Original Article

Quantitative synthetic MRI reveals grey matter abnormalities in patients with spinal muscular atrophy types 2 and 3

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Background: Several studies have shown that spinal muscular atrophy (SMA) is not limited to lower motor neurons. This cross-sectional study aimed to quantitatively investigate the gray matter (GM) alterations in patients with SMA types 2 and 3.

Methods: This is a cross-sectional study. T1 and T2 maps that were extracted from synthetic magnetic resonance imaging (SyMRI) were compared between patients with SMA and healthy controls (HC). Between-group comparisons were made between SMA type 2 and type 3. The association between brain regions with significantly altered T1 and T2 values and clinical measurements were evaluated with Pearson correlation analysis.

Results: Compared with HC, patients with SMA showed widespread altered T1 and T2 values in GM, mainly referring to the cerebellum, default mode network, attention and execution control network, and salience network. Negative correlations were found between Hammersmith Functional Motor Scale Expanded (HFMSE) scores and T2 values of the left orbital part of superior frontal gyrus (P=0.013) and the right olfactory cortex (P=0.008) in the patient group.

Conclusions: Altered T1 and T2 values involving multiple GM regions of the brain demonstrate widespread microscopic alterations in patients with SMA, which might provide an idea for quantitative measurement of SMA nerve damage.

Keywords: Spinal muscular atrophy (SMA); quantitative synthetic magnetic resonance imaging (quantitative SyMRI); grey matter (GM); microscopic alterations

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Introduction

Spinal muscular atrophy (SMA) is an autosomal-recessive disease related to homozygous disruption of the survival-motor-neuron 1 (*SMN1*) gene (1). The loss of function of *SMN1* results in a defective and insufficient production of the SMN protein, which eventually leads to progressive muscle atrophy and weakness (2). According to the age of disease onset, the severity of clinical symptoms, and best acquired motor development milestones, SMA can be divided into five subtypes from 0 to 5 (3). The key factor in this clinical classification is the number of copies of *SMN2*, which can partially compensate the function of *SMN1* (4).

SMA type 2 and type 3 are considered two main mild courses with pediatric onset. Children with SMA type 2 usually develop the disease between 6 and 18 months, and do not develop the ability to walk independently. SMA type 3 retains the ability to walk independently and occurs between 18 months and 18 years; the motor capacity gradually declines from the proximal lower extremity muscles to the distal muscles and upper extremities over time (3). Unlike SMA type 1, which deteriorates rapidly with respiratory and bulbar deterioration and >90% mortality by the age of 2 years (1), and SMA type 4, which develops until adulthood with very slow disease progression and little impact on longevity and movement, type 2 and 3 progress slowly and research on these two types is expected to improve their survival and quality of life (5). Regarding the pathological process of SMA, researchers have fully studied the degeneration caused by SMN deficiency at the lower motor neuron and neuromuscular junction of the spinal cord (6,7). Furthermore, studies have found that SMA not only affects lower motor neurons in the spinal cord and somatic motor nuclei in the brainstem, but also affects multiple regions of the central nervous system (CNS) (8,9). SMA pathology inside the upper motor neuron process and the brain is not well understood (10). Currently, there is no way to determine whether the patient's brain damage is due to ischemic encephalopathy or the loss of *SMN1* itself.

Given the widespread expression of the SMN protein in multi-system (11), it is worth investigating the effects of SMA on other areas of the nervous system. Animal models using structural and diffusion magnetic resonance imaging (MRI) have shown extensive volume reduction and afferent tracts decrease in the cerebellum of SMA mice (12). Several studies have highlighted the progressive diffuse cerebral atrophy and loss of gray and white matter (GM and WM) using MRI in both infant and adult patients with SMA (13-15). Another study focusing on cerebellar degeneration in adult SMA patients also found partial atrophy of volume and GM of cerebellum (16). Though structural MRI studies have performed macromorphological measurements of the brain, it is still unclear what role the microscopic biophysical processes perform behind the macroscopic changes.

Recently, quantitative MRI methods have been widely used in the field of neuroscience to investigate microscopic biological processes of the brain. However, so far, there have been no studies conducted to explore brain microstructure abnormalities using T1, T2 relaxation times in SMA. The SMN protein has been confirmed to play a critical role in various cell homeostatic pathways (17). Furthermore, relaxation rates in tissues depend on the local physical and chemical milieu in a complex manner, and are sensitive to the presence of myelin, which is considered as water closely associated with proteins and phospholipids, as well as the size of axons (18). In general, tissue myelin content greatly influences the T2 relaxometry (18), whereas T1 relaxometry is mainly related to myelin content and iron content, which are involved in the microstructural tissue integrity (19). Thus, it is valuable to infer the microstructure and composition of myelinated tissue using T1 and T2 relaxometry. Furthermore, the synthetic magnetic resonance imaging (SyMRI) could offer a B1-corrected T1 map and a T2 map within 5–6 minutes. Although SyMRI also provides other images such as proton density (PD) and fluid-attenuated inversion recovery (FLAIR) maps, only T1 and T2 maps have the characteristics of both quantitative computation and clear physiological significance, so this study only evaluates the T1 and T2 maps. This scanning method allows both T1 and T2 values to be measured simultaneously and has been shown to be repeatable and reproducible, which makes the measurement more convenient and reliable (20).

This study aimed to investigate the brain microstructure alterations of GM with SyMRI method in patients with SMA type 2 and type 3. In addition, those brain regions with significantly altered T1 or T2 values were correlated with the disease symptom severity (Hammersmith Functional Motor Scale Expanded, HFMSE) to evaluate the relationships between brain changes and the disease severity. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1095/rc).

Methods

This cross-sectional study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (No. [2021]710) and informed consent was provided by all individual participants.

Participants

This study recruited 53 patients with SMA and 56 age- and sex-matched healthy controls (HC). All participants were right-handed and ranged in age from 5 to 19 years. All patients underwent genetic testing, confirming the diagnosis of *SMN1*-related SMA. According to the clinical classification system, 29 patients that developed SMA between 6 and 18 months and could only sit but not walk independently were defined as SMA type 2; another 24 patients that developed SMA after 18 months and can walk independently were defined as SMA type 3. All patients were treatment-naïve before this examination.

The exclusion criteria included prior CNS pathology and presence of medical devices incompatible with high-field MRI.

Healthy participants were recruited through an online advertisement. Through a questionnaire completed by the parents and a clinical interview with an experienced pediatrician, it was confirmed that these healthy children had no neurological disease and had normal cognitive and learning abilities.

Clinical evaluation

All patients underwent a motor function assessment with the HFMSE (range, 0–66), which is used to measure motor function in high functioning patients with SMA type 2 and 3 (21). The assessment was performed after the MRI scanning and a lower score indicated poorer motor capacity and function.

MRI acquisition

A 3-T MRI scanner (SIGNA Pioneer; GE Healthcare, Wauwatosa, WI, USA) with 32-channel head coils was used for MRI examination. Participants lay supine in the examination bed with foam padding fixing the head to minimize head movement.

A 1.00 mm structural sagittal 3-dimensional T1-weighted sequence and axial SyMRI scan were performed for each participant. The SyMRI scan comprising 2 echo times and 4 saturation delay times was a 2-dimensional multiple-dynamic multiple-echo (MDME) pulse sequence. The parameters of SyMRI scan were as follows: repetition time (TR) =10,205.0 ms, echo time (TE) =11.3 ms, fip angle =20°, thickness =2 mm/no gap, number of excitations (NEX) =1.00, echo train length (ETL) =16, pixel size =2.0 mm × 2.0 mm, scanning time =5.5 minutes.

Image processing

From the SyMRI data, we estimated the quantitative maps (T1, T2) using the postprocessing software (SyntheticMR, v11.2.2) which was vendor-provided. Firstly, the T1 map was co-registered to the T1 stuctural image for each participant. Then, we normalized the co-registered T1 images to the Montreal Neurological Institute (MNI) standard space using FSL software (www.fmrib.ox.ac.uk/fsl, v6.0). Thereafter, the T1, T2 maps could be aligned to MNI standard space using the non-linear registration approach. Finally, we applied the Anatomical Automatic Labeling (AAL) atlas (https://www.gin.cnrs.fr/en/tools/aal/) to all the normalized images to extract the T1 and T2 values of all 116 regions, including cerebrum and cerebellum with code based on MATLAB (v2016b, https://ww2.mathworks.cn/downloads/) (22). This process is shown in *Figure 1*.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). The normality of the data was assessed via the Shapiro-Wilk test. The data of normal distribution were compared by independent sample *t*-tests, and the data of non-normal distribution were compared with chi-square tests. Differences between patients and HC were assessed by means of an independent sample *t*-test. Bonferroni method was performed to control the error of multiple comparisons with a $P \leq 0.05$ (corrected for 116 brain regions) considered statistically significant. To explore the differences between the subtypes of SMA, independent sample *t*-tests were then performed between SMA type 2 and SMA type 3 groups.

We conducted Pearson correlation analysis between the significantly altered regional quantitative indices and HFMSE scores within the SMA group. A P value ≤0.05 was

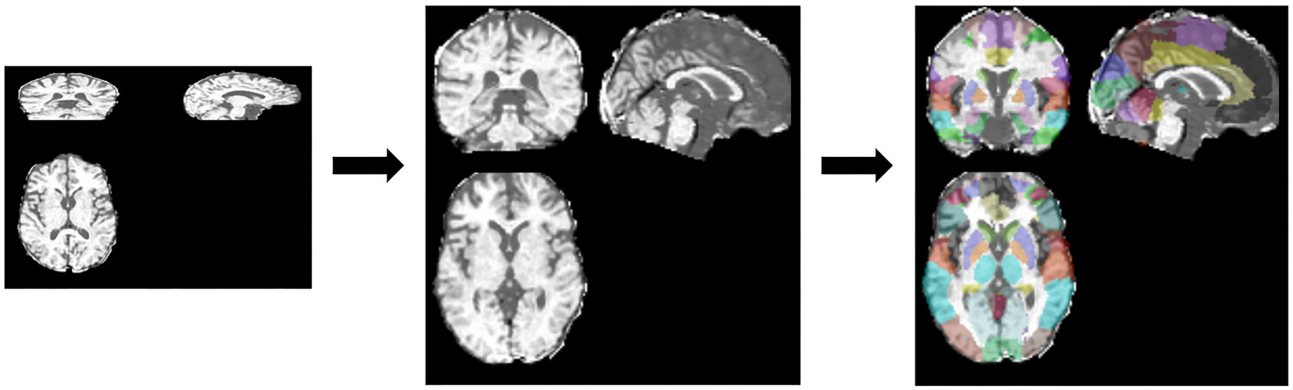

Figure 1 The process and effect of image registration.

Table 1 Demographic data of patients with SMA type 2, SMA type 3 and healthy controls

Characteristics	Type 2 (n=29)	Type 3 (n=24)	Controls (n=56)	P value
Sex				0.110
Male	20	13	42	
Female	9	11	14	
Age, years	9.03±3.40	11.25±5.03	9.16±2.70	0.186

Data are presented as n or mean ± standard deviation. SMA, spinal muscular atrophy.

considered statistically significant with a false-discovery rate (FDR) for the multiple comparison correction.

Results

Demographic data

There were no differences between patients and HC in age and sex (mean age: 10.04±4.31 *vs.* 9.16±2.70, P=0.21; male/female: 33:20 *vs.* 42:14, P=0.15). For subtypes of SMA, SMA type 2, SMA type 3, and the HC group were all comparable in age and sex (*Table 1*).

Alterations of T1 relaxometry value in patients with SMA

The SMA group showed higher T1 relaxation times than the HC in 14 brain regions including bilateral dorsolateral superior frontal gyrus, orbital part of inferior frontal gyrus, insula, median and paracingulate gyrus, Heschl's gyrus, cerebellum 7b, the right middle frontal gyrus, and left temporal pole of superior temporal gyrus (*Figure 2A*, *Table 2*). There was no significant difference between SMA type 2 and type 3.

Alterations of T2 relaxometry value in patients with SMA

When compared with HC, a large number of brain regions of the SMA group showed higher T2 relaxation time. These brain regions anatomically mainly involved prefrontal, limbic, frontal and temporal lobe, and cerebellum, in addition to some brain regions involved in a small portion of the occipital and parietal lobe. As for the functional network, these significantly altered brain regions were mainly involved in the composition of the default mode network (DMN), attention and execution control network (EAN), salience network (SN), and cerebellum (*Figure 2B*, *Table 2*). Overall, alterations of T2 relaxometry value were mainly observed in the cerebellum and prefrontal lobes, referring to the function networks of DMN, EAN, and cerebellum. Besides, there was no difference between the 2 subtypes of SMA.

Correlations with HFMSE scores

No significant relationship was found between T1 relaxation times and HFMSE scores. As for T2 relaxation times, negative correlation relationships were observed

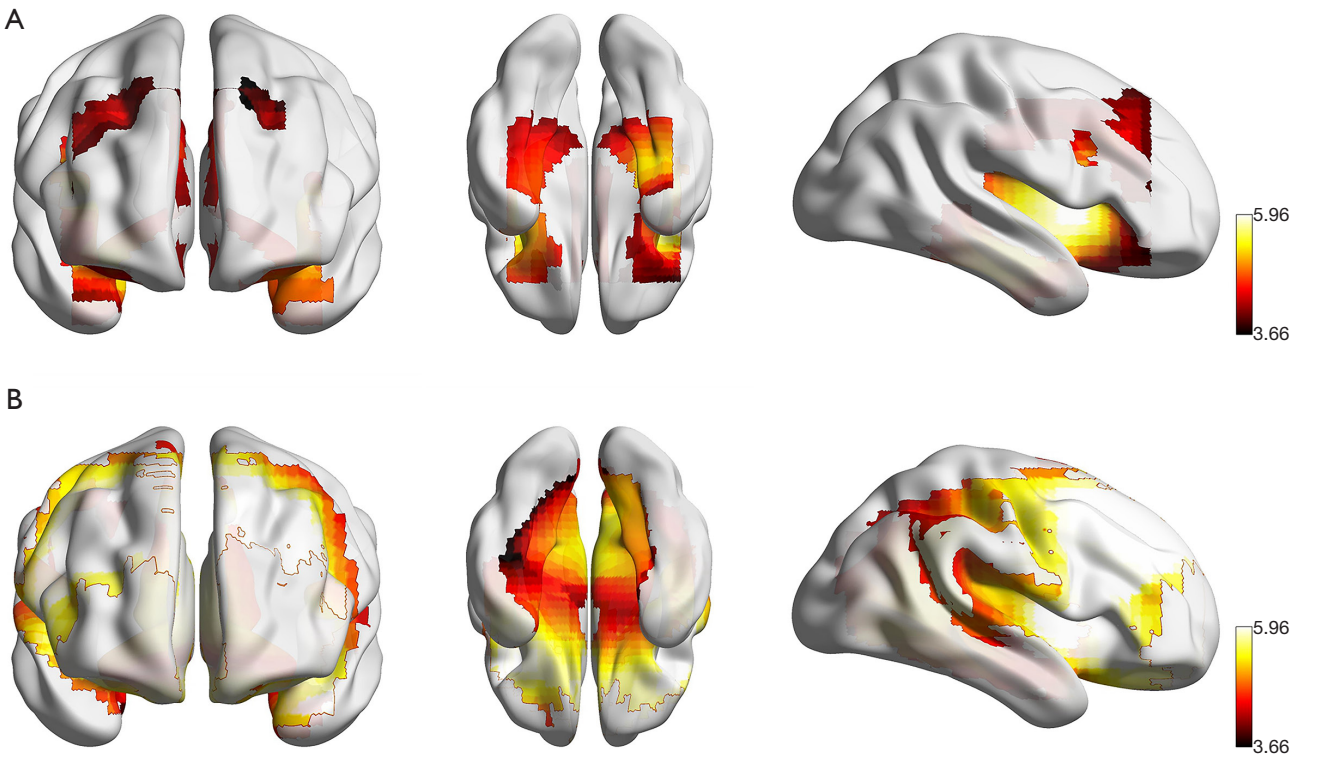

Figure 2 The significantly altered brain regions with T1 (A) and T2 (B) relaxation times. Compared with healthy controls, patients with SMA showed wide grey matter alterations in T1 and T2 relaxation time (P<0.05, Bonferroni-corrected). The detailed information could be found in *Table 2*. The color scale indicated the *t*-values. SMA, spinal muscular atrophy.

between HFMSE scores and T2 relaxation times of the left orbital part of superior frontal gyrus (P=0.0132, *Figure 3A*) and the right olfactory cortex (P=0.0085, *Figure 3B*) in the SMA group.

Discussion

Our current study found widespread microstructural changes in cortical and subcortical regions in patients with SMA type 2 and type 3, including cerebellum, DMN, EAN, SN, sensorimotor network (SMN), and auditory network (AN). Moreover, T2 relaxation times of the left orbital part of superior frontal gyrus and the right olfactory cortex were negatively connected with HFMSE scores.

Alterations of T1 and T2 relaxation times reflecting brain microstructural change

Several studies have reported that cortical and subcortical brain alterations in patients with SMA were not limited to lower motor neuron pathways (13,15,16,23,24). A study reported the delayed myelination and dysplasia of the corpus callosum, with high-intensity areas in the cerebral hemispheres in a 12-month-old female with SMA type 2 (24). In adults from the SMA types 3 and 4 patient group, morphological alterations were found in the bilateral anterior cingulate, the orbitofrontal cortices, the dorsolateral prefrontal cortex, and the precentral gyrus (15). Another study which focused on the cerebellum reported that there were cerebellum abnormalities in patients with SMA (16). In our study, these brain regions were also found with T1 and T2 relaxation times alterations in patients with SMA type 2 and 3, which together reflect macrostructural and microstructural changes in these brain regions in patients with SMA.

The SMN protein, a critical factor related to SMA, is well-known to be critical to motor system, and is involved in the spliceosome and biogenesis of ribonucleoproteins (25). Recent studies have indicated that the SMN protein is a ubiquitously expressed protein, required by all cells and tissue types, and is involved in many other fundamental cellular homeostatic pathways including messenger

Table 2 Altered grey matter regions with T1 or T2 relaxation times between patients with spinal muscular atrophy and healthy controls

AAL number	Network	Regions	Anatomical classification	Metric	P value
3, 4	DMN	SFGdor	Prefrontal	T1, T2	0.003, 0.002/<0.001[†]
23, 24	DMN	SFGmed	Prefrontal	T2	<0.001
27	DMN	REC.L	Paralimbic	T2	<0.001
33, 34	DMN	DCG	Paralimbic	T1, T2	0.001/<0.001
37	DMN	HIP.L	Limbic	T2	<0.001
39	DMN	PHG.L	Paralimbic	T2	<0.001
45	DMN	CUN.L	Occipital	T2	<0.001
48	DMN	LING.R	Occipital	T2	<0.001
5	EAN	ORBsup.L	Prefrontal	T2	<0.001
7, 8	EAN	MFG	Prefrontal	T1 [8], T2	0.001/<0.001
11, 12	EAN	IFGoperc	Prefrontal	T2	<0.001
13, 14	EAN	IFGtriang	Prefrontal	T2	<0.001
15, 16	EAN	ORBinf	Prefrontal	T1, T2 [16]	<0.001/<0.001
17, 18	EAN	ROL	Frontal	T2	<0.001
25, 26	EAN	ORBsupmed	Prefrontal	T2	<0.001
62	EAN	IPL.R	Parietal	T2	<0.001
21, 22	SN	OLF	Prefrontal	T2	<0.001
29, 30	SN	INS	Paralimbic	T1, T2	<0.001/<0.001
31, 32	SN	ACG	Prefrontal	T2	<0.001
41, 42	SN	AMYG	Temporal	T2	<0.001
1, 2	SMN	PreCG	Frontal	T2	<0.001
19, 20	SMN	SMA	Frontal	T2	<0.001
58	SMN	PoCG.R	Parietal	T2	<0.001
79, 80	AN	HES	Temporal	T1, T2 [80]	<0.001/<0.001
81, 82	AN	STG	Temporal	T2	<0.001
83	AN	TPOsup.L	Temporal	T1, T2	<0.001/<0.001
96	Cerebellum	Cbe3.R	Cerebellum	T2	<0.001
97	Cerebellum	Cbe4-5.L	Cerebellum	T2	<0.001
101, 102	Cerebellum	Cbe7b	Cerebellum	T1	0.001
103	Cerebellum	Cere8.L	Cerebellum	T2	<0.001
111	Cerebellum	Ver4-5	Cerebellum	T2	<0.001
112	Cerebellum	Ver6	Cerebellum	T2	<0.001

P values were adjusted for multiple comparisons using Bonferroni correction with significance threshold set at 0.05 (corrected for 116 brain regions). [†], P values: T1, T2 for AAL3 respectively/T1, T2 for AAL4. AAL, anatomical automatic labeling; DMN, default mode network; SFGdor, dorsolateral superior frontal gyrus; SFGmed, medial superior frontal gyrus; REC.L, left gyrus rectus; DCG, median cingulate and paracingulate gyri; HIP.L, left hippocampus; PHG.L, left parahippocampal gyrus; CUN.L, left cuneus; LING.R, right Lingual gyrus; EAN, attention and execution control network; ORBsup.L, left orbital part of superior frontal gyrus; MFG, middle frontal gyrus; IFGoperc, opercular part of inferior frontal gyrus; IFGtriang, triangular part of inferior frontal gyrus; ORBinf, orbital part of inferior frontal gyrus; ROL, rolandic operculum; ORBsupmed, medial orbital of superior frontal gyrus; IPL.R, right inferior parietal; but supramarginal and angular gyri; SN, salience network; OLF, olfactory cortex; INS insula; ACG, anterior cingulate and paracingulate gyri; AMYG, amygdala; SMN, sensorimotor network; PreCG, precental gyrus; SMA, supplementary motor area; PoCG.R, right postcentral gyrus; AN, auditory network; HES, heschl gyrus; STG, superior temporal gyrus; TPOsup.L, left temporal pole: superior temporal gyrus.

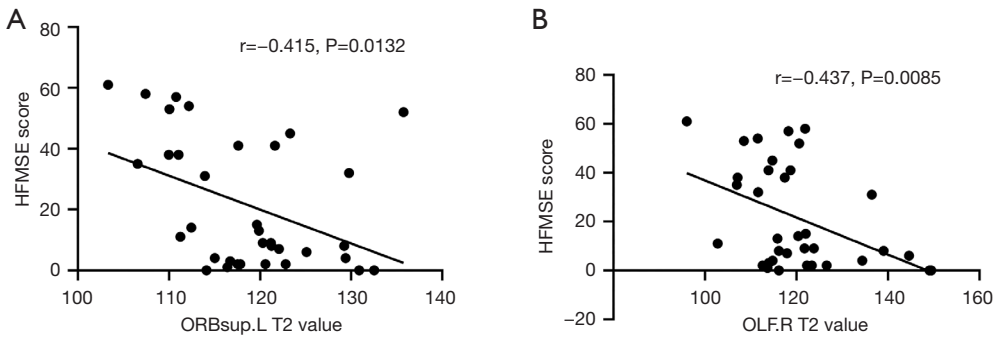

Figure 3 Relationship between HFMSE scores and the significantly altered T2 relaxation times. These relationships involved the left orbital part of superior frontal gyrus (A) and the right olfactory cortex (B) in patients with SMA. HFMSE, Hammersmith Functional Motor Scale Expanded; ORBsup.L, left orbital part of superior frontal gyrus; OLF.R, right olfactory cortex; SMA, spinal muscular atrophy.

RNA (mRNA) trafficking (26) and local translation (27), cytoskeletal dynamics (28), and endocytosis (29). Dysregulation of the SMN protein has also been shown to be associated with a variety of degenerative diseases such as amyotrophic lateral sclerosis (30). Wishart *et al.* explored the reduced level of SMN protein in a mouse model with severe SMA, and demonstrated that SMN deficiency could disrupt brain development, which was associated with decreased cell density and reduced cell proliferation (31). In our study, increased T1 maps referring to 14 regions were observed, which were affected by myelin and iron content. Indeed, longer T1 relaxation times were correlated to lower myelin and iron content, although accurate measurements of iron content need to be made with specific sequences for further study such as R2* mapping and quantitative susceptibility mapping (QSM) (19). The changes of T1 mapping in our study indicated myelination dysplasia in patients with SMA type 2 and 3. Moreover, increased T2 mapping involved a wider range, including 46 brain regions. Generally, T2 relaxation times in axons, myelin, and extracellular cells are gradually elevated, and increased T2 relaxation times of the brain can be explained by reduced myelin content and correspondingly increased water content (18). These alterations of MRI relaxometry times demonstrated the changes of the microstructure and composition of myelinated tissue in patients with SMA and presumably relate to the lack of SMN protein. It is speculated that the alterations of T1, T2 relaxation times are correlated with the dysregulation of cellular environmental homeostasis caused by SMN deficiency. The lack of SMN protein affects the growth and development of neurocyte, disrupting the structure and living environment and the information transmission along neurons, ultimately resulting in extensive microenvironmental damage to the brain. Recently a study demonstrated that the deficiency of SMN protein affects early neurodevelopment, which may underlie later motor neuronal degeneration (32). Furthermore, the limited motor activity reduces the motor and sensory stimulation that the brain receives from body, which can also affect brain development. Therefore, it is plausible to assume that the brain abnormalities in patients with SMA are the result of a combination of SMN protein deficiency and minimally active life, but more basic experiments are necessary to confirm the physiological mechanism behind this hypothesis.

The varied brain regions and the network involved

The varied brain regions observed in our study are mainly located in some special functional areas including the cerebellum, the DMN, and attention and EAN. The DMN is an integrated network composed of a distributed collection of brain regions and is responsible for monitoring the external environment, episodic memory, generating spontaneous thoughts, and maintaining self-awareness (33). The EAN network is closely related to externally directed cognition and the control of memory and attention (34). In an SMNΔ7 mouse model of SMA, a significantly disproportionate loss in cerebellar volume was reported (12). de Borba *et al.* also reported the decreased volumes of cerebellar lobules VIIIB (right), IX, and X in patients with SMA types 3 and 4 (16). Although our results complement studies on cerebellum changes in SMA patients and may explain the decrease in cerebellum volume from a microscopic perspective, they need to be confirmed by further studies. In our study, DMN and EAN networks

with longer T2 relaxation times mainly involved prefrontal, limbic, parietal, and occipital lobes, which were consistent with a previous study that found increased GM density in the bilateral anterior cingulate, orbitofrontal cortices, and the dorsolateral prefrontal cortex in adult SMA patients (15). A follow-up study in patients with severe SMA type 0 presented diffuse and progressive brain abnormalities especially the severe hippocampal atrophy on MRI (13). Furthermore, Querin *et al.* also found GM density increase in the significant portions of the precentral gyrus representing the motor cortex, which was observed in our study of the SMN network (15). Our results suggest that patients with SMA have not only macroscopic structural, but also microscopic, abnormalities in these brain regions. In general, the microstructural alteration may be the pathophysiological basis for the structural and functional abnormalities. The increased cortical volumes were interpreted as an attempted compensatory mechanism in a previous study (15), but whether longer T2 relaxation times is a microscopic manifestation of this compensatory mechanism needs careful consideration.

These DMN and EAN networks observed in our study play critical roles in cognitive function. Kizina *et al.* explored the cognitive performance of patients with SMA types 2 and 3 with the Wechsler Adult Intelligence Scale, and found that patients with SMA type 2 had lower scores for working memory and perceptual reasoning compared to HC (35). In addition, dysfunction of the SMN network was associated with the loss of motor function in patients with SMA. These results showed that the abnormalities of GM have displayed obvious clinical symptoms in patients with SMA. Furthermore, the negative correlations between T2 relaxation times of the left orbital part of the superior frontal gyrus and the right olfactory cortex and HFMSE scores demonstrated that these microscopic changes in brain regions correlated with disease severity, reflecting that microscopic abnormality of the brain is the basis of abnormal function.

Additionally, this study found no significant difference between SMA type 2 and type 3. This was inconsistent with our hypothesis that a lack of SMN protein leads to a longer T1/T2 relaxation time. However, it may have been due to the insufficient subgroup sample size and further study in the future is warranted.

There are some limitations to our study. First, the sample size was insufficient. Our cohort is the largest SMA cohort ever reported because SMA is a rare disease, but the number of cases in neurodevelopmental disease studies is still relatively small. Second, our study lacked neuropsychological and behavioral outcomes to measure patient's mental and physical conditions; this needs to be supplemented by future research. Finally, this study was a cross-sectional study and could not show the progression of SMA. Therefore, longitudinal studies with larger sample sizes of SMA are needed to more thoroughly clarify the effects of SMA on the brain.

Conclusions

This study explored the GM alterations with T1 and T2 relaxometry times in patients with SMA type 2 and type 3. Widespread GM microstructure abnormalities were found that mainly related to iron deficiency and low myelin content. These results could help to better understand the pathophysiology of SMA to the central nervous system in the brain, and also provide ideas for quantitative measurement of SMA nerve damage. Longitudinal studies with larger sample sizes are needed to further investigate the disease course of SMA and the differences in brain alterations between different subtypes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-1095/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1095/coif). B.X. was an employee of MR Research China of GE Healthcare throughout his involvement in the study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (No. [2021]710) and informed consent was provided by all individual participants.

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