	p<0.001
15	Sub-cortical Gray Matter	213520±31914	233454±31628	p=0.01
16	Total Gray Matter	427273±63957	464618±63220	p=0.01
17	Optic Chiasm	211±85	205±58	p=0.7
18	Left Middle Frontal Gyrus	8062±1448	10049±1960	p<0.001
19	Left Superior Frontal Lobule Gyrus	13741±1817	17091±2289	p<0.001
20	Left Inferior Parietal Lobule Angular Gyrus	4529±883	5471±1139	p=0.001
21	Left Inferior Parietal Lobule-Supramarginal Gyrus	5207±699	6665±1372	p<0.001
22	Left Superior Parietal Lobule Gyrus	4579±817	6047±1048	p<0.001
23	Left Post-central Gyrus	3300±630	4159±821	p<0.001
24	Left Pre-central Gyrus	4836±971	6333±813	p<0.001
25	Right Middle Frontal Gyrus	7408±1217	9193±1806	p<0.001
26	Right Superior Frontal Lobule Gyrus	13100±1785	16408±2243	p<0.001
27	Right Inferior Parietal Lobule Angular Gyrus	5594±1099	6721±1370	p<0.001
28	Right Inferior Parietal Lobule-Supramarginal Gyrus	4930±731	6458±1159	p<0.001
29	Right Superior Parietal Lobule Gyrus	3781±652	4859±880	p<0.001
30	Right Postcentral Gyrus	2934±466	3698±680	p<0.001
31	Right Precentral Gyrus	4976±762	6004±855	p<0.001
32	Right Postcentral	7384±1052	9250±1390	p<0.001
33	Right Precentral	10884±1429	13311±1622	p<0.001
34	Right Superior Frontal	17804±2330	21873±2859	p<0.001

35	Right Superior Parietal	10430±1476	13467±1809	p<0.001
36	Left Postcentral	7978±1231	9786±1353	p<0.001
37	Left Precentral	10815±1928	13572±1485	p<0.001
38	Left Superior Frontal	18156±2137	22741±2839	p<0.001
39	Left Superior Parietal	10179±1567	13082±1602	p<0.001
40	Left cerebellar WM	13636±2172	16116±2078	p<0.001
41	Right cerebellar WM	13625±2399	16525 ±2318	p<0.001
42	Left Cortical WM	192212±18796	237767 ±27595	p<0.001
43	Right Cortical WM	383367±39034	473349 ±54911	p<0.001
44	Cortical WM	213752±34354	231164±31703	p=0.035
45	WM hypointensities	8273±5928	1946±1872	p<0.001
.Abbreviations: STD, standard deviation; WM, white matter				

Table 7

volumes values of 45 ROI's for ABI-group and elderly group, values are means±STD and p-value.

Regions		ABI group Mean- $\pm$ STD	Elderly Control Mean $\pm$ STD	p-value
1	Left Lateral Ventricle	20041 $\pm$ 10867	26055 $\pm$ 11418	p=0.02
2	Left cerebellar cortex	45447 $\pm$ 4324	47580 $\pm$ 6040	p=0.1
3	Left thalamus	6529 $\pm$ 1411	7149 $\pm$ 1244	p=0.06
4	Left Caudate	3512 $\pm$ 1194	3605 $\pm$ 549	p=0.7
5	Left Putamen	4592 $\pm$ 1239	4104 $\pm$ 644	p=0.002
6	Brain stem	18429 $\pm$ 2368	20138 $\pm$ 2388	p=0.005
7	Right Lateral Ventricle	20990 $\pm$ 10246	25178 $\pm$ 11498	p=0.08
8	Right cerebellar cortex	45469 $\pm$ 4954	49220 $\pm$ 5861	p=0.007
9	Right thalamus	5597 $\pm$ 1024	6277 $\pm$ 784	p=0.021
10	Right Caudate	3675 $\pm$ 1193	3538 $\pm$ 507	p=0.5
11	Right Putamen	4572 $\pm$ 1193	3979 $\pm$ 767	p=0.01
12	Brain Sagittal	1030492 $\pm$ 113295	1063884 $\pm$ 104720	p=0.2
13	Left Cortex	191155 $\pm$ 22801	203386 $\pm$ 21691	p=0.02
14	Right Cortex	192212 $\pm$ 18796	206146 $\pm$ 21234	p=0.007
15	Sub-cortical Gray Matter	49250 $\pm$ 7420	49973 $\pm$ 5065	p=0.6
16	Total Gray Matter	523177 $\pm$ 51075	5564392 $\pm$ 53659	p=0.01
17	Optic Chiasm	211 $\pm$ 85	233 $\pm$ 44	p=0.1
18	Left Middle Frontal Gyrus	8062 $\pm$ 1447	8545 $\pm$ 1390	p=0.1
19	Left Superior Frontal Lobule Gyrus	13741 $\pm$ 1817	14526 $\pm$ 1875	p=0.09
20	Left Inferior Parietal Lobule Angular Gyrus	4529 $\pm$ 882	4409 $\pm$ 749	p=0.5
21	Left Inferior Parietal Lobule-Supramarginal Gyrus	5207 $\pm$ 699	5616 $\pm$ 943	p=0.05
22	Left Superior Parietal Lobule Gyrus	4579 $\pm$ 817	5079 $\pm$ 880	p=0.02
23	Left Post-central Gyrus	3300 $\pm$ 630	3452 $\pm$ 539	p=0.2
24	Left Pre-central Gyrus	4836 $\pm$ 971	5387 $\pm$ 715	p=0.01
25	Right Middle Frontal Gyrus	7409 $\pm$ 1217	7845 $\pm$ 1409	p=0.1
26	Right Superior Frontal Lobule Gyrus	13100 $\pm$ 1785	14340 $\pm$ 2258	p=0.01
27	Right Inferior Parietal Lobule Angular Gyrus	5594 $\pm$ 1099	5430 $\pm$ 981	p=0.5
28	Right Inferior Parietal Lobule-Supramarginal Gyrus	4930 $\pm$ 731	5068 $\pm$ 874	p=0.4
29	Right Superior Parietal Lobule Gyrus	3781 $\pm$ 652	3933 $\pm$ 624	p=0.3
30	Right Post-central Gyrus	2934 $\pm$ 466	3188 $\pm$ 550	p=0.04
31	Right Prec-entral Gyrus	4976 $\pm$ 762	5109 $\pm$ 672	p=0.4
32	Right Post-central	7384 $\pm$ 1052	8064 $\pm$ 941	p=0.007

33	Right Pre-central	10884±1429	11554±1166	p=0.04
34	Right Superior Frontal	17804±2330	19170±2528	p=0.02
35	Right Superior Parietal	10430±1476	11528±1763	p=0.008
36	Left Post-central	7977±1231	8412 ±906	p=0.1
37	Left Pre-central	10815±1928	12201±1297	p=0.001
38	Left Superior Frontal	18156±2137	19566±2459	p=0.01
39	Left Superior Parietal	10179±1567	11614±1618	p=0.001
40	Left cerebellar WM	13636±2172	14089±1997	p=0.3
41	Right cerebellar WM	13625±2399	13866±2094	p=0.6
42	Left Cortical WM	213752±34354	207036±24251	p=0.35
43	Right Cortical WM	213520±31913	209391±24340	p=0.55
44	Cortical WM	427272±63957	416427±48454	p=0.43
45	WM hypointensities	8273±5928	11392±11452	p=0.4
Abbreviations: STD, standard deviation; WM, white matter.				

Figures

Figure: 1

Figure 1

Two resting-state networks of interest identified by ICA: Sensorimotor (left) and Cerebellar (right). A: Left, ICA component corresponding to the sensorimotor network. right, ICA component corresponding to the cerebellar network (transverse brain section-right figure), (coronal brain section-left figure). B: Contrasts of both networks between pre (T1) and post-intervention (T2). Left, Sensorimotor network. Right, Cerebellar network (axial section (left) and coronal section (right)). Color maps represent voxels' significance. N=31.

Figure: 2

Figure 2

Brain Volume analysis-comparison with age-matched control subjects. Percent change of subcortical and cortical brain volumes with respect to age-matched control subjects. Each “x” representing the volume percent change in a specific brain region of a single participant post-ABI. Different colors represent different ABI participants.

Figure: 3

Figure 3

Brain Volume analysis-comparison of ventricles. Percent of volume change of left and right ventricles compared to age-matched control subjects. Each "x" represents the volume percent change of the ventricles of a single participant post-ABI. Different colors represent different ABI participants.

A

B

C

Figure: 4

Figure 4

A scatter plot representing the dependence between brain volume and time since injury. A. Total gray matter volume (mm³) and time since injury. B. Left cortical white matter volume (mm³) and time since injury. C. Right cortical white matter volume (mm³) and time since injury. Black line depicts the linear trend of the data. The range of time since injury range is between 10 and 563 months. Abbreviations: mm³=3 cubic millimetres.