NeuroGage® 4.0 Cross-sectional Brain Volumetric Analysis

Patient: AB

Location of MRI: Facility – Location

Date of MRI: mm/dd/21

Date of report: mm/dd/22

Age at MRI: 47 years old

Referring physician: FirstName LastName, M.D.

Note: This cross-sectional (1 timepoint) analysis complements the related NeuroQuant® 4.0 cross-sectional analyses (appended).

Summary (*Note: for detailed information, see the sections further below.)*

NeuroQuant® MRI brain volume analysis showed the following:

- Their intracranial volume was abnormally large.
- 11 brain regions were abnormally small.
- 19 brain regions were abnormally large.

NeuroGage® brain volume analyses showed the following:

- 11 pairs of brain regions had abnormal asymmetry.
- The TBI Biomarker test:
  - TBI ✓
  - Normal Ø
- The TBI Biomarker test (a test based on artificial intelligence algorithms) showed that the patient's overall pattern of brain volumes matched that of patients with chronic mild or moderate TBI better than that of normal controls.

Although the patient had brain disorders other than traumatic brain injury, their pattern of brain volume abnormalities better matched that of chronic mild or moderate TBI. The findings were consistent with traumatic brain injury. However, other disorders

generally are known to be associated with this pattern of volume abnormalities and might be considered depending on their relevance and clinical context.

The pattern of extensive abnormal enlargement was consistent with chronic acquired brain injury but uncommon in most other chronic brain disorders.

Several of the patient's volume abnormalities correlated with specific symptoms.

Overall, the pattern of brain volumes constituted objective evidence consistent with the diagnosis of TBI.

Brain volume measurement does not, by itself, allow diagnosis of TBI. The volumetric findings should be integrated with other clinical data in order to arrive at the best diagnosis.

Recommendations

Repeat MRI with NeuroQuant® and NeuroGage® cross-sectional and longitudinal analyses now to assess for possible progressive volume changes.

Sources

- VIN NQ/NG Only New Caller Questionnaire
- 04/09/21 report by Diagnostic Specialists
- MRI Order
- 05/04/21 MRI Brain radiology report

History

48-year-old woman who, on mm/dd/18, was in a motor vehicle collision. Her diagnoses and symptoms included the following:

- mm/dd/18 motor vehicle collision:
  - Rear-ended and "run over" by tractor-trailer
  - Airbags deployed
  - Car totaled
  - Transported by ambulance to ER
- Traumatic brain injury, mild to moderate
  - Loss of consciousness, amnesia, disorientation, stunned

  - GCS at ER: 15
  - Multiple head lacerations
  - CT scan revealed multiple pieces of glass embedded in her scalp.
- Cognitive impairment
  - Memory changes
  - Reading retention difficulties
  - Speech difficulties including stuttering
  - Word-finding difficulties
- Impaired fine motor coordination
- Mood impairment
  - Mild depression
  - Irritability
  - Anxiety
- Impaired sleep and wakefulness
  - Insomnia
  - Fatigue
  - Snoring
- Change in libido
- Impaired visual system
  - Horizontal gaze nystagmus
  - Dizziness [sounded like vertigo]
- Tinnitus, right ear
- Posttraumatic stress disorder
  - Flashbacks
  - Nightmares
  - Excessive nervousness while driving, especially with trucks behind her
- Posttraumatic headaches
  - Cervicogenic, apparently
  - Occipital location
- Cervical spine pain
  - Post C5-6 artificial disc replacement
- Thoracic spine pain
  - T6-7 central disc herniation
- Lumbar spine pain

  - L3-4, L4-5, and L5-S1 disc herniations
- Bilateral TMJ tenderness
- Bilateral shoulder pain
- Right elbow pain
- Right hip pain
- Severe numbness and tingling bilateral upper and lower extremities
- Vitamin D deficiency

Note: This cross-sectional (1 timepoint) analysis complements the related NeuroQuant® 3.1 cross-sectional analyses (appended).

Visual inspection of brain images

The brain MRI was interpreted based on visual inspection by Dr. B., radiologist, as showing the following:

- Diffusion tensor imaging with a C-FAST score of 2. This does not meet statistical significance to definitely confirm traumatic axonal injury. However, this does not exclude the possibility of postconcussion syndrome, which should be based on clinical grounds.

Quality control

- *Summary*: The grayscale and segmented DICOM images were high quality and provided a valid basis for the NeuroQuant results.
- *Details*:
  - MRI scanner:
  - Brand: Siemens, 3T
  - Model: Verio
  - Scanner software version: syngo MR B19
- Inspection of the MRI grayscale images showed:
  - The images were high quality and showed good differentiation between gray and white matter.
  - The ears, nose and vertex all were present.
- Visual inspection of the segmented DICOM images showed no segmentation errors.
- Manual comparison of the scanning parameters used versus those recommended by CorTechs Labs showed good compatibility.
- NeuroQuant® 4.0 automated Compatibility Assessment (attached) showed good quality but noted the following problems:

- EchoTime was 2.36 and expected value was 21 (not within 10% tolerance). This was a known technical issue that typically did not reduce the quality of the segmented images (Micki Maes, CorTechs Labs Clinical Operations Manager, email communication on 08/05/20).
- SpacingBetweenlices was set at [blank] instead of the expected value of equal to or less than <= 1.2, which was not within 10% tolerance.
- SpacingBetweenSlices was noted as "nan," [not a number], indicating that it was missing. But in fact it was included in the metadata under a different tag/label and therefore was not missing. More generally, the NeuroQuant® 4.0 software occasionally will not match DICOM parameter tags/labels with scanner tags/labels which could result in a blank parameter. This issue will not affect the scan quality reported on the Image Quality Scale section of the Compatibility Assessment report because the Image Quality Scale indicates the amount of noise and quality of contrast. Therefore, the results of the scan may still be reliable. (Micki Maes, CorTechs Labs Clinical Operations Manager, email communication on 11/03/22).
- More generally, per email communication on 05/12/23 with Micki Maes, CorTechs Labs Clinical Operations Manager:
  - The Compatibility Assessment report is a useful tool that can help point out problems with scanner parameters but is not always diagnostic of whether the results are accurate.
  - Visual inspection of the segmented DICOM images generally is a better way to determine whether the results are accurate.
  - Reviewing the Compatibility Assessment report and visually inspecting DICOMs is a better approach than either one alone.

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Summary of NeuroQuant® Volumetric Analyses

NeuroQuant® Table	Left	Right	Total
Region	Normative Percentile		
Intracranial Volume (ICV)	-	-	99
Whole brain parenchyma	86	95	92
Forebrain parenchyma	80	93	87
Cerebral white matter	86	91	89
Cortical gray matter	41	52	46
Ventricles	18	9	12
• Superior lateral ventricle	21	11	15
• Inferior lateral ventricle	36	30	31
Subcortical Structures			
• Cerebellum	67	67	67
• Cerebellar white matter	96	95	96
• Cerebellar gray matter	51	53	52
• Brainstem	-	-	69
• Thalamus	22	67	44
• Ventral diencephalon	99	77	95
Basal ganglia	32	44	37
• Putamen	22	46	34
• Caudate	60	33	46
• Nucleus accumbens	11	81	41
• Pallidum	66	61	64
Cingulate	30	1	2
• Anterior cingulate	3	1	1
▪ Rostral anterior cingulate	10	1	1
▪ Caudal anterior cingulate	6	2	1
• Posterior cingulate	40	9	17
• Isthmus cingulate	90	60	82
Cortical Structures			
Frontal lobe	27	38	32
• Superior frontal	18	26	19
• Middle frontal	13	33	20
• Anterior middle frontal	29	36	31
• Inferior frontal	93	82	92
▪ Pars opercularis	70	85	81

Region	Left	Right	Total
Frontal lobe (continued)	Normative Percentile		
▪ Pars triangularis	99	89	97
▪ Pars orbitalis	79	18	40
• Frontal pole	35	70	51
• Lateral orbitofrontal	58	57	57
• Medial orbitofrontal	3	84	46
• Paracentral	69	8	28
• Primary motor	37	32	33
• Premotor	5	34	13
Parietal lobe	38	61	49
• Primary sensory	48	35	40
• Medial parietal	70	84	79
• Superior parietal	29	71	49
• Inferior parietal	80	77	82
• Supramarginal	11	20	11
Occipital lobe	87	96	93
• Medial occipital	87	83	87
▪ Cuneus	66	77	73
▪ Lingual gyrus	77	52	66
▪ Pericalcarine	99	99	99
• Lateral occipital	78	99	94
Temporal lobe	56	60	58
▪ Superior temporal	44	71	57
▪ Transverse temporal	58	83	71
• Posterior superior temporal sulcus	39	47	39
• Middle temporal	38	38	34
• Inferior temporal	70	16	43
• Fusiform	21	90	59
• Parahippocampal	99	95	99
• Entorhinal cortex	60	6	25
• Temporal pole	73	51	63
• Amygdala	89	99	97
• Hippocampus	80	87	85

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

Pink background indicates an abnormally small region from the NeuroQuant® normative percentile.

Green background indicates an abnormally large region from the NeuroQuant® normative percentile.

The volumes and normative percentiles listed above were taken from their respective NeuroQuant reports (attached).

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Summary of NeuroQuant® Asymmetry Analyses

Region	Asymmetry index	Normative Percentile
ICV		-
Whole brain parenchyma	-1.68	10
Forebrain parenchyma	-1.86	7
Cerebral white matter	-1.74	15
Cortical gray matter	-2.04	11
Ventricles	16.82	91
• Superior lateral ventricle	26.54	91
• Inferior lateral ventricle	-3.40	61
Subcortical structures		
• Cerebellum	0.89	51
• Cerebellar white matter	3.73	74
• Cerebellar gray matter	-0.01	40
• Brainstem	-	-
• Thalamus	-7.93	**1**
• Ventral diencephalon	16.86	**99**
Basal ganglia	-1.26	18
• Putamen	-2.56	**4**
• Caudate	3.38	90
• Nucleus accumbens	-22.78	**1**
• Pallidum	6.13	62
Cingulate	3.73	**99**
• Anterior cingulate	-23.48	86
▪ Rostral anterior cingulate	-17.45	**98**
▪ Caudal anterior cingulate	-31.01	60
• Posterior cingulate	15.32	87
• Isthmus cingulate	21.85	84
Cortical structures		
Frontal lobe	-4.73	17
• Superior frontal	-4.29	35
• Middle frontal	-3.90	13
• Anterior middle frontal	-1.70	36
• Inferior frontal	5.68	72
▪ Pars opercularis	13.49	31
▪ Pars triangularis	-2.29	74

Region	Asymmetry index	Normative Percentile
Frontal lobe (continued)		
▪ Pars orbitalis	5.77	**97**
• Frontal pole	-48.54	12
• Lateral orbitofrontal	3.66	51
• Medial orbitofrontal	-67.29	**1**
• Paracentral	16.90	**98**
• Primary motor	4.67	59
• Premotor	-9.79	11
Parietal lobe	-2.67	13
• Primary sensory	11.45	70
• Medial parietal	0.83	31
• Superior parietal	-8.73	**5**
• Inferior parietal	-14.76	56
• Supramarginal	6.51	31
Occipital lobe	-4.98	17
• Medial occipital	1.06	59
▪ Cuneus	2.06	36
▪ Lingual gyrus	6.33	79
▪ Pericalcarine	-12.24	42
• Lateral occipital	-11.03	8
Temporal lobe	2.00	45
▪ Superior temporal	-0.13	23
▪ Transverse temporal	0.17	58
• Posterior superior temporal sulcus	3.82	43
• Middle temporal	-6.87	39
• Inferior temporal	21.17	95
• Fusiform	-14.47	**1**
• Parahippocampal	17.47	81
• Entorhinal cortex	27.82	99
• Temporal pole	4.30	77
• Amygdala	-4.70	18
• Hippocampus	-6.20	34

The asymmetry indices and normative percentiles listed above were taken from their respective NeuroQuant reports (attached). Asymmetries <5%tile are associated with L<R volumes, and asymmetries >95%tile are associated with R<L volumes.

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

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

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

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Pink background indicates abnormal asymmetry with L<R for parenchymal regions, or similarly, L>R for ventricular regions.

Blue background indicates abnormal asymmetry with R<L for parenchymal regions, or similarly, R>L for ventricular regions.

NeuroGage® 3.0 TBI Biomarker test:

Result: 66.7% (TBI)

Comparison ranges:

- Normal: 0-50%
- Chronic mild or moderate TBI: >50%

Key: TBI = traumatic brain injury. *Note*: The TBI Biomarker test was developed in order to predict whether a given participant is a healthy normal control or a patient with chronic mild or moderate TBI. For patients with other disorders, the results may or may not be valid and should be interpreted accordingly.

Methods

MRI brain segmentation and volumetry was performed with NeuroQuant® 4.0, developed by CorTechs Labs, Inc. Tables summarizing brain volume and asymmetry data were generated using NeuroQuant® 4.0 additional data output provided by Cortechs.ai. The NeuroQuant® csv file provides additional data through Cortechs.ai on a given MRI sequence. It includes 71 regions and subregions, absolute brain volumes, percent of intracranial volume, and 5th and 95 normative percentile references. This additional information expands on the information provided by the NeuroQuant® reports which may be utilized for further comparisons and potential research.

The TBI Biomarker test was based on NeuroQuant® 3.0 volume data and NeuroGage® 3.0 asymmetry data. 61 patients with chronic mild or moderate TBI, selected using our previously published criteria, were compared to the NeuroQuant normal controls and the NeuroGage® normal controls (N=80). Neural network analyses using JMP 16.2 software were used to predict whether each subject belonged to the group of normal controls or patients. Each neural network model was developed using a K-fold method for validation of the results and then a leave-one-out method for testing the results. (The leave-one-out method is a conservative method that minimizes overfitting of the models.) The final method consisted of the average of 3 neural networks for each subject, yielding the following results:

		Diagnosis	
		Normal	TBI
Test result	Normal	76	0
	TBI	4	61
	Sensitivity:	100.0%	
	Specificity:	95.0%	

Since the development of the TBI Biomarker test, we have tested its validity in an additional sample of patients with chronic mild or moderate TBI, many of whom had brain disorders other than TBI. Of that sample (N=47), 93.6% tested positive for a diagnosis of TBI, confirming very good sensitivity of the test. For a subgroup of that sample that included patients with mild TBI but not moderate TBI (N=34), 97.1% tested positive for a diagnosis of TBI, again confirming excellent sensitivity of the test.

Interpretation

In contrast to the results based on traditional visual inspection, the patient had multiple brain volume abnormalities. This finding was consistent with previous reports that NeuroQuant® and NeuroGage® are more sensitive for detecting brain volume abnormalities than is the traditional method of simple visual inspection (Ross, Ochs et al. 2013, Ross, Ochs et al. 2015).

7 brain regions were abnormally large (i.e. parenchymal regions were abnormally large, or similarly ventricular regions were abnormally small), which was less than the number expected by chance alone (9.4 regions = 5% x 188 regions [excluding hypointensities]). 8 brain regions were abnormally small (i.e. parenchymal regions were abnormally small, or similarly ventricular regions were abnormally large), which was less than expected by chance alone (also 9.4 regions).

3 pairs of brain regions had abnormal asymmetry (R<L for parenchymal regions, or R>L for ventricular regions), which was less than the number expected by chance alone (3.1 pairs of regions = 5% x 62 pairs of regions). 12 pairs of brain regions had abnormal asymmetry (L<R for parenchymal regions, or L>R for ventricular regions), which was greater than the number expected by chance alone (also 3.1 pairs of regions).

The multiple regions with abnormal asymmetry constituted a clearly abnormal pattern. Abnormal asymmetry suggests that an abnormal process (for example, atrophy or inflammation) affected one structure but not its contralateral counterpart.

Many studies have shown that TBI causes abnormal asymmetry of brain structures (Bigler 2011, Ross, Ochs et al. 2013, Ross, Ochs et al. 2015, Barcelona, Ross et al.

2022). More recently, we found multiple areas of abnormal asymmetry in a study comparing 50 patients with chronic mild or moderate TBI to 80 NeuroGage® normal controls (Ross, Seabaugh et al. 2023).

Furthermore, the patient had no diagnosis other than TBI that typically was characterized by extensive abnormal asymmetry. Therefore, the findings of abnormal asymmetry in the patient were consistent with TBI.

Regarding anatomic correlations:

- The abnormal enlargement of the left ventral diencephalic region correlated with abnormal asymmetry of the ventral diencephalic regions (L>R).
- The abnormal diminution of the right cingulate cortex correlated with abnormal asymmetry of the cingulate cortices (R<L).
- The abnormal diminution of the right rostral cingulate cortex correlated with abnormal asymmetry of the rostral cingulate cortices (R<L).
- The abnormal enlargement of the left pars orbitalis cortex correlated with abnormal asymmetry of the pars orbitalis cortices (L>R).
- The abnormal diminution of the left medial orbitofrontal cortex correlated with abnormal asymmetry of the medial orbitofrontal cortices (R<L).

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).

The following 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 multiple brain regions:

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TBI Table

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	(Bigler, Anderson and Blatter 2002, Farbota, Sodhi et al. 2012, Ross, Ochs et al. 2014, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020)
Cortical gray matter	Small or Large	(Toth, Kovacs et al. 2013, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Subcortical nuclei + infratentorial regions	Large	(Ross, Ochs et al. 2014, Ross, Ochs et al. 2016, Ross, Seabaugh et al. 2021)
Cerebellum (gray + white matter)	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)
Ventricles	Large	(Toth, Kovacs et al. 2013)
Lateral ventricles	Large	(Bigler 2005, Bigler 2011)
Superior lateral ventricles	Small or Large	(Bigler 2005, Bigler 2011, 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)

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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 (gray + white matter)	Small	(Bigler 2005, Bigler 2011)
Frontal lobe cortex	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 lobe cortex	Small or Large	(Govindarajan, Narayana et al. 2016, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
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)

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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 lobe cortex	Small or Large	(Farbota, Sodhi et al. 2012, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Medial occipital cortex	Large	(Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Cuneus	Large	(Govindarajan, Narayana et al. 2016)
Temporal lobes (gray + white matter)	Small	(Bigler 2005, Bigler 2011)
Temporal lobe cortex	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 or Large	(Bigler 2005, Bigler 2011, Zagorchev, Meyer et al. 2016, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)
Hippocampus	Small or Large	(Bigler, Anderson and Blatter 2002, Bigler 2005, Bigler 2011, Maller, Thomson et al. 2014, Cole, Jolly et al. 2018, Ross, Seabaugh et al. 2020, Ross, Seabaugh et al. 2021)

Inferior lateral ventricles	Small or Large	(Bigler, Anderson and Blatter 2002, Ross, Seabaugh et al. 2021)

The patient had multiple volume findings consistent with the diagnosis of TBI

- Abnormally large whole brain parenchyma
- Abnormally large bilateral cerebellar white matter regions
- Abnormally large left ventral diencephalic region
- Abnormally small right cingulate cortex
- Abnormally small left medial orbitofrontal cortex
- Abnormally large right occipital cortex
- Abnormally large right amygdala region

The patient had some volume findings opposite the volume findings consistent with TBI cited in the literature: abnormally small bilateral anterior cingulate region, abnormally large left pars triangularis region, and an abnormally large bilateral parahippocampal cortex. However, given the patient's asymmetry and volume findings consistent with TBI, their pattern of brain volume abnormalities better matched that of TBI.

The pattern of multiple NeuroQuant® volumes matching the known TBI pattern, and the asymmetry of multiple brain regions, likely contributed to the TBI Biomarker test being positive for TBI.

The records indicated that the patient had a diagnosis of depression which was likely due to the indirect or direct effects of TBI. More generally, and independent of TBI, major depression has been associated with abnormally small volume of the prefrontal cortex (PFC)—including the dorsolateral PFC, medial PFC, and ventrolateral PFC—orbitofrontal cortex, hypothalamus, and limbic areas (including the hippocampus, amygdala, anterior cingulate cortex, and isthmus cingulate cortex) (Lener and Losifescu 2015, McLaren, Szymkowicz et al. 2016, Schindler, Schmidt et al. 2019). The patient had an abnormally small left medial orbitofrontal cortex, which comprises a portion of the orbitofrontal cortex, and the opposite volume finding of an abnormally large bilateral amygdala region. The patient's pattern of brain volume abnormalities matched that of TBI much better than that of major depression independent of TBI.

The records indicated that the patient had a diagnosis of anxiety which was likely due to the indirect or direct effects of TBI. More generally, and independent of TBI, generalized anxiety disorder (GAD) has been associated with abnormal volume (small

or large for parenchymal regions) of the following regions: 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). The patient had an abnormally small anterior cingulate cortex, abnormally small left medial orbitofrontal cortex, which comprises a portion of the orbitofrontal cortex, and an abnormally large right amygdala region, but no other findings consistent with GAD. The patient's pattern of brain volume abnormalities matched that of TBI much better than that of GAD independent of TBI.

The records indicated that the patient had a diagnosis of insomnia which was likely due to the indirect or direct effects of TBI. More generally, and independent of TBI, chronic insomnia has been associated with abnormal volume (small or large for parenchymal regions) of the intracranial volume (small), thalamus (small) (Li, Wang et al. 2019) anterior cingulate (large) (Winkelman, Plante et al. 2013), left medial frontal gyrus (medial portion of the superior frontal region) (small), and left middle temporal gyrus (small) (Joo, Noh et al. 2013). The patient had no findings consistent with chronic insomnia independent of TBI.

The records indicated that the patient had a diagnosis of posttraumatic stress disorder due to the incident. 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). The patient had abnormally small volume of the middle frontal regions (which are a part of the prefrontal cortex) and abnormally large volume of the bilateral amygdala regions but no other findings consistent with PTSD. The pattern of brain volume abnormalities matched that of TBI better than that of PTSD.

NeuroGage®

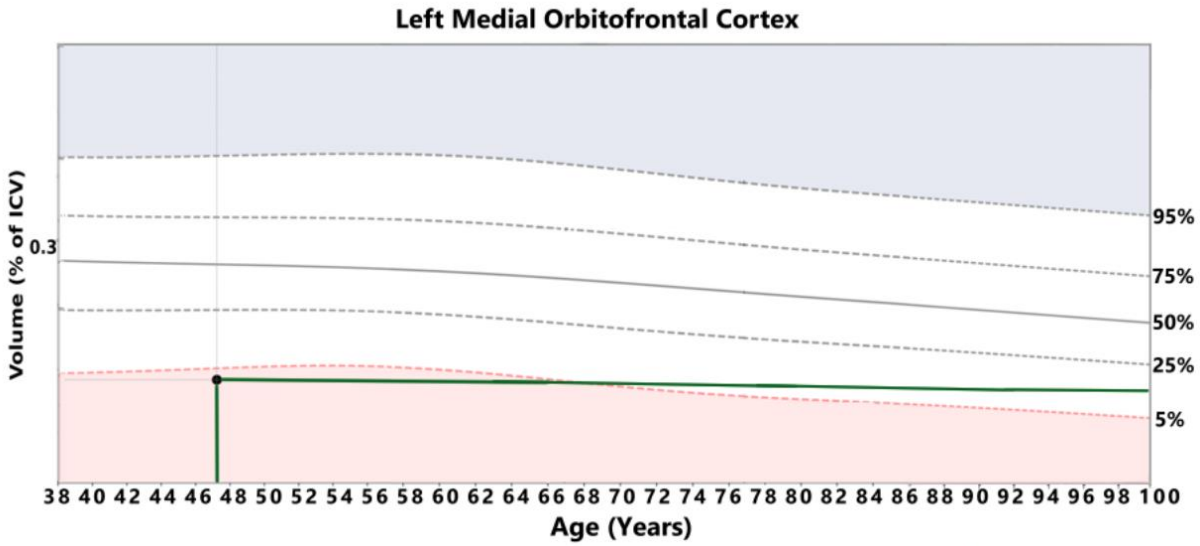

Figure: The volume of the patient's left medial orbitofrontal cortex was abnormally small and was as small as that of the average 100-year-old woman based on NeuroQuant® normal control data.

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

- Abnormal asymmetry of the thalamus correlated with impaired sleep and wakefulness (Steriade and Llinas 1988).
- Impaired mood correlated with abnormal volume of the anterior cingulate gyrus (Drevets, Savitz and Trimble 2008, Hillis 2014, Smith, Ahern and Lane 2019)
- Abnormally small volume of the orbitofrontal cortex correlated with depression (Lener and Losifescu 2015, McLaren, Szymkowicz et al. 2016, Schindler, Schmidt et al. 2019).
- Abnormally small volume of the left parahippocampal region correlated with impaired short-term memory (Zola-Morgan, Squire et al. 1989, Davachi, Mitchell et al. 2003, Diana, Yonelinas et al. 2010, Aminoff, Kveraga et al. 2013).
- With regard to patients with PTSD or PTSD-spectrum conditions, the amgydala has been reported to have abnormally small volume (Mehta, Golembo et al. 2009, Morey, Gold et al. 2012, Starcevic, Postic et al. 2014,

O'Doherty, Chitty et al. 2015, Ahmed-Leitao, Spies et al. 2016, Moyer 2016) or abnormally large volume (Mehta, Golembo et al. 2009, Moyer 2016). In animal models of PTSD, the amygdala has been found to have abnormally large volume (Coplan, Fathy et al. 2014, Hoffman, Paode et al. 2017).

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