# Supplementary Text 1

## Detailed List of Neuropsychological Tests

The Hopkins Verbal Learning Test – Revised[1] is a verbal memory test in which subjects are read a list of 12 recall words and are then asked to repeat the 12 words back in any order. The test is repeated using the same words for two additional trials back to back, to compile a Total Recall score. After a 20–25 min delay, subjects are then asked to recall as many words on the list as possible for a Delayed Recall test score. For the final Recognition Discrimination test score, subjects are asked to recognize the recall words from a list of 24 words including the 12 original recall words with 12 additional words.

The Brief Virtuospatial Memory Test - Revised[2] is a memory test in which the subject is asked to review an image of six geometric figures for 10 sec and is then asked to recreate the image with as many of the figures properly oriented on the page as possible. The test is repeated using the same image for two additional trials back to back, to compile a Total Recall score. After a 25 min delay, subjects are again asked to recreate the image again for a Delayed Recall test score. For the final Recognition Discrimination test score, subjects are asked to identify the six original figures from 12 geometric figures.

The Grooved Peg Board test[3] assesses the time taken for the subject to orient and place 25 grooved pegs into a peg board with 25 grooved slots arranged in a 5 x 5 grid. This test is conducted first with the dominant hand and then repeated with the non-dominant hand. The score indicates the number of seconds required to complete the 25 peg task.

The Color-Word Interference Test[4] is a four part test, each of which involves progressing through a series of cards and naming the color associated with each card. During the first test (CW1), the subject is asked to name the color of a colored patch on each card. The second test (CW2) includes reading a color name printed in black ink on each card. During the third test (CW3), each card has a color word printed in a disparate color ink and the subject must name the color of the print ink. During the final test (CW4), multiple color words are printed on the card in disparate ink color, and the subject must name the ink color of the word indicated with a box around it. The reported score is the time in seconds required to complete the bank of cards for each test.

The Verbal Fluency Test[4] includes two tests that require the subject to generate lists of as many words as possible in 1 min based on semantic (categorical) or phenomic (starting with the same letter) cues.

The Digit Span[5] Digits Forward is a test of working memory in which subjects are asked to repeat sequences of three to nine numbers in order. During the Digits Backward test, subjects are once again asked to repeat a sequence of three to nine numbers, but in reverse order.

The Beck Depression Inventory-II (BDI-II)[6] is a self-reported 21 item inventory assessing symptoms of depression with a higher score indicating more depression symptoms. The BDI-II manual indicates that a score of <13 = minimal symptoms of depression, a score of 14–19 = mild symptoms of depression, a score of 20–28 = moderate symptoms of depression, and a score of >29 = severe symptoms of depression.

The Processing Speed Index from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV)[7] is a test of visuomotor processing speed. The test is composed of two written portions, including a coding test in which subjects must translate symbols using an alpha-numeric key, and a symbol search test in which subjects search a series of symbols for two specific cued symbols. The total score reflects the combined number of correct responses within 120 sec for each test.

# Supplementary Text 2

## Detailed List of Mood, Sleep, and Fatigue Questionnaires

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI)[8] was used to assess self-reported subject fatigue over the past 7 days at baseline and again at 12 months. Both baseline and post-treatment scores were collected for 10 subjects. Total fatigue score includes subscales of general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor. Three questions were overlooked by one subject at baseline and were imputed from overlapping identically scaled questions from the Profile of Mood States (POMS) survey given within the same questionnaire session. Average individual subtest and overall fatigue scores were determined from these 10 subjects.

The Profile of Mood States (POMS Standard Form; Multi-Health Systems Inc., North Tonawanda, NY) was used to assess subject mood states over the past 7 days at baseline and 12 months. Both baseline and post-treatment scores were collected for 10 subjects. Total mood disturbance score was assessed as well as subscales of tension/anxiety, depression, anger/hostility, vigor, fatigue, and confusion. Average individual subtest and overall fatigue scores were determined from these 10 subjects.

The Brief Fatigue Inventory[9] was used to assess self-reported subject fatigue over the past 7 days and over the past 24 h at baseline and again at 12 months. Both baseline and post-treatment scores were collected for 10 subjects. Average individual subtest and overall fatigue scores were determined from these 10 subjects.

The Pittsburg Sleep Quality Index (PSQI)[10] was used at baseline and again at 12 months to assess subject sleep quality over the past month. Both baseline and post-treatment scores were collected for 10 subjects. Average individual subtest and overall fatigue scores were determined from these 10 subjects.

Supplementary Table S1. List of Ten *a Priori* Selected Regions of Interest Chosen to Assess Altered Connectivity for Mild TBI Subjects Over One Year Including Nine Months of GH Therapy

| *Region of interest* | *Representing* | *References* | *Relevant findings* |
|---|---|---|---|
| Posterior cingulate cortex | Default mode network | [11, 12] | Decreased resting state functional connectivity in posterior cingulate cortex region of default mode network following mild TBI |
| Frontal eye field (R) | Dorsal attention network | | Selected as a region in the dorsal attention network as a contrast to the default mode network. |
| Thalamus (L) | Thalamus | [13, 14] | Altered resting state functional connectivity in thalamus following mild TBI is correlated with levels of fatigue. |
| Thalamus (R) | Thalamus | [13, 14] | Altered resting state functional connectivity in thalamus following mild TBI is correlated with levels of fatigue. |
| Post-central gyrus (L) | Somatosensory cortex | [13] | Altered resting state functional connectivity in post-central gyrus following mild TBI is correlated with levels of fatigue. |
| Pre-central gyrus (L) | Primary motor cortex | [13] | Altered resting state functional connectivity in pre-central gyrus following mild TBI is correlated with levels of fatigue. |
| Cerebellar lobules IV/V | Cerebellum | [15] | Altered resting state functional connectivity in cerebellum of post-concussive athletes |
| Cerebellar lobule VIII | Cerebellum | [15] | Altered resting state functional connectivity in cerebellum of post-concussive athletes |
| Nucleus accumbens (L) | Reward and motivation | [16, 17] | Selected as a region related directly to reward and motivation for movement as related to fatigue. |
| Supplementary motor area (L) | Motor initiation and motivation | [18] | Selected as a region related to behavioral apathy with decreased functional connectivity associated with greater behavioral apathy and decreased action initiation. |

TBI, traumatic brain injury; GH, growth hormone.

Supplementary Table S2. Average Body Composition and Resting Energy Expenditure (REE) for Mild TBI Subjects Before and After One Year Including Nine Months of GH Therapy

| | *Pre-treatment* | *Post-treatment* | p |
|---|---|---|---|
| Body mass (kg) | 86.8 ± 22.7 | 87.3 ± 23.8 | 0.507 |
| Lean mass (kg) | 50.7 ± 15.4 | 53.0 ± 15.4 | < 0.001* |
| Fat mass (kg) | 33.3 ± 9.8 | 31.6 ± 10.5 | 0.054 |
| Bone mineral content (g) | 2,780 ± 657 | 2,726 ± 645 | < 0.001* |
| REE (mL $O_2$*$kg^{-1}$*$min^{-1}$) | 2.53 ± 0.34 | 2.70 ± 0.25 | 0.018* |

Baseline and 12 month measures were compared using paired *t* tests.
*Statistical significance ($p < 0.05$).
TBI, traumatic brain injury; GH, growth hormone.

Supplementary Table S3. Regions of Altered Connectivity for Mild TBI Subjects Over One Year Including Nine Months of GH Therapy

| | | | *Cluster coordinates* | | | | |
|---|---|---|---|---|---|---|---|
| *Seed region* | *Connected region* | *Connectivity change* | *x* | *y* | *z* | $k_E$ | $p_{FWE}$ |
| Left post-central gyrus | Left hippocampus | Increased | -18 | -32 | -4 | 8 | 0.003 |
| Left post-central gyrus | Left superior temporal gyrus | Increased | -50 | -10 | -8 | 13 | 0.006 |
| Left thalamus | Left post-central gyrus | Increased | -60 | -22 | 34 | 88 | 0.001 |
| Right frontal eye field | Left post-central gyrus | Decreased | -50 | -26 | 62 | 77 | <0.001 |
| Posterior cingulate cortex | Left cerebellar lobule VIIb | Decreased | -44 | -54 | -46 | 33 | <0.001 |

Connectivity was examined using whole-brain intrinsic connectivity analysis as well as 10 *a priori* selected seed regions of the posterior cingulate cortex (PCC), right frontal eye field (FEF), left thalamus, right thalamus, left post-central gyrus, left pre-central gyrus, right cerebellar lobule IV/V, right cerebellar lobule VIII, left nucleus accumbens, and left supplementary motor area (SMA). Significant change in connectivity was determined with flexible factorial analysis using peak-level familywise error (FWE) corrected $p < 0.05$, with clusters ≥8 voxels reported.
TBI, traumatic brain injury; GH, growth hormone.

Supplementary Table S4. Regions of Altered GM Volume for Mild TBI Subjects Over One Year Including Nine Months of GH Therapy

| *Brain region* | *Volume change* | *Cluster coordinates* | | | $k_E$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| Left mid cingulate gyrus | Increased | -3 | -2 | 45 | 46 | 0.002 |
| Left mid frontal gyrus | Increased | -24 | 2 | 59 | 35 | 0.013 |
| Left inferior frontal gyrus | Increased | -45 | 17 | -9 | 12 | 0.003 |
| Left inferior frontal gyrus | Decreased | -36 | 24 | -12 | 12 | 0.014 |

Significant change in GM volume was determined with flexible factorial analysis using peak-level familywise error (FWE) corrected $p < 0.05$, with clusters ≥8 voxels reported.

GM, gray matter; TBI, traumatic brain injury; GH, growth hormone.

Supplementary Table S5. Regions of Altered Cortical Thickness for Mild TBI Subjects Over One Year Including Nine Months of GH Therapy

| *Brain region* | *Thickness change* | *Cluster coordinates* | | | $k_E$ | $p_{FWE}$ |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| Left superior frontal gyrus | Increased | -17 | 43 | 42 | 564 | <0.001 |
| Right superior frontal gyrus | Increased | 16 | 41 | 43 | 147 | 0.003 |
| Right superior frontal gyrus | Increased | 18 | 54 | 24 | 16 | 0.021 |
| Right mid frontal gyrus | Increased | 31 | 30 | 41 | 40 | 0.015 |
| Left angular gyrus | Decreased | -39 | -61 | 27 | 11 | 0.001 |
| Left pre-central gyrus | Decreased | -37 | 2 | 30 | 28 | 0.003 |
| Right cuneus | Decreased | 19 | -77 | 35 | 21 | 0.007 |
| Right post-central gyrus | Decreased | 41 | -31 | 39 | 38 | 0.008 |

Significant change in cortical thickness was determined with flexible factorial analysis using peak-level familywise error (FWE) corrected $p < 0.05$, with clusters ≥8 voxels reported.

TBI, traumatic brain injury; GH, growth hormone.

## Supplementary References


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