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Diffusion Tensor Imaging of Basal Ganglia and Thalamus in Amyotrophic Lateral Sclerosis

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Abstract

Purpose—To assess the involvement of basal ganglia and thalamus in patients with amyotrophic lateral sclerosis (ALS) using diffusion tensor imaging (DTI) method.

Methods—Fourteen definite-ALS patients and 12 age-matched controls underwent whole brain DTI on a 3T scanner. Mean-diffusivity (MD) and fractional anisotropy (FA) were obtained bilaterally from the basal ganglia and thalamus in the regions-of-interest (ROI).

Results—The MD was significantly higher ($p < 0.02$) in basal ganglia and thalamus in patients with ALS compared with controls. Correspondingly, the FA was significantly lower ($p < 0.02$) in these structures, except in caudate ($p = 0.04$) and putamen ($p = 0.06$) in patients compared with controls.

There were mild to strong correlations ($r: 0.3 - 0.7$) between the DTI measures of basal ganglia and finger-tap, foot-tap, and lip-and-tongue-movement-rate.

Conclusions—The increased MD in basal ganglia and thalamus, and decreased FA in globus pallidus and thalamus are indicative of neuronal loss or dysfunction in these structures.

Keywords

Amyotrophic Lateral Sclerosis; Basal Ganglia; DTI; Extra-motor; Thalamus

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neuro-degenerative disorder characterized by variable destruction of upper motor neuron (UMN) in the motor cortex of the brain, brainstem motor nuclei (lower motor neuron [LMN]), and anterior horn cells in the spinal cord.¹ However, pathological,^{2,5} neuropsychological,⁶ and neuroimaging studies,^{7,12} have challenged the view that ALS is a disorder restricted to the motor system.

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Furthermore, results from several studies²⁻⁶ have established dysfunction of the nonmotor cortex, especially the pre-frontal and temporal lobe cortex, in patients with ALS.

Similar to the involvement of extramotor system in the brain cortex, the pathological²⁻⁵ and neuroimaging studies⁷⁻¹² have demonstrated widespread neuronal degeneration in the other subcortical structures in patients with ALS. These include basal ganglia, substantia nigra, thalamus, subthalamic nucleus and cerebellum. *In vivo* studies using techniques such as positron emission tomography (PET),¹⁰ diffusion tensor imaging (DTI),⁷⁻⁹ functional magnetic resonance imaging (fMRI),⁸ tensor-based morphometry¹¹ and proton magnetic resonance spectroscopy¹² have confirmed the pathological findings of involvement of several subcortical structures in ALS.

DTI provides an objective quantitative marker of water diffusion within living tissue and represents a surrogate marker for active neuronal degeneration. The majority of the previous DTI studies have focused on the evaluation of corticospinal tracts and extramotor white matter tracts in patients with ALS. Three studies⁷⁻⁹ have evaluated the involvement of the thalamus, and all noted significantly reduced fractional anisotropy (FA) in the thalamus of patients with ALS compared with the controls.

The objective of this exploratory study was to evaluate the subclinical involvement of basal ganglia and thalamus in ALS patients using DTI. The primary hypothesis of this study is that mean-diffusivity (MD) is increased and FA is decreased in the basal ganglia and thalamus in patients with ALS relative to the age-matched controls and the secondary hypothesis is that these DTI changes would correlate with the measures of extrapyramidal/pyramidal tract function and neurological disability.

Methods

Subjects

Fifteen consecutive patients who met the revised El Escorial criteria¹³ for sporadic definite ALS were recruited. Data from one of these patients was excluded from analysis due to incomplete data acquisition. The data of the remaining 14 patients (7 males; age: 51±9 yrs, range 32-60 yrs; median 55 yrs; 12 with limb onset and 2 with bulbar onset; symptom duration: 22 ± 11 months; median 20 months; range: 6-40 months) and 12 age-matched controls (6 males) was analyzed. All patients and controls provided written informed consent approved by the Institutional Review Board.

Clinical Assessments

All patients with sporadic, definite ALS had detailed physical and neurological examinations to assess for clinical evidence of extramotor involvement (extrapyramidal tract, sensory, cerebellar). The disease severity was evaluated using the ALS Functional Rating Scale-Revised (ALSFRS-R; range of scores: 0-48, with scores 0 and 48 indicate total disability and no disability),¹⁴ respectively and percentage of predicted forced vital capacity (FVC). The maximum finger-and foot tap rates^{15, 16} were obtained to evaluate extrapyramidal and pyramidal tract function of these muscles, and are also components of the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS).¹⁷ Pyramidal tract functions, in

addition to the standard measures such as muscle stretch reflex and muscle tone, were quantified by counting the number of rapid foot taps, finger taps, lip movements with *pa-pa* syllable repeat and tongue movements with *la-la* syllable repeat all in 10-seconds, and converted to per second scores (rate).^{18, 19} Furthermore, the rapid muscle movement rate at all these sites was repeated twice during the same session of the examination, after an interval of one minute to obtain the representative average rate for each site. The Montreal Cognitive Assessment (MoCA)²⁰ was administered on all the patients and controls as a screening instrument for cognitive impairment.

For the remainder of this report, measures of pyramidal and extrapyramidal tract function constitute number of rapid foot and finger taps, lip movements with *pa-pa* syllable repeat and tongue movements with *la-la* syllable repeat and the measure of neurological disability constitutes ALSFRS-R score.

Magnetic Resonance Diffusion Tensor Imaging Protocol

All patients and controls underwent MR examination on a 3-Tesla scanner (Siemens, Tim Trio) with an eight-channel phased-array head coil. An hour-long MR protocol included: T1-weighted MRI (~5 min.); T2-weighted MRI (~3 min.); FLAIR MRI (~3min.); DTI (~9 min.). T2-weighted and FLAIR images were used to identify any pathology in basal ganglia and thalamus. Diffusion-weighted single-shot spin-echo echoplanar imaging sequence was applied, with data acquisition matrix: 128×128; field of view (FOV): 256×256 mm²; TR: 6400 ms, TE: 87 ms, parallel imaging GRAPPA factor 2, signal averages: 6, total acquisition time: ~ 9 minutes, 34 contiguous axial slices (slice thickness = 3mm; voxel size = 2×2×3 mm³) covering the entire brain and brain stem. Images were obtained with diffusion gradients applied along 12 non-collinear directions and *b* values of 0 and 1000 s/mm² were used.

Data Processing

Data were processed using DtiStudio software (<https://www.mristudio.org/>) and images for the DTI measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), were calculated. One of the authors who selected the ROIs of interest for obtaining data from the scans (Figure 1) was blinded to individual scan (patient or control) to avoid biasness.

Data Analysis

The diffusion-weighted images were first co-registered with non-diffusion-weighted images (*b*=0) using the automated image registration procedure provided in DtiStudio to correct for the subject motion and Eddy current induced distortions. Diffusion tensor calculations were performed on these co-registered images to obtain MD, FA, AD and RD images. All ROIs were first created on AD images that delineated the basal ganglia substructures and thalamus. Then, fractional anisotropy (FA), mean-diffusivity ($MD = [\lambda_1 + \lambda_2 + \lambda_3]/3$; $\lambda_1, 2, 3 =$ eigen values in the three orthogonal directions), AD and radial diffusivity ($RD = [\lambda_2 + \lambda_3]/2$) mean values were obtained from their respective images for group comparisons. Square-shaped regions-of-interest (ROI; 2×2 or 3×3 pixels) were used for the small basal ganglia substructures so as to keep the sampled pixel content approximately the same across

the subjects. Irregular shaped ROIs (18-47 pixels) were used for the thalamus. The basal ganglia and thalamus structures were identified using the anterior commissure (AC) as a landmark. The ROIs were drawn on a single axial representative slice (3mm thickness) for each of the structures. The representative slice was the largest in size for that structure. The ROIs within the basal ganglia and thalamus were drawn on single axial slices (3mm thickness), located one and three slices from the AC, respectively. For identifying the basal ganglia substructures on AD images, well-defined anatomical landmarks were used. For identifying the head of the caudate nucleus, the external capsule and frontal horn of the lateral ventricle were used as lateral and medial boundaries, respectively, on the AD images. Similarly, for putamen the external capsule laterally and anterior limb of the internal capsule medially, and for globus pallidus lateral medullary lamina laterally and the posterior limb of the internal capsule medially were used. The thalamus was identified using the posterior limb of the internal capsule and the third ventricle as lateral and medial boundaries on AD images, respectively.

Statistics

For data analysis, Stat View II (Abacus concepts, Inc, Berkley, California) was used. To evaluate differences between the measures of patients and controls, a 2-tailed unpaired t-test was used. A two-tailed paired t-test was used to evaluate differences in measures between the left and right side rapid-movement-rate of various muscles (see above, Clinical Assessments) and DTI measures for the groups of controls and patients. Pearson's product moment partial correlation was used to evaluate correlation between DTI measures and clinical measures (see above, Clinical Assessments) and was reported as coefficients (r-values). All the data are expressed as mean $\pm$ SD. The median values are also provided for the ALSFRS-R score, percentage of predicted FVC, symptom duration of the disease, MoCA scores and age of the patients and controls.

In this study, our primary hypothesis is that MD is increased and FA is decreased in the basal ganglia and thalamus in patients with ALS as compared to the age-matched controls. The secondary hypothesis is that these DTI parameters would correlate with the measures of pyramidal/extrapyramidal function (timed movements of finger taps, foot taps, and bulbar muscles) and neurological disability measure (ALSFRS-R score). Consistent with the primary aim of evaluating abnormality of MD and FA in basal ganglia and thalamus, the *p* value corrected for multiple comparisons (Bonferroni correction) was set to <0.025 for identifying significant differences between the groups. The *p*-value of significance for the secondary hypothesis, AD and RD in basal ganglia and thalamus was set to <0.05 and it was not corrected for the multiple comparisons.

Results

Clinical Features

Fourteen patients with ALS had a variable degree of functional motor disability with mean ALSFRS-R of 36.3 ± 8.1 (range 23-47; median 34) and mean FVC of $80.1 \pm 15.8\%$ (range 42-104%; median 77%). The MoCA score was significantly lower in patients compared with controls (26.5 ± 1.6 , median 26, range 25-30 vs 27.9 ± 1.3 , median 28, range 26-30; $p = 0.02$).

Three of these fourteen patients had MoCA scores of 25 (2 bulbar onset, one limb onset). None of the patients had other extramotor abnormality on clinical examination and standard nerve conduction studies. All the patients had significant abnormality of fine-rapid movement (pyramidal/extrapyrarnidal tract function) in the muscles of the bulbar region (*pa-pa*-rate 3.0 ± 0.6 vs 4.4 ± 0.3 , $p < 0.01$; *la-la*-rate 2.9 ± 0.7 vs 4.41 ± 0.3 , $p < 0.01$), upper limbs (right finger-tap-rate 2.4 ± 0.8 vs 4.2 ± 0.5 , $p < 0.01$; left finger-tap-rate 2.4 ± 0.9 vs 4.0 ± 0.6 , $p < 0.01$), and lower limbs (right foot-tap-rate 1.8 ± 1.2 vs 3.4 ± 0.4 , $p < 0.01$; left foot-tap-rate 1.5 ± 1.0 vs 3.2 ± 0.5 , $p < 0.01$) compared to the controls.

Diffusion Tensor Imaging Measures

Mean and standard deviation values of DTI measures obtained at selected ROIs across both patient and control groups are shown in Table 1. No left versus right asymmetry was found either in controls or in patients' DTI measures. Therefore, data from the left and right sides in each group were averaged for all the subsequent group comparisons. The MD was significantly higher in patients as compared with controls in caudate, putamen, globus pallidus and thalamus (Table 1). The FA was significantly lower in patients compared with controls in globus pallidus and thalamus. There was a trend for a lower FA in caudate ($p = 0.04$) and putamen ($p = 0.06$; Table 1).

The AD was significantly higher in patients as compared with controls in caudate, putamen, globus pallidus and thalamus (Table 1). Similarly, the RD was significantly higher in patients as compared with controls in putamen, globus pallidus and thalamus (Table 1). There was a trend for increased RD in caudate as well ($p = 0.06$, Table 1).

Correlation Between DTI Parameters And Clinical Measurements—The correlations between the clinical and DTI measures (FA, MD, AD, RD) are provided in Table 2. It revealed a significant positive correlation between maximum number of finger-tap rate and FA values of globus pallidus and a trend for a correlation for caudate FA ($r = 0.5$, $p = 0.07$), putamen FA ($r = 0.5$, $p = 0.07$), and caudate AD ($r = 0.5$, $p = 0.07$; Table 2). There was no correlation between the finger-tap rate and remaining DTI measurements (Table 2).

Similarly, the correlations between the maximum rate of foot-taps, and the measures of DTI of basal ganglia of ALS patients revealed a positive correlation between the FA values of caudate, globus pallidus and a negative correlation between MD of globus pallidus (Figure 2), AD and RD of globus pallidus (Table 2). There was a trend for a negative correlation for AD values of caudate and putamen (Table 2).

The correlation between the maximum bulbar muscle movement rates of syllable repeats, and DTI measures of basal ganglia of ALS patients revealed a positive correlation for FA values of putamen and a negative correlation for AD values of globus pallidus (Table 2). There was a trend for a positive correlation for FA values of caudate and negative correlation for AD, RD values of caudate and putamen (Table 2).

The ALSFRS-R score correlated negatively with the MD values of putamen ($r = -0.6$, $p = 0.02$), and a trend for a positive correlation with the FA values of caudate ($r = 0.6$, $p = 0.05$) and a trend for a negative correlation with the AD values of putamen ($r = -0.5$, $p = 0.06$).

The MoCA score correlated negatively only with the MD values of caudate ($r = -0.6$, $p = 0.04$) among the DTI measures of the basal ganglia.

Discussion

The major findings of this study in patients with ALS as compared to controls were: firstly, the MD was significantly higher in basal ganglia and thalamus; secondly, the FA was significantly decreased in globus pallidus and thalamus; thirdly, the AD and RD were significantly higher in basal ganglia and thalamus except RD in the caudate; and fourthly, there was a significant correlation between DTI measures of basal ganglia and maximum motor movement rates subserved by pyramidal/extrapyramidal systems (Table 2, Figure 2).

The DTI abnormalities observed *in vivo* in the basal ganglia and thalamus of ALS patients support the results from previous *in vitro* pathological^{2,5} and *in vivo* imaging studies,⁷⁻¹² suggesting subclinical dysfunction of these subcortical structures in ALS.

Decreased FA and increased diffusivity have been observed in various neurological disorders associated with neuronal loss or damage. This may result from either an increase in intracellular water diffusion due to loss of organized coherent structure in white matter tract, or an increase in extracellular matrix due to accumulation of axonal spheroids and astrogliosis within interaxonal spaces. Our findings of diffusion abnormalities (decreased FA, increased diffusivity) in basal ganglia and thalamus of patients with ALS suggest that there is degeneration or dysfunction of neurons in these subcortical structures, which is supported by the immunohistopathological studies of neuronal loss, astrogliosis, and ubiquitin-immunoreactive cytoplasmic inclusions in these structures in patients with ALS.^{4,5}

Basal ganglia, through their afferent and efferent pathways, not only influence the primary motor cortex but also premotor and prefrontal cortices that are involved in language and cognitive functions.^{21,22} We also observed cognitive abnormality on MoCA in patients. However, it is established that nonmotor cortices (pre-frontal, parietal, temporal), which are involved in cognitive functions, are dysfunctional in ALS.^{2,8} Therefore, it is unclear from this pilot data that the observed dysfunction of the subcortical structures (basal ganglia, thalamus) contributed to the cognitive abnormality found in ALS. Further studies, by performing detailed neuropsychological examination and neuroimaging of both cortical and subcortical structures, are required to delineate the type and extent of cognitive dysfunction contributed by the abnormality of cortical and subcortical structures found in ALS.

Similar to that of our observation of subclinical dysfunction of basal ganglia in ALS patients, investigations using *in vivo* imaging techniques (PET^{23,24} and single photon emission computed tomography [SPECT]²⁵) have shown an abnormal pre-synaptic and post-synaptic striatal dopaminergic function in ALS patients. The intensity of reduction of post-synaptic striatal D2-receptor binding in some of the ALS patients was similar to that of seen in the patients with multisystem atrophy.²⁶ Degeneration in the dopaminergic neurons in basal ganglia and midbrain has also been observed in a transgenic mouse model of familial ALS.²⁷ Neurodegeneration beyond motor neurons in cortex, brain stem and spinal

cord is particularly evident in ALS patients who survived for prolonged periods on a respirator.³ It is uncertain whether this widespread neurodegeneration, observed beyond motor neurons in cortex at an advanced stage of the disease, is a primary^{28, 29} or secondary degeneration.¹⁰ Moreover, this uncertainty of the extent of contribution from either of these two degenerative processes may account for the variability in the degree of dysfunction of subcomponents of the basal ganglia and thalamus in the patients with ALS observed in this study and others.^{2, 5, 8, 12, 23-25} Further studies are required to resolve this issue.

The division of the motor system into pyramidal system and extrapyramidal systems, a simple dichotomy, is not satisfactory, as several other brain structures such as red nucleus, motor nuclei of the brainstem and cerebellum are known to mediate voluntary movements.^{30, 31} The extrapyramidal and pyramidal systems are extensively interconnected and functionally cooperate in the control of movement.^{30, 31} The impairment of fine rapid movements of various muscles may occur in the dysfunction of either system.^{15, 16, 30, 31}

Measures of the extrapyramidal tract/pyramidal tract correlated more strongly with the basal ganglia DTI measurements (Table 2) than with the ALS FRS-R score. The ALS FRS-R score correlated only with MD in the putamen. The reasons for these discrepancies are less clear. Although the ALSFRS-R score represents disability related to both LMN and UMN, the extent of the contribution from each component is very variable based on the results of clinicopathological and cliniconeurophysiological correlation studies in ALS.^{2, 32-34}

FA and MD are commonly used DTI measures to evaluate structural and functional status of the neuronal axon in the pyramidal tract, which has dominant unidirectional bundles of fibers with a limited number of branching and crossing fiber tracts, especially in the posterior limb of the internal capsule and cerebral peduncle.³¹ However, even in this unidirectional tract, the FA and MD results are widely variable with respect to the congruence between them (that is, a decrease in FA corresponds with an increase in MD in a given voxel and *vice versa*).^{35, 38} Unlike the pyramidal tract, extrapyramidal and thalamic tracts^{21, 22} have multiple crossings, branching and directional changes. Furthermore, the compounding effects of the Wallerian degeneration on DTI measurements, such as no change in FA, significant change in the measured orientation of fibers and moderate increase in MD³⁹ warrants that individual Eigen value/vector should be measured. Our data along with others^{38, 39} support the view that the combined measures (FA, MD, AD, RD) may help in demonstrating the structural and functional status of the neuronal axon (white matter tract) especially when studying complex white matter tract.

The limitations of this exploratory study were the small sample size and use of MoCA²⁰ to evaluate the cognitive function, which is less sensitive in detecting subtle cognitive abnormality and also differentiating the cortical from the subcortical cognitive abnormalities.

In conclusion, this study has shown the presence of abnormal diffusivity and fractional anisotropy in the basal ganglia and thalamus in patients with ALS, indicating that these extramotor non-cortical anatomical structures also are affected in the disease. The use of

clinical tools sensitive and specific for the evaluation of the extrapyramidal tract dysfunction may help in eliciting subtle signs related to the abnormality of basal ganglia in patients with ALS. Additional studies are necessary to evaluate whether the degree and extent of involvement of subcortical structures are similar to that of extra motor cortex in patients with ALS and, whether the alterations in these extra-motor structures are of primary or secondary origin.

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Figure 1. (A - D): Regions Of Interests For Basal Ganglia, Thalamus

Figure 1 (A-D): Axial diffusivity (1A and 1C) and color-coded fractional anisotropy (1B and 1D) images from a control subject showing the regions-of interest for the right-side basal ganglia substructures (caudate nucleus [a], putamen [b] and globus pallidus [c]; 1A and 1B) and thalamus (1C and 1D). The inset in A indicates the locations of the basal ganglia substructures ROIs. In Figures 1B and 1D, the red, blue and green color indicate the white matter fibers going from left to right, superior to inferior and anterior to posterior directions, respectively.

Figure 2.

Scattered plot demonstrates a significant negative correlation ($r = -0.7$, $p = 0.01$) between the averages of left- and right-foot maximum foot-tap rates/s (horizontal axis) and the mean of left-and-right mean diffusivity $\times 10^{-3} \text{ mm}^2/\text{s}$ (vertical axis) in globus pallidus of 14 patients with sporadic definite amyotrophic lateral sclerosis.

DTI Metrics for the Regions-of-interest in Basal Ganglia and Thalamus for the ALS (n=14) and Control (n=12) groups

Table 1

Location	Group	MD (Mean $\pm$ 1 SD) [†]	FA (Mean $\pm$ 1 SD)	AD (Mean $\pm$ 1 SD) [†]	RD (Mean $\pm$ 1 SD) [†]
Caudate	ALS	2.34 $\pm$ 0.14	0.12 $\pm$ 0.02	0.93 $\pm$ 0.06	0.76 $\pm$ 0.06
	Control	2.18 $\pm$ 0.16	0.15 $\pm$ 0.03	0.83 $\pm$ 0.08	0.70 $\pm$ 0.04
	p-value	0.02 *	0.04	<0.01 #	0.06
Putamen	ALS	2.27 $\pm$ 0.14	0.12 $\pm$ 0.04	0.88 $\pm$ 0.07	0.74 $\pm$ 0.09
	Control	2.06 $\pm$ 0.10	0.15 $\pm$ 0.02	0.77 $\pm$ 0.06	0.66 $\pm$ 0.04
	p-value	<0.01 *	0.06	<0.01 #	0.02 #
Globus pallidus	ALS	2.55 $\pm$ 0.18	0.14 $\pm$ 0.03	1.10 $\pm$ 0.13	0.78 $\pm$ 0.08
	Control	2.29 $\pm$ 0.23	0.20 $\pm$ 0.04	0.99 $\pm$ 0.09	0.70 $\pm$ 0.08
	p-value	<0.01 *	<0.01 *	0.02 #	0.02 #
Thalamus	ALS	2.34 $\pm$ 0.13	0.24 $\pm$ 0.02	1.00 $\pm$ 0.07	0.69 $\pm$ 0.07
	Control	2.15 $\pm$ 0.1	0.27 $\pm$ 0.02	0.91 $\pm$ 0.03	0.60 $\pm$ 0.06
	p-value	<0.01 *	0.02 *	<0.01 #	<0.01 #

DTI = diffusion tensor imaging, MD = mean diffusivity, FA = fractional anisotropy, AD = axial diffusivity, RD = radial diffusivity, ALS = amyotrophic lateral sclerosis, SD = standard deviation, [†] $\times 10^{-3}$ mm²/s,

* significant p-value, corrected for multiple comparisons with cut-off set to <0.025 for primary objectives which include MD and FA of basal ganglia and thalamus;

significant p-value, not corrected for multiple comparisons with cut-off set to <0.05 for AD and RD of basal ganglia and thalamus.

Correlation between the DTI and clinical measures

* significant p-value, not corrected for multiple comparisons with cut-off set to $p < 0.05$.