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NeuroGage® 3.0 Longitudinal Brain Volumetric Analysis

Patient: Patient JB

Location of MRI: Hospital/Institution Richomond, VA

Dates of MRIs: 09/XX/18 (t1) & 05/XX/21 (t2)

Date of report: 06/17/2021

Age at midpoint: 47 years old

Date of injury: 03/XX/2018

Brain Region	LH percent change per year	LH normative percentile rank	RH percent change per year	RH normative percentile rank
Whole Brain Parenchyma	-0.37%	45.86%	-0.05%	71.83%
Forebrain Parenchyma	-0.64%	26.24%	-0.26%	50.53%
Cerebral white matter	0.84%	97.89%	1.82%	99.96%
Cortical gray matter	-1.87%	**2.49%**	-2.09%	**0.68%**
SCN+IFT	0.58%	95.46%	0.84%	99.65%
Ventricles	0.78%	13.12%	-0.20%	1.90%
Superior Lateral Ventricles	0.79%	7.79%	-0.38%	0.80%
3rd ventricle	0.33%	79.51%	2.79%	53.61%
Inferior lateral ventricle	3.57%	93.39%	-2.61%	9.56%
Cerebellum	1.25%	98.06%	1.02%	99.17%
Cerebellar White Matter	8.11%	100.00%	5.98%	99.95%
Cerebellar Gray Matter	-0.63%	9.69%	-0.35%	61.24%
Brainstem	0.22%	85.72%	1.80%	99.94%
Thalamus	1.87%	99.90%	2.70%	99.99%
Ventral Diencephalon	-2.42%	8.21%	-0.47%	82.93%
Basal Ganglia	-2.53%	**0.04%**	-2.40%	**4.68%**
Putamen	-1.20%	23.11%	-1.54%	43.83%

Virginia Institute of Neuropsychiatry

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Caudate	-2.16%	**0.91%**	-1.26%	21.07%
Nucleus Accumbens	-5.41%	**2.13%**	-3.13%	13.64%
Pallidum	-8.90%	**0.09%**	-9.17%	**1.48%**
Cingulate	-0.64%	22.05%	-2.81%	**1.26%**
Anterior cingulate	-4.85%	**0.70%**	-4.85%	**1.24%**
Posterior cingulate	3.26%	90.76%	1.63%	60.62%
Isthmus cingulate	0.83%	50.27%	-1.73%	**4.00%**
Frontal Lobe	-2.34%	**1.73%**	-1.72%	**2.29%**
Superior frontal	-2.30%	**4.19%**	-2.86%	**1.55%**
Middle frontal	-3.87%	8.47%	-0.66%	37.23%
Inferior frontal	-2.89%	9.02%	3.79%	99.18%
Lateral orbitofrontal	-2.17%	**2.42%**	-3.08%	**1.36%**
Medial orbitofrontal	-2.62%	**4.55%**	-2.96%	**0.52%**
Paracentral	-0.66%	38.35%	-1.11%	23.76%
Primary motor	-1.15%	31.39%	-6.18%	**0.21%**
Parietal Lobe	-0.39%	51.32%	-1.98%	9.13%
Primary sensory	0.49%	68.72%	0.42%	58.95%
Medial parietal	0.10%	53.63%	-0.41%	58.20%
Superior parietal	-0.74%	59.94%	-1.59%	27.28%
Inferior parietal	1.37%	58.45%	-4.86%	**0.95%**
Supramarginal	-3.24%	9.69%	-0.57%	37.90%
Occipital lobe	-3.34%	**0.50%**	-3.73%	**0.60%**
Medial occipital	-5.96%	**0.00%**	-3.51%	**4.01%**
Lateral occipital	-0.04%	50.30%	-3.94%	**2.14%**
Temporal lobe	-1.76%	**0.88%**	-1.48%	**3.36%**
Transverse temporal + superior temporal	1.92%	93.79%	-0.50%	36.97%
Posterior superior temporal sulcus	-9.66%	9.02%	-0.55%	34.07%
Middle Temporal	-2.76%	6.54%	0.14%	59.79%
Inferior temporal	-5.89%	**0.00%**	-2.41%	7.24%
Fusiform	-2.36%	**2.39%**	-3.09%	**0.86%**
Parahippocampal	-1.84%	16.07%	-1.48%	19.65%

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Entorhinal cortex	-3.12%	**3.29%**	2.36%	83.21%
Temporal pole	-3.56%	7.51%	-8.61%	**0.01%**
Amygdala	-2.48%	**3.34%**	-1.28%	**4.39%**
Hippocampus	-1.62%	16.64%	0.83%	97.93%

Key: t1 = time of first NeuroQuanted MRI. t2 = time of second NeuroQuanted MRI. L = left hemisphere. R = right hemisphere. Vol = volume. %tile = normative percentile.

~~---~~ (strikethrough) indicates that the data were unreliable.

Bold font indicates a normative percentile which was statistically significantly abnormal, defined as ≤ 5th or ≥ 95th normative percentile

Red background indicates a normative percentile which was associated with parenchymal atrophy (or similarly, ventricular enlargement).

Methods: MRI brain segmentation and volumetry was performed with NeuroQuant® 3.0 (https://www.cortechslabs.com/neuroquant). The individual subject's data were compared to normal control data (N=80: 40 women, 40 men) obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database using NeuroGage®, proprietary software developed by NeuroGage LLC (www.NeuroGage.com).

Our methods describing the NeuroGage® Longitudinal analysis have been published previously (Ross, Ochs et al. 2012, Ross, Castelvecchi et al. 2013, Ross, Graham et al. 2013, Ross, Ochs et al. 2014, Ross, Ochs et al. 2015). The results were adjusted for sex.

The effects of age on brain volume were accounted for using our previously published method; in brief, if a younger patient's brain decreased volume at a significantly faster rate than the older normal controls, then there was high confidence that the brain truly atrophied. The ages (t1) of the NeuroGage® ADNI normal control subjects ranged from 60-72, and the mean age at the midpoint of the t1-t2 interval was 69.1 years for men and 68.8 years for women. The patient's results should be interpreted accordingly, consistent with the effects of age on brain volume, especially if the patient's age fell outside these cutoffs.

Inspection for image quality: NeuroQuant® segmented DICOM (colored MRI brain) images were inspected visually by D.E.R. The following issue was identified:

- Also see accompanying NeuroGage® Cross-sectional analyses.

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Summary of abnormal findings: Abnormal volume changes consistent with parenchymal atrophy were found in the following regions:

- The left and right cortical gray matter regions atrophied abnormally fast.
- The left and right basal ganglia regions atrophied abnormally fast.
- The left caudate atrophied abnormally fast.
- The left nucleus accumbens region atrophied abnormally fast.
- The left and right pallida atrophied abnormally fast.
- The right cingulate region atrophied abnormally fast.
- The left and right anterior cingulate regions atrophied abnormally fast.
- The right isthmus cingulate region atrophied abnormally fast.
- The left and right frontal lobes atrophied abnormally fast.
- The left and right superior frontal regions atrophied abnormally fast.
- The left and right lateral orbitofrontal regions atrophied abnormally fast.
- The left and right medial orbitofrontal regions atrophied abnormally fast.
- The right primary motor region atrophied abnormally fast.
- The right inferior parietal region atrophied abnormally fast.
- The left and right occipital lobes atrophied abnormally fast.
- The left and right medial occipital regions atrophied abnormally fast.
- The right lateral occipital region atrophied abnormally fast.
- The left and right temporal lobes atrophied abnormally fast.
- The left inferior temporal region atrophied normally fast.
- The left and right fusiform regions atrophied abnormally fast.
- The left entorhinal cortical region atrophied abnormally fast.
- The right temporal pole atrophied abnormally fast.
- The left and right amygdalae atrophied abnormally fast.

Interpretation

In contrast to the interpretation based on simple visual inspection, he had multiple abnormal longitudinal brain volume changes. This finding was consistent with previous reports that NeuroGage® is more sensitive for detecting longitudinal brain volume abnormalities than are radiologists using the traditional method of simple visual inspection (Ross, Ochs et al. 2015) .

35 brain regions atrophied abnormally fast (or equivalently, ventricular regions enlarged abnormally fast), which was greater than the number expected by chance alone (5 regions = 5% x 104 regions).

Regarding anatomic correlations:

- Abnormally fast atrophy of the left superior frontal region correlated with cross-sectional abnormally small volume at t2 but not t1.
- Abnormally fast atrophy of the left inferior temporal region correlated with cross-sectional abnormally small volume at t2 but not t1.

Decades of research has shown that traumatic brain injury (TBI) is characterized by extensive brain atrophy and, similarly, ventricular enlargement (Bigler 2005, Bigler 2011). Most of the early research was conducted on patients with moderate or severe TBI.

Previously published studies of patients with mild or moderate TBI often have found atrophy (Hofman, Stapert et al. 2001, MacKenzie, Siddiqi et al. 2002, Ross, Ochs et al. 2012, Toth, Kovacs et al. 2013, Zhou, Kierans et al. 2013, Maller, Thomson et al. 2014, Ross, Ochs et al. 2014, Wang, Xie et al. 2015, Epstein, Legarreta et al. 2016, Govindarajan, Narayana et al. 2016, Ross, Ochs et al. 2016, Zagorchev, Meyer et al. 2016, Rajesh, Cooke et al. 2017) but also have found abnormal enlargement (Ross, Ochs et al. 2014, Wang, Xie et al. 2015, Govindarajan, Narayana et al. 2016, Ross, Ochs et al. 2016, Niu, Bai et al. 2020, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021).

These studies have found that traumatic brain injury is characterized by abnormal volume (small or large for parenchymal regions, small or large for ventricular regions) of the following brain regions:

Brain region	Small or large?	References
Whole brain parenchyma	Small or Large	(Bigler 2005, Bigler 2011, Ross, Ochs et al. 2012, Ross, Ochs et al. 2014, Ross, Seabaugh et al. 2021)
Cerebral white matter	Small	(Farbota, Sodhi et al. 2012, Ross, Ochs et al. 2014, Cole, Jolly et al. 2018)
Cortical gray matter	Small or Large	(Toth, Kovacs et al. 2013, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Cerebellum	Small	(Bigler 2005, Bigler 2011, Farbota, Sodhi et al. 2012, Cole, Jolly et al. 2018)
Cerebellar white matter	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Brainstem	Small	(Farbota, Sodhi et al. 2012)

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Ventricles	Large	(Toth, Kovacs et al. 2013)
Lateral ventricles	Large	(Bigler 2005, Bigler 2011)
Superior lateral ventricles	Small	(Ross, Seabaugh et al. 2021)
Inferior lateral ventricles	Small	(Ross, Seabaugh et al. 2021)
Third ventricle	Large	(Bigler 2005, Bigler 2011)
Thalamus	Small or Large	(Bigler 2005, Bigler 2011, Farbota, Sodhi et al. 2012, Zagorchev, Meyer et al. 2016, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Diencephalon	Small or Large	(Bigler 2005, Bigler 2011, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Caudate	Small or Large	(Bigler 2005, Bigler 2011, Zagorchev, Meyer et al. 2016, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020)
Putamen	Small	(Bigler 2005, Bigler 2011, Zagorchev, Meyer et al. 2016, Cole, Jolly et al. 2018)
Nucleus accumbens	Large	(Ross, Seabaugh et al. 2021)
Pallidum	Small	(Bigler 2005, Bigler 2011, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Cingulate gyrus	Small or Large	(Bigler 2005, Bigler 2011, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Anterior cingulate gyrus	Large	(Govindarajan, Narayana et al. 2016, Niu, Bai et al. 2020, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Posterior cingulate gyrus	Large	(Niu, Bai et al. 2020, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Isthmus cingulate	Large	(Ross, Seabaugh et al. 2021)
Frontal lobes	Small	(Bigler 2005, Bigler 2011)

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Frontal cortical regions	Small	(Farbota, Sodhi et al. 2012, Govindarajan, Narayana et al. 2016, Cole, Jolly et al. 2018)
Superior frontal cortex	Small	(Rajesh, Cooke et al. 2017)
Middle frontal gyrus	Small or Large	(Rajesh, Cooke et al. 2017, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Rostral middle frontal gyrus	Large	(Wang, Xie et al. 2015)
Pars triangularis	Small	(Maller, Thomson et al. 2014)
Lateral orbitofrontal cortex	Small	(Zhou, Kierans et al. 2013, Ross, Seabaugh et al. 2020)
Medial orbitofrontal cortex	Small	(Zhou, Kierans et al. 2013, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Paracentral cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Primary motor cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Parietal lobes	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Parietal cortical regions	Small	(Govindarajan, Narayana et al. 2016)
Primary sensory cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Medial parietal cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Precuneus	Small or Large	(Zhou, Kierans et al. 2013, Wang, Xie et al. 2015)
Superior parietal cortex	Large	(Govindarajan, Narayana et al. 2016, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Inferior parietal cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Supramarginal cortex	Small	(Maller, Thomson et al. 2014, Govindarajan, Narayana et al. 2016)
Angular cortex	Small	(Maller, Thomson et al. 2014)

Posterior parietal cortical regions	Small	(Farbota, Sodhi et al. 2012)
Occipital lobes	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Occipital cortical regions	Small	(Farbota, Sodhi et al. 2012, Cole, Jolly et al. 2018)
Medial occipital cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Cuneus	Large	(Govindarajan, Narayana et al. 2016)
Temporal lobes	Small	(Bigler 2005, Bigler 2011)
Temporal cortical regions	Small	(Farbota, Sodhi et al. 2012, Cole, Jolly et al. 2018)
Posterior superior temporal sulcus cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Middle temporal cortex	Small or Large	(Wang, Xie et al. 2015, Govindarajan, Narayana et al. 2016, Ross, Seabaugh et al. 2021)
Inferior temporal cortex	Small	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Fusiform cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Parahippocampal gyrus	Small	(Farbota, Sodhi et al. 2012)
Entorhinal cortex	Large	(Ross, Seabaugh et al. 2020)
Amygdala	Small	(Bigler 2005, Bigler 2011, Zagorchev, Meyer et al. 2016, Cole, Jolly et al. 2018)
Hippocampus	Small	(Bigler 2005, Bigler 2011, Maller, Thomson et al. 2014, Cole, Jolly et al. 2018)

In Mr. Booker's case, the regions of longitudinal volume decrease likely were due to TBI, possibly due to progressive atrophy or to reversal of previous abnormal enlargement. Based on these studies, he had the following brain regions that showed abnormally fast decrease of brain volume and were consistent with TBI:

- Cortical gray matter
- Caudate
- Pallidum

- Cingulate gyrus
- Frontal lobes
- Superior frontal gyrus
- Lateral orbitofrontal regions
- Medial orbitofrontal regions
- Inferior parietal region
- Occipital lobes
- Medial occipital regions
- Lateral occipital region
- Temporal lobes
- Inferior temporal region
- Amygdala

Regions that were opposite of the pattern previously reported with TBI included the following:

- Nucleus accumbens
- Anterior cingulate region
- Isthmus cingulate region
- Primary motor cortex
- Inferior parietal cortex
- Fusiform cortex
- Entorhinal cortex

Although he had several brain volume findings opposite of the pattern previously reported to occur with TBI, he had many more regions consistent with the TBI pattern.

Regarding differential diagnosis of volume abnormalities, Mr. Booker had a diagnosis of posttraumatic stress disorder due to the 03/07/18 collision and due to pre-collision emotional trauma. Posttraumatic stress disorder (PTSD) has been associated with abnormal brain volume (small or large for parenchymal regions) in the prefrontal cortex (small) (Moyer 2016), anterior cingulate (small) (Moyer 2016), hippocampus (small) (O'Doherty, Chitty et al. 2015, Ahmed-Leitao, Spies et al. 2016, Moyer 2016), and amygdala (large or small) (Ahmed-Leitao, Spies et al. 2016). Consistent with this pattern, Mr. Booker had abnormally fast volume decrease of the anterior cingulate regions and amygdalae. Overall, his pattern was more consistent with that of TBI.

Mr. Booker had a diagnosis of generalized anxiety disorder not due to the incident. Generalized anxiety disorder is characterized by abnormal volume (small or large for parenchymal regions) of the dorsolateral prefrontal cortex (small), ventral inferior

prefrontal cortex (small), orbitofrontal cortex (small), anterior cingulate cortex (small), posterior cingulate cortex (small), precuneus (large) and amygdala (large) (Kolesar, Bilevicius et al. 2019). Consistent with this pattern, Mr. Booker had abnormally fast volume decrease of the orbitofrontal regions and anterior cingulate regions. In opposition to this pattern, he had abnormally fast enlargement of the amygdalae. Overall, his pattern better matched that of TBI.

The patient had a diagnosis of restless legs syndrome not due to the incident. A recent PubMed search of "Restless legs syndrome mri volumetry" found no references.

He had a history of cocaine use (last use in January 2019) but not cocaine use disorder (also called "addiction" or "dependence"). There is no evidence that--in the absence of dependence--cocaine use causes abnormal brain volume. However, cocaine use disorder has been found to be associated with brain volume abnormalities. Despite the fact that he did not have cocaine use disorder, that literature will be reviewed here for the sake of thoroughness. Cocaine use disorder is characterized by abnormal volume (small or large for parenchymal regions, small or large for ventricular regions, or abnormal asymmetry) of the following brain regions: inferior lateral ventricle (large) (Bittencourt, Bampi et al. 2021), cerebellar white matter (small) (Sim, Lyoo et al. 2007), cerebellar gray matter (small) (Ersche, Barnes et al. 2011), thalamus (small) (Sim, Lyoo et al. 2007), caudate (large) (Jacobsen, Giedd et al. 2001), putamen (large) (Jacobsen, Giedd et al. 2001) or small (Bittencourt, Bampi et al. 2021), ventral diencephalon (small) (Bittencourt, Bampi et al. 2021), nucleus accumbens (small) (Schuch-Goi, Goi et al. 2017, Bittencourt, Bampi et al. 2021), cingulate (small) (Ersche, Barnes et al. 2011), anterior cingulate cortex (small) (Franklin, Acton et al. 2002), orbitofrontal cortex (small) (Franklin, Acton et al. 2002, Sim, Lyoo et al. 2007, Ersche, Barnes et al. 2011, Bittencourt, Bampi et al. 2021), premotor cortex (small) (Sim, Lyoo et al. 2007), temporal lobe (small) (Bartzokis, Beckson et al. 2000, Sim, Lyoo et al. 2007), superior temporal cortex (small) (Franklin, Acton et al. 2002), inferior temporal cortex (small) (Bittencourt, Bampi et al. 2021), amygdala (small, and abnormal asymmetry) (Makris, Gasic et al. 2004), and hippocampus (small) (Bittencourt, Bampi et al. 2021). Consistent with this pattern, he had abnormally fast diminution of the nucleus accumbens, anterior cingulate cortex, orbitofrontal cortex, premotor cortex, temporal lobes, inferior temporal region and amygdalae. In opposition to this pattern, he had abnormally fast diminution of the caudate. However, for most of the regions that decreased volume abnormally fast, they did so at fast rates that were much more consistent with his history of TBI than with a possible history of much more chronic cocaine use. As an example, I will discuss the nucleus accumbens, a classical brain region for addiction disorders. Mr. Booker's rate of volume decrease for the left nucleus accumbens was -5.41% per

year, a fast rate of atrophy. Hypothetically, if he had cocaine use disorder for 20 years causing the accumbens to shrink at that rate, his accumbens would have shrunk to 32.9% of its original volume and would have been extremely small on the t1 and t2 cross-sectional analyses, which was not the case. In contrast, if his 03/07/18 TBI caused the accumbens to shrink at that rate, it would have shrunk (over the 1.8 year interval from date of injury to midpoint of t1-t2 analysis) to about 90% of its original volume, consistent with normal volumes of the left accumbens at t1 (53rd normative %tile) and t2 (23rd normative %tile). Therefore, his longitudinal diminution of the nucleus accumbens was much more consistent with the fast rates of atrophy seen in the first couple years after TBI than with the smaller rates of atrophy seen with many years of cocaine use disorder. Furthermore, his cross-sectional findings were much more consistent with TBI than with cocaine use disorder (see related t1 and t2 cross-sectional reports).

The patient had the following associations between longitudinal volume abnormalities and clinical symptoms:

- Abnormally fast longitudinal volume decrease of the anterior cingulate gyrus correlated with impaired mood (Smith, Ahern et al. 2019) and PTSD symptoms (Moyer 2016).
- Abnormally fast longitudinal volume decrease of the superior frontal gyri correlated with executive dysfunction. Previous research has shown that damage to the lateral prefrontal cortex (including the superior frontal gyrus, middle frontal gyrus and inferior frontal gyrus) impairs planning, executive attention, working memory, decision-making, and inhibitory controls (Fuster 2019).
- Abnormally fast longitudinal volume decrease of the inferior parietal region correlated with dyscalculia. Previous research has shown that abnormal volume of the inferior parietal region is associated with dyscalculia (Seghier 2013).
- Abnormally fast longitudinal volume decrease of the entorhinal cortex correlated with impaired short-term memory. Previous research has found that abnormal volume of the entorhinal cortex was associated with impaired short-term memory (Schwartz, Jessell et al. 2013).
- Abnormally fast longitudinal volume decrease of the amygdalae correlated with PTSD. Previous research has found that abnormal volume of the amygdalae was associated with PTSD (Ahmed-Leitao, Spies et al. 2016)

In summary, he had a clearly abnormal pattern of brain volumes that provided objective evidence supporting the diagnosis of TBI.

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