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Fatigue in the Preataxic and Ataxic Stages of Spinocerebellar Ataxia Type 3

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ABSTRACT

Objective: Fatigue is a significant symptom in patients with spinocerebellar ataxia type 3 (SCA3). This study explores the role of fatigue in SCA3, examining its impact on quality of life and its potential as an indicator of disease progression.

Methods: We prospectively recruited 128 molecularly confirmed SCA3 patients and 125 sex-, age-, and education-matched healthy controls (HCs). Age at onset, disease duration, length of normal and expanded CAG repeats, and 14-item Fatigue Scale score were compared. MRIs evaluated the cerebellum and brain lesions.

Results: Our study found that the preataxic SCA3 group exhibited lower fatigue incidence and score than HCs (Incidence: 13% vs. 36%, $p = 0.031$; FS-14 score: 3.0 ± 2.7 vs. 5.6 ± 2.8, $p < 0.001$). Ataxic SCA3 patients experienced significantly higher fatigue incidence and score compared to both the preataxic SCA3 group (Incidence: 63.8% vs. 13%, $p < 0.001$; FS-14 score: 8.1 ± 3.9 vs. 3.0 ± 2.7, $p < 0.001$) and HCs (Incidence: 63.8% vs. 36%, $p < 0.001$; FS-14 score: 8.1 ± 3.9 vs. 5.6 ± 2.8, $p < 0.001$). Moreover, fatigue severity in SCA3 correlated with disease duration and expanded CAG repeat length. Neuroanatomical correlations revealed volume reductions in cortical and cerebellar regions linked to higher physical and mental fatigue scores in SCA3 patients.

Conclusions: Monitoring fatigue effectively evaluates a patient's overall quality of life and disease progression, making it a key indicator. Future treatments can target specific brain regions, with their effectiveness being evaluated through FS-14 assessments of fatigue changes.

Abbreviations: AAL3, automated anatomical labeling atlas 3; AAO, age at onset; ANOVA, analysis of variance; CAG, cytosine-adenine-guanine; CAT12, computational anatomy toolbox; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; FOV, field of view; FS-14, 14-Item Fatigue Scale; FWE, family-wise error rate; FWHM, full-width at half-maximum; GM, gray matter, WMwhite matter; HCs, healthy controls; MJD, Machado Joseph disease; MP-RAGE, magnetization-prepared rapid gradient-echo; PCR, polymerase chain reaction; polyQ, polyglutamine; PSM, propensity score matching; SARA, scale for the assessment and rating of ataxia; SCA, spinocerebellar ataxia type; SCA3, spinocerebellar ataxia type 3; SPM12, statistical parametric mapping; TIV, total intracranial volume; VBM, voxel-based morphometry.

Zhi-li Chen, Li-mei Xiao, and Chun Li contributed equally to this work.

1 | Introduction

Spinocerebellar ataxia type 3 (SCA3), also known as Machado Joseph disease (MJD), is the most common subtype of spinocerebellar ataxia (SCAs), belonging to polyglutamine (polyQ) disease [1, 2]. In SCA3 patients, the substantia nigra and cerebellopontine dentate nuclei are involved and are the most severely affected, and have a distinct pattern of episodic progression to cortical brain structural changes [3].

Fatigue is defined as difficulty in initiating or maintaining voluntary mental and physical activities [4]. Studies have reported increased fatigue in SCA3 patients [5] and the incidence of fatigue is as high as 52.9%–63.5% [6–8]. A previous study by our research team found a positive correlation between fatigue and ataxic severity [9]. Later studies [10] found that patients with ataxia have more severe fatigue at the fatigue severity score than healthy controls. It has also been found [11, 12] that fatigue is a severely disabling symptom in SCA patients in the early stages of the disease and that in the absence of differences in physical activity levels, fatigue was higher SCA3 patients.

The early stage of ataxia can serve as a period of preventive intervention. A recent study [10] proposed a similar viewpoint to ours, suggesting that the optimal time to introduce correlated therapy to delay the onset or slow down disease progression may be in the early stages of ataxia. From a neuroanatomical perspective, current studies are unclear about the relationship between structural brain alterations and fatigue in ataxia, leaving the intervention targets ambiguous. Meanwhile, detailed research on whether fatigue symptoms can serve as an indicator for monitoring disease progression and their importance in improving quality of life is still lacking. To clarify this issue, our study presents clinical and imaging data to gain a deeper understanding of the impact and role of fatigue in SCA3 patients.

2 | Materials and Methods

2.1 | Standard Protocol Approvals, Registrations, and Patient Consent

The study was approved by the Ethics Committee for Medical Research of the First Affiliated Hospital of Fujian Medical University ([2019]195). The ClinicalTrials.gov identifier is NCT04010214 for this study. All participants gave written informed consent.

2.2 | Subjects

All participants were recruited consecutively from the Organization in South-East China for Cerebellar Ataxia Research (OSCCAR) in the Department of Neurology of the First Affiliated Hospital of Fujian Medical University in China between 1 March 2021 and 31 October 2022; we enrolled 128 molecular-confirmed SCA3 patients. To qualify for participation, patients must meet our inclusion and exclusion criteria (details in Data S1).

Based on previous research [9, 13], 125 sex-, age-, and education level-matched healthy controls (HCs) with normal CAG repeat numbers ranging from 12 to 44 [14] were enrolled at the same hospital.

2.3 | Subjective Questionnaires and Surveys

Each patient conducted face-to-face interviews with ataxia experts (SRG, HLX, and JSY) to collect demographic data and neurological characteristics. Age at onset (AAO) was defined as the time when the patient or close relatives/caregivers could recall the first appearance of any symptoms related to SCA3. The symptoms include gait instability, diplopia, dysarthria, and dystonia [15]. Disease duration was defined as the time between AAO and age at the first visit. The progression degree of ataxia was measured by a patient's SARA score divided by duration. Patients with a SARA score <3 were defined as preataxic SCA3 mutation carriers; those with a SARA score ≥ 3 were defined as ataxic SCA3 patients [16]. Total SCA3 patients were categorized into 2 groups: preataxic SCA3 group (preataxic SCA3 mutation carriers) and ataxic SCA3 group (ataxic SCA3 patients). A flowchart of participant selection and data processing is shown in Figure 1.

Five subgroups defined according to disease duration were created [17], and two subgroups were defined according to the median length of expanded CAG repeats.

To rate the severity of fatigue, the 14-Item Fatigue Scale (FS-14) was used, which is often divided into two components: physical fatigue and mental fatigue [18]. Patients with an FS-14 score of <7 were classified as a non-fatigue group, while those with an FS-14 score of ≥ 7 were classified as a fatigue group [19].

2.4 | MRI Acquisition and Data Analysis

SCA3 patients performed 3.0-Tesla brain MRI examinations (Siemens Skyra scanner). Eighty-two participants underwent a brain MRI exam within 1 month after neurocognitive and neuropsychiatric assessment. Due to insufficient image quality in 3 SCA3 patients, the MRIs from 79 patients were ultimately included in the study. Detailed information on MRI acquisition and analysis is provided in supplemental materials.

2.5 | Statistical Analyses

Statistical analysis was performed using SPSS version 22.0 software for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were evaluated by Pearson's chi-square test and were presented as frequencies and percentages. Continuous variables were presented as the mean $\pm$ SD and evaluated by Student's independent sample *t*-test or Mann–Whitney *U* Test. To reduce potential confounding bias, propensity score matching (PSM) was performed (details in supplemental materials). Whole-brain correlation analysis with a one-tailed approach between GM volume and FS-14 score was performed using the "multiple regression" design function of SPM12 (details in supplemental materials).

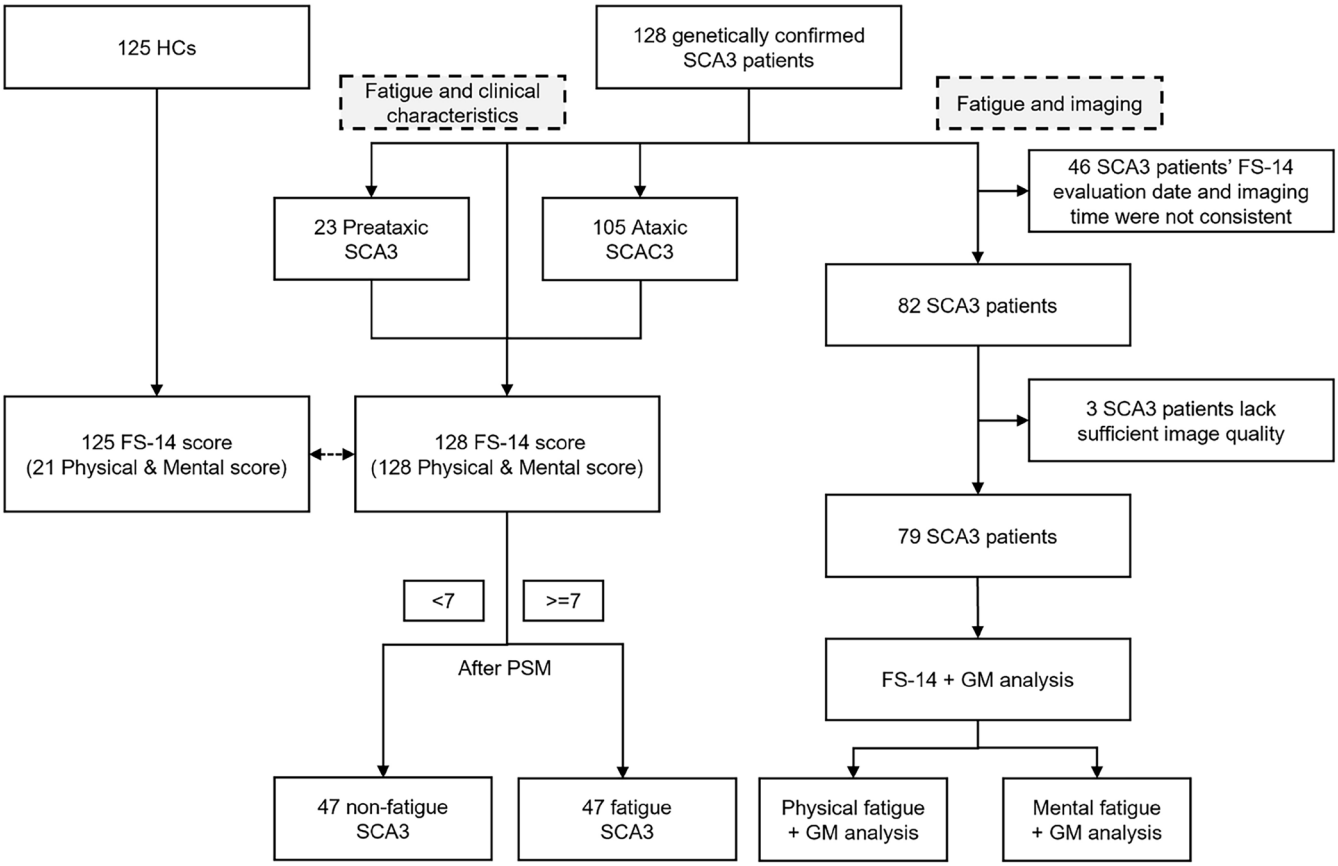

FIGURE 1 | Trial profile. FS-14, 14-Item Fatigue Scale; GM, gray matter; HCs, healthy controls; PSM, propensity score matching; SCA3, Spinocerebellar ataxia type 3.

3 | Results

3.1 | Clinical and Demographic Characteristics of Participants

Clinical and Demographic Characteristics of HCs and SCA3 patients are shown in Table 1. The mean lengths of normal and expanded CAG repeat in the total SCA3 group were 20.9 and 74.4, respectively. There were no significant differences in age, sex, and education between HCs and the total SCA3 group (Age: 37.7 ± 12.9 vs. 40.2 ± 11.6, $p = 0.064$; Female %: 48.8 vs. 38.3, $p = 0.092$; Some college or more %: 38.4 vs. 28.9, $p = 0.110$). After dividing the SCA3 patients into preataxic and ataxic groups, we found that the comparisons show that the preataxic SCA3 group is younger than both HCs and the ataxic SCA3 group (HCs vs. Preataxic: 37.7 ± 12.9 vs. 28.0 ± 5.6, $p = 0.002$; Preataxic vs. Ataxic: 28.0 ± 5.6 vs. 42.8 ± 10.8, $p < 0.001$). Comparing HCs and the ataxic SCA3 group, there is a significant difference in gender distribution (Female %: 48.8 vs. 35.2, $p = 0.038$). There are no gender differences between HCs and the preataxic SCA3 group (Female %: 48.8 vs. 52.2, $p = 0.766$), nor between the preataxic SCA3 group and the ataxic SCA3 group (Female %: 52.2 vs. 35.2, $p = 0.130$). Furthermore, compared to HCs and the ataxic SCA3 groups, the preataxic SCA3 group has a higher level of education (HCs vs. Preataxic: 38.4% vs. 60.9%, $p = 0.045$; HCs vs. Ataxic: 38.4% vs. 21.9%, $p = 0.007$; Preataxic vs. Ataxic: 60.9% vs. 21.9%, $p < 0.001$). The Ataxic SCA3 group exhibited a mean disease duration of 6.9 years. There were no significant differences in the mean length of normal or expanded CAG repeats between the preataxic SCA3 group and the ataxic SCA3 group (normal: 20.7 ± 6.8 vs. 20.9 ± 7.4, $p = 0.910$; expanded: 73.4 ± 5.2 vs. 74.7 ± 4.2, $p = 0.215$).

3.2 | Fatigue Characteristics in SCA3

The incidence and level of fatigue were significantly higher in SCA3 than in HCs (Incidence: 54.7% vs. 36%, $p = 0.004$; FS-14 score: 7.2 ± 4.1 vs. 5.6 ± 2.8, $p = 0.001$; RR = 1.5). In patients with SCA3, the scores of not only physical fatigue but also mental fatigue were both noticeably higher compared with HCs (Physical fatigue: 4.1 ± 2.7 vs. 2.9 ± 2.1, $p < 0.001$; Mental fatigue, 3.1 ± 1.9 vs. 1.9 ± 1.6, $p < 0.001$) (Table 2).

3.3 | The Differences in Fatigue Score Between HCs and Preataxic SCA3 Group

The incidence and level of fatigue were significantly lower in the preataxic SCA3 group than in HCs (Incidence: 13% vs. 36%, $p = 0.031$; FS-14 score: 3.0 ± 2.7 vs. 5.6 ± 2.8, $p < 0.001$; RR = 0.4). In patients with the preataxic SCA3 group, the score of physical fatigue was lower compared with HCs (1.6 ± 1.7 vs. 2.9 ± 2.1, $p = 0.032$). But there were no differences in mental fatigue scores compared with HCs (1.4 ± 1.5 vs. 1.9 ± 1.6, $p = 0.256$) (Table 2 and Figure 2).

TABLE 1 | Baseline characteristics.

	HCs $n=125$	Total SCA3 $n=128$	Preataxic SCA3 $n=23$	Ataxic SCA3 $n=105$	p^a	p^b	p^c	p^d
Age, year	37.7 ± 12.9	40.2 ± 11.6	28.0 ± 5.6	42.8 ± 10.8	0.064	**0.002**	**0.002**	**< 0.001**
Female, *n* (%)	61 (48.8)	49 (38.3)	12 (52.2)	37 (35.2)	0.092	0.766	**0.038**	0.130
Education, *n* (%)								
High school or less	77 (61.6)	91 (71.1)	9 (39.1)	82 (78.1)	0.110	**0.045**	**0.007**	**< 0.001**
Some college or more	48 (38.4)	37 (28.9)	14 (60.9)	23 (21.9)				
Age at onset, year	NA	35.9 ± 10.4	NA	35.9 ± 10.4	NA	NA	NA	NA
Disease duration, year	NA	6.9 ± 5.7	NA	6.9 ± 5.7	NA	NA	NA	NA
Length of normal CAG repeats	NA	20.9 ± 7.2	20.7 ± 6.8	20.9 ± 7.4	NA	NA	NA	0.910
Length of expanded CAG repeats	NA	74.4 ± 7.4	73.4 ± 5.2	74.7 ± 4.2	NA	NA	NA	0.215

Note: Variables are expressed as mean ± SD, and categorical variables are expressed as percentages of total. Bold values indicate statistically significant results with $p < 0.05$.
Abbreviations: CAG, cytosine-adenine-guanine; HCs, healthy controls; *n*, number; NA, non-application; SCA3, spinocerebellar ataxia type 3.
[a]HCs versus total SCA3 group.
[b]HCs versus preataxic SCA3 group.
[c]HCs versus ataxic SCA3 group.
[d]Preataxic SCA3 group vs. Ataxic SCA3 group.

TABLE 2 | Fatigue Characteristics of the Patients with a pathologic ATXN3 expansion (HCs, preataxic SCA3 group, ataxic SCA3 group, and total SCA3 group).

	HCs $n=125$	Preataxic SCA3 $n=23$	Ataxic SCA3 $n=105$	Total SCA3 $n=128$
FS—14 score	5.6 ± 2.8	3.0 ± 2.7	8.1 ± 3.9	7.2 ± 4.1
Score ≥ 7, *n* (%)	45 (36.0)	3 (13.0)	67 (63.8)	70 (54.7)
Rate ratio (95% CI)	Ref	0.4 (0.1–1.1)	1.8 (1.6–2.3)	1.5 (1.2–2.0)
Physical fatigue score	2.9 ± 2.1	1.6 ± 1.7	4.7 ± 2.5	4.1 ± 2.7
Z-score > 1.96, *n* (%)	Ref	0 (0)	19 (18.1)	19 (14.8)
Mental fatigue score	1.9 ± 1.6	1.4 ± 1.5	3.4 ± 1.7	3.1 ± 1.9
Z-score > 1.96, *n* (%)	Ref	0 (0)	13 (12.4)	13 (10.1)

Note: Variables are expressed as mean ± SD, and categorical variables are expressed as percentages of total.
Abbreviations: CAG, cytosine-adenine-guanine; FS-14, 14-Item Fatigue Scale; HCs, healthy controls; *n*, number; SCA3, spinocerebellar ataxia type 3.

3.4 | The Differences in Fatigue Score Between HCs and Ataxic SCA3 Group

The incidence and level of fatigue were significantly higher in the ataxic SCA3 group than in HCs (Incidence: 63.8% vs. 36%, $p < 0.001$; FS-14 score: 8.1 ± 3.9 vs. 5.6 ± 2.8, $p < 0.001$; RR = 1.8). In patients with the ataxic SCA3 group, the score of not only physical fatigue but also mental fatigue was noticeably higher compared with HCs (Physical fatigue: 4.7 ± 2.5 vs. 2.9 ± 2.1, $p = 0.006$; Mental fatigue, 3.4 ± 1.7 vs. 1.9 ± 1.6, $p = 0.001$) (Table 2 and Figure 2).

3.5 | The Differences in Fatigue Score Between Preataxic SCA3 Group and Ataxic SCA3 Group

The incidence and level of fatigue were significantly lower in the preataxic SCA3 group than in the ataxic SCA3 group (Incidence: 63.8% vs. 13%, $p < 0.001$; FS-14 score: 8.1 ± 3.9 vs. 3.0 ± 2.7, $p < 0.001$) (Table 2).

In patients with the ataxic SCA3 group, the incidence and level of physical fatigue were both higher compared with the preataxic SCA3 group (Physical fatigue: 4.7 ± 2.5 vs. 1.6 ± 1.7, $p < 0.001$;

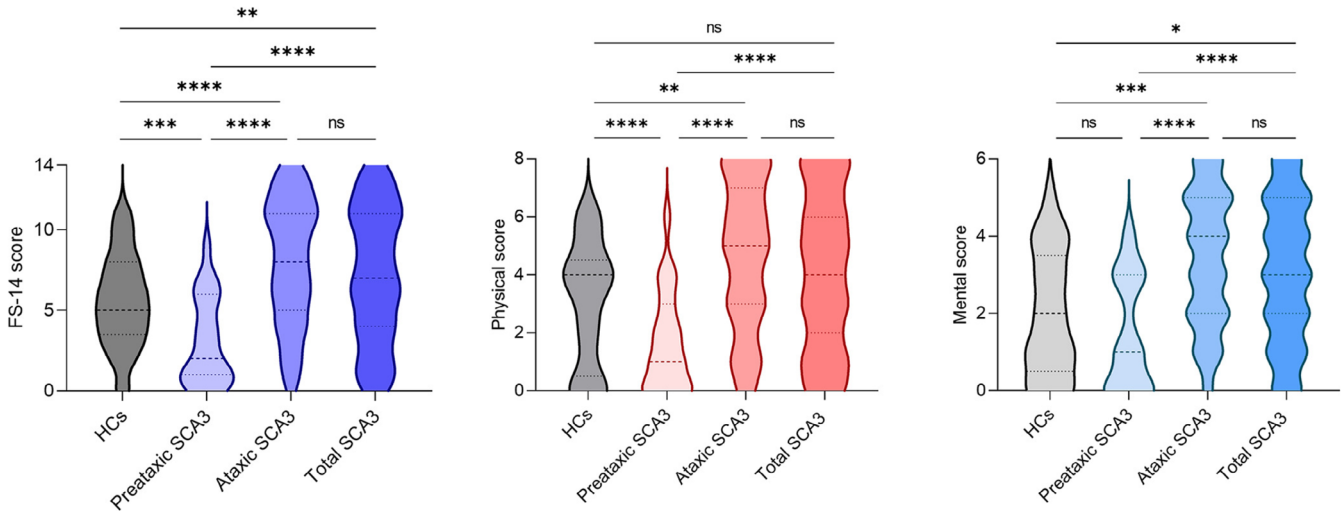

FIGURE 2 | Violin plots comparing the FS-14, physical, and mental scores between HCs and SCA3 patients (preataxic SCA3 group, ataxic SCA3 group, and total SCA3 group). The median was represented by the middle dashed line, and the outer dashed lines represented the interquartile ranges. Data was evaluated by Mann–Whitney *U* test, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$, ns = not significant. FS-14, 14-Item Fatigue Scale; HCs, healthy controls; SCA3, spinocerebellar ataxia type 3.

Incidence of physical fatigue: 0% vs. 18.1%, $p = 0.024$; Mental fatigue: 3.4 ± 1.7 vs. 1.4 ± 1.5, $p < 0.001$;) (Table 2 and Figure 2). The score of mental fatigue was also higher compared with the preataxic SCA3 group (3.4 ± 1.7 vs. 1.4 ± 1.5, $p < 0.001$).

The mean *Z*-score of physical fatigue score was 0.51 ± 1.24, and the mean *Z*-score of mental fatigue score was 0.68 ± 1.13. As expected, SCA3 patients with ataxia were significantly more severe than those without ataxia. Surprisingly, those without ataxia had lower overall FS-14 score, physical fatigue score, and mental fatigue score than HCs.

3.6 | Fatigue in the Patients With SCA3 Was Related to Disease Duration and Length of Expanded CAG Repeats

Clinical characteristics of SCA3 patients with or without fatigue are shown in Table 3.

Before PSM, patients with fatigue had higher education, disease duration, and length of expanded CAG repeats than patients without fatigue (High school or less %: 82.9 vs. 56.9, $p = 0.001$; Disease duration: 7.5 ± 5.1 vs. 3.5 ± 6.0, $p < 0.001$; Expanded CAG repeats: 75.4 ± 3.7 vs. 73.3 ± 4.9, $p = 0.037$). There were no differences in age, sex, age at onset, and Length of normal CAG repeats between patients with and without fatigue (Age: 42. 6 ± 11.3 vs. 37.2 ± 11.3, $p = 0.080$; Female %: 35.7 vs. 41.4, $p = 0.512$; Age at onset: 35.4 ± 10.5 vs. 36.7 ± 10.8, $p = 0.0539$; Normal CAG repeats: 21.8 ± 7.2 vs. 20.1 ± 7.3, $p = 0.290$).

After PSM, there are 47 subjects in each of the patients with and without fatigue groups. There were no significant differences in age, sex, education, age at onset, and Length of normal CAG repeats. Patients with fatigue still had a higher disease duration and length of expanded CAG repeats than patients without fatigue (Disease duration: 7.3 ± 5.6 vs. 4.0 ± 6.5, $p < 0.001$; Expanded CAG repeats: 75.6 ± 3.7 vs. 72.9 ± 4.8, $p = 0.012$). This reflects that the fatigue of SCA3 patients is related to disease duration and length of expanded CAG repeats. We could see the fatigue increasing gradually through disease duration (Figure S1A). Also, we could see an overall upward trend of fatigue increase through the length of expanded CAG repeats (Figure S1B).

3.7 | Correlation Between GM Volume and Fatigue Score

A common anatomical pattern of correlation between GM volume loss and FS-14 score increase was identified in all SCA3 patients; we found a volumetric reduction in the cerebral cortex and the cerebellum (Figure 3A, peak *t* value = 4.73, $p < 0.05$, FWE-corrected at cluster level). By distinguishing between physical and mental fatigue, we found a volumetric reduction in the bilateral area VIII, left area IX, and Vermis IX that correlated with mental fatigue increase (Figure 3B, peak *t* value = 4.99, $p < 0.05$, FWE-corrected at cluster level). The volumetric reduction in the left postcentral and inferior parietal lobes correlated with physical fatigue increase (Figure 3C, peak *t* value = 4.73, $p < 0.05$, FWE-corrected at cluster level).

4 | Discussion

In this cross-sectional study involving 128 patients with SCA3, 54.7% reported experiencing fatigue, a rate higher than that of HCs. Notably, ataxic SCA3 patients exhibited significantly higher fatigue incidence and scores compared to both preataxic SCA3 carriers and HCs. Conversely, preataxic SCA3 carriers reported lower physical and mental fatigue than HCs. Moreover, the study identified disease duration, the length of expanded CAG repeats, and MRI abnormalities in the cerebellum and brain as significant predictors of fatigue. By contrast, factors such as age, sex, education, age at onset, and the length of normal CAG repeats did not show a significant correlation

TABLE 3 | Baseline characteristics for SCA3 patients with and without fatigue in unmatched and matched cohorts.

Characteristics	Before PSM			After PSM		
	nF—SCA3 $n=58$	F—SCA3 $n=70$	p	nF—SCA3 $n=47$	F—SCA3 $n=47$	p
Corrected variables						
Age, year	37.2 ± 11.3	42. 6 ± 11.3	0.080	39.1 ± 11.5	41.9 ± 11.5	0.241
Female, *n* (%)	24 (41.4)	25 (35.7)	0.512	19 (40.4)	18 (38.3)	0.833
Education						
High school or less, *n* (%)	33 (56.9)	58 (82.9)	**0.001**	33 (70.2)	36 (76.6)	0.484
Some college or more, *n* (%)	25 (43.1)	12 (17.1)		14 (29.8)	11 (23.4)	
Measure covariates						
Age at onset[a], year	36.7 ± 10.8	35.4 ± 10.5	0.539	38.1 ± 10.1	34.8 ± 10.7	0.178
Disease duration[b], year	3.5 ± 6.0	7.5 ± 5.1	**< 0.001**	4.0 ± 6.5	7.3 ± 5.6	**< 0.001**
Length of normal CAG repeats	20.1 ± 7.3	21.8 ± 7.2	0.290	19.0 ± 6.8	21.8 ± 7.7	0.141
Length of expanded CAG repeats	73.3 ± 4.9	75.4 ± 3.7	**0.037**	72.9 ± 4.8	75.6 ± 3.7	**0.012**

Note: Variables are expressed as mean ± SD, and categorical variables are expressed as percentages of total. Bold values indicate statistically significant results with $p < 0.05$.
Abbreviations: CAG, cytosine-adenine-guanine; F, fatigue; *n*, number; nF, non-fatigue; PSM, propensity score matching; SCA3, spinocerebellar ataxia type 3.
[a]SCA3 patients without ataxia were excluded.
[b]The disease duration of SCA3 patients without ataxia was set to 0.

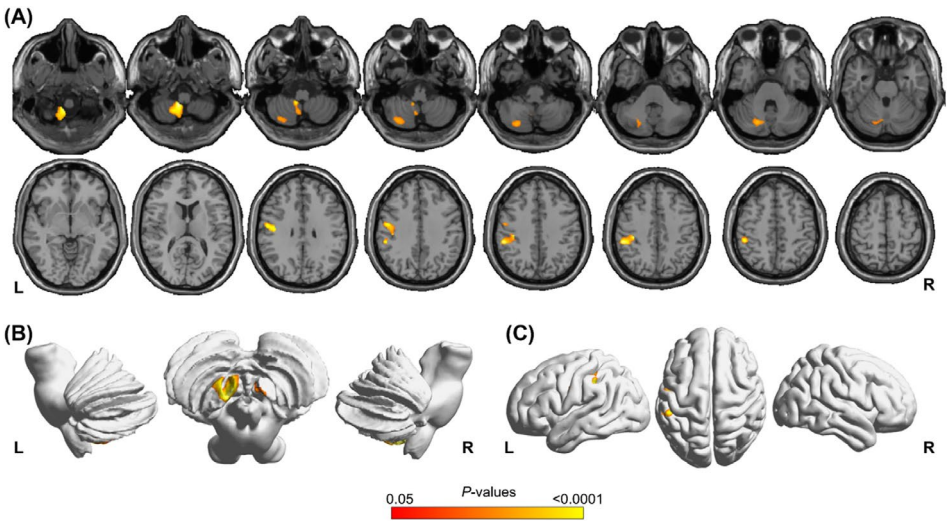

FIGURE 3 | Voxel-based morphometry analysis of the correlation between GM volume loss and (A) FS-14 score, (B) mental fatigue score, and (C) physical fatigue score increase. Covariates were age, sex, education, and TIV. The color bar displayed *p*-values. FS-14, 14-Item Fatigue Scale; L, left; R, right.

with fatigue. Our findings highlight that fatigue is more severe and prevalent among ataxic SCA3 patients and is associated with cerebellar involvement. These results suggest potential risk factors contributing to fatigue and point to developing interventions to alleviate fatigue in SCA3.

Fatigue symptoms may occur in the early stages of SCA3 [12], potentially due to early damage to the nervous system [20]. Additionally, SCA3 patients who experience fatigue tend to have a longer disease duration [21]. Patients typically experience more pronounced and persistent fatigue in the middle

and later stages of the disease [12]. In our study, fatigue was found to be lower in the preataxic stage compared to HCs and the ataxic stage. The lower fatigue levels in preataxic SCA3 mutation carriers compared to HCs may be attributed to their younger age and higher education levels. As ataxia manifests, the level of fatigue increases significantly. Similarly, in the READISCA study [10], despite the preataxic mutation carriers being of similar age to the control group, their fatigue score was lower than that of the control group. FS-14 assesses both physical and mental fatigue [18]. Physical fatigue includes symptoms such as lack of energy and exhaustion, whereas mental fatigue involves difficulty concentrating and reduced memory. Fatigue levels closely relate to quality of life. By monitoring fatigue, one can evaluate a patient's overall quality of life effectively, making it a key indicator.

Length of expanded CAG repeats in fatigue patients is longer than [21] and is an important predictor of fatigue in SCA3 patients [8]. Our study also found that the more CAG repetitions, the more severe the fatigue symptoms. Due to its correlation with fatigue, we believe that symptoms of the disease process itself may cause fatigue in SCA3 patients, and the number of CAG repetitions may serve as a potential biomarker for predicting fatigue levels in SCA3 patients.

SCA3 patients have extensive white matter and cerebellar damage [3, 20]. Our research findings confirm that mental fatigue is associated with reduced cerebellar volume, while physical fatigue is associated with reduced brain volume. Based on the imaging results, mental fatigue was associated with structural changes in the cerebellum, while physical fatigue was associated with cortical changes. This may be because structural brain changes in SCA3 patients progress from the bottom up toward the cerebral cortex [3], leading to an earlier onset of mental fatigue than physical fatigue.

The limitations of this article are as follows: (1) Our findings are based on cross-sectional data and cannot accurately estimate the time-dependent association and evolution between fatigue and structural changes in brain regions. (2) Although we have found that FS-14 has good reliability and effectiveness in our SCA3 cohort, further research may be needed to evaluate its applicability in monitoring fatigue in SCA3 patients. (3) As our study is based on FS-14 and structural MRI neuroimaging, it would be ideal if future research could seek confirmation based on autopsy tissue pathology.

5 | Conclusions

Given the high incidence of fatigue in SCA3 patients, we believe that fatigue has a significant impact on their daily lives. Additionally, there is a correlation between fatigue, disease duration, and the length of expanded CAG repeats. Therefore, we consider the degree of fatigue to be related to SCA3 progression. Monitoring changes in patient fatigue can serve as an indicator for observing disease progression. Furthermore, future treatments or interventions can target the cerebellar lobules VIII and IX, the vermis IX, and the left postcentral and inferior parietal lobes. The effectiveness of these treatments or interventions can be evaluated by assessing patient fatigue changes through FS-14.

Author Contributions

Zhi-li Chen: writing – original draft, methodology, data curation, software, investigation, visualization, formal analysis. **Li-mei Xiao:** writing – original draft, validation, formal analysis. **Chun Li:** writing – original draft, data curation, methodology, investigation. **Liang-liang Qiu:** software, visualization. **Wei Lin:** investigation. **Zhi-xian Ye:** data curation. **Yuan-yuan Zhang:** investigation. **Zhi-bao Zhu:** validation. **Meng-cheng Li:** investigation. **Min-ting Lin:** investigation. **Wan-jin Chen:** writing – review and editing. **Ning Wang:** writing – review and editing, supervision, funding acquisition, visualization. **Ying Fu:** writing – review and editing, supervision, validation, visualization, funding acquisition, project administration, resources. **Shi-rui Gan:** writing – review and editing, supervision, validation, visualization, funding acquisition, project administration.

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Consent

All authors gave final approval to publish the version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.