Med & Health Jan 2026; 21(1): 388-399 https://doi.org/10.17576/MH.2026.2101.25

ORIGINAL ARTICLE

A Resting-state fMRI Investigation of Brain Networks in Spinocerebellar Ataxia Type 3

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Received: 26 February 2025 / Accepted: 22 August 2025

ABSTRAK

Ataksia spinocerebellar jenis 3 (SCA3) dicirikan oleh pemutusan sambungan dalam rangkaian serebelum-serebrum. Dalam kajian ini, kami menyiasat perbezaan rangkaian tersebut antara kumpulan individu sihat (n = 14) dan individu dengan SCA3 (n = 14) menggunakan pengimejan resonans magnetik fungsi dalam keadaan rehat. Dengan menjadikan Crus I serebelum sebagai kawasan benih, kajian ini memberi tumpuan kepada rangkaian frontoparietal dan rangkaian mod lalai, dua rangkaian yang telah dikenal pasti secara meluas tetapi masih kurang dikaji dalam populasi SCA3. Selain itu, kami turut menilai kesalinghubungan tidak spesifik dengan 115 kawasan otak lain sebagai keadaan kawalan, berdasarkan atlas 'Automated Anatomical Labeling'. Individu dengan SCA3 menunjukkan penurunan kesalinghubungan fungsi dalam rangkaian serebelum-serebrum. Kajian ini mengenal pasti kedua-dua kekhususan rangkaian dan lateralisasi hemisfera dalam proses neurodegenerasi berkaitan SCA3, khususnya yang melibatkan frontoparietal kiri. Sebagai kesimpulan, kajian ini memberikan dapatan awal mengenai perubahan dalam kesalinghubungan fungsi antara Crus I dan frontoparietal dalam SCA3. Kajian lanjutan disarankan untuk menilai potensi rangkaian ini sebagai penunjuk hasil eksploratori dalam ujian klinikal SCA3.

Kata kunci: *Ataksia spinocerebellar jenis 3; Crus I; fungsi eksekutif; keadaan rehat; pengimejan resonans magnetik berfungsi keadaan rehat; rangkaian frontoparietal*

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ABSTRACT

Spinocerebellar ataxia type 3 (SCA3) is characterised by disconnection within the cerebellar-cerebral network. In the present study, we examined differences in this network between healthy controls (n = 14) and individuals with SCA3 (n = 14) using resting-state functional magnetic resonance imaging. Using cerebellar Crus I as the seed region, we focused on the frontoparietal network and the default-mode network, as both are well-established but remain under-characterised in the SCA3 population. Additionally, we examined non-specific connectivity with 115 other brain regions, based on the Automated Anatomical Labelling atlas, as a control condition. Individuals with SCA3 exhibited reduced functional connectivity within cerebellar-cerebral networks. We identified both network specificity and hemispheric lateralisation in SCA3-related neurodegeneration, particularly implicating the left frontoparietal network. In conclusion, this study provides preliminary evidence of altered functional connectivity between Crus I and the frontoparietal network in SCA3. Future research may consider this network as a potential exploratory outcome measure in SCA3 clinical trials.

Keywords: Crus I; executive function; frontoparietal network; resting-state functional magnetic resonance imaging; spinocerebellar ataxia type 3

INTRODUCTION

Spinocerebellar ataxia type 3 (SCA3) is a neurodegenerative disease that primarily affects the cerebellum (Bodranghien et al. 2016). In addition to ataxia symptoms, a systematic review has identified a core impairment in executive function among individuals with SCA3 (Yap et al. 2022b). This executive dysfunction is linked to the gradual deterioration and disconnection within the cerebellar-cerebral network, resulting from progressive degeneration of both the cerebrum and cerebellum (Yap et al. 2022a). The cognitive cerebellar-cerebral network includes extensive reciprocal connections between the cerebellum and the cerebral cortex, particularly the prefrontal cortex (PFC) and the posterior parietal cortex (Bostan et al. 2013), the latter of which is part of the frontoparietal network (FPN) (Gratton et al. 2018).

The FPN, also known as the central executive network, plays a crucial role in executive function and goal-oriented, cognitively demanding tasks (Uddin et al. 2019), a role facilitated by its connectivity with Crus I of the posterior cerebellum (Buckner et al. 2011). Within this network, the cerebellum acts as a hub that prepares neural processing to optimise action sequencing for executive tasks (Beuriat et al. 2020). Greater executive function is associated with stronger functional connectivity (FC) between the posterior cerebellum and the FPN (Reineberg et al. 2015). While disruptions in the FPN have been observed in neurodegenerative diseases such as Alzheimer's disease (Menon 2011), similar findings in SCA3 are currently lacking (Yap et al. 2022a). The only existing study on FC in SCA3 is a recent investigation that identified a SCA3-related connectivity pattern, involving the cerebellum, anterior striatum and various cortical regions (van der Horn et al. 2022).

This study investigated the difference in FPN between healthy controls (HC) and individuals with SCA3 using resting-state functional magnetic resonance imaging (rs-fMRI). We also examined the default mode network (DMN), which supported introspective processes and was often conceptualised as functionally opposed to the FPN within the triple-network model (Menon 2011). The DMN includes the medial PFC, precuneus and angular gyrus (Sormaz et al. 2018), and is frequently implicated in cognitive decline (i.e., executive function and memory) in rs-fMRI studies. Changes in the brain state, such as those caused by aging, lesions and neurodegenerative disease, can alter FC within the DMN (Ramírez-Barrantes et al. 2019).

To date, no rs-fMRI studies have explored

the FPN and DMN in individuals with SCA3. Although these networks are well established in the fMRI literature, they represent novel targets in the context of SCA3. Given the central role of cerebellum in SCA3, we selected a seed region in the cerebellum, specifically Crus I, known to be functionally connected to both FPN and DMN (Buckner et al. 2011). We hypothesised that individuals with SCA3 would show reduced FC between the cerebellum and cerebral networks (i.e., FPN and DMN) compared to HC.

MATERIALS AND METHODS

Participants

This study was a part of our previously published clinical trial (Yap et al. 2024), with additional HC recruited for the fMRI scan. It was conducted at Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia, from March 2020 to May 2022. Ethical approval was obtained from the Faculty of Medicine, Universiti Kebangsaan Malaysia Research Ethics Committee (JEP-2019-826). Written informed consent was obtained from patients or their next of kin (due to ataxia-related capacity limitations in decision-making capacity) and the study adhered to the Declaration of Helsinki.

Patients aged 26-67 years who were genetically and clinically confirmed to have SCA3 and were able to read, speak and understand either English or Malay were recruited. Additionally, healthy volunteers were recruited for the HC group. Exclusion criteria included any concomitant neurological condition that might interfere with the study, as well as MRI contra-indications (Dill 2008). Demographic information such as age, gender, ethnicity, and education level was recorded for all participants. For individuals with SCA3, age at onset and disease duration were also documented (Table 1).

TABLE 1: Baseline sociodemographic and clinical variables between SCA3 vs HC

Sociodemographic & clinical variables	HC (n = 14)	SCA3 (n = 14)	Statistical value	p-value
Age, year [Mean (SD), range]	34.29 (SD 9.83), 28 – 63	39.07 (SD 10.75), 26 – 67	t = 1.228	0.231
Gender, n (%)				
Male	11 (43.7 %)	7 (21.9 %)	χ^2 = 2.489	0.115
Female	3 (12.5 %)	7 (21.9 %)		
Education level, n (%)				
Secondary	2 (9.4 %)	1 (3.1 %)	χ^2 = 0.373	0.541
Tertiary	12 (46.9 %)	13 (40.6 %)		
Ethnicity, n (%)				0.171
Malay	13 (53.2 %)	9 (28.1 %)	χ^2 = 3.526	
Chinese	1 (3.1 %)	4 (12.5 %)		
Indian	0	1 (3.1 %)		
Onset age, year [Mean (SD)]	-	33.00 (SD 9.67)	-	-
Disease duration, year [Mean (SD)]	-	6.07 (SD 2.56)	-	-
SARA [Mean (SD)]	-	16.54 (SD 6.47)	-	-

*t-test for age, onset age and gender; Chi-square (χ^2) for gender, education level and ethnicity.
HC: Healthy comparisons; SCA3: Spinocerebellar ataxia type 3; SARA: Scale for the assessment and rating of ataxia

Data Acquisition

The imaging process began with image acquisition using a MAGNETOM Verio 3.0 Tesla (T) MRI scanner (Siemens Healthineers AG, Erlangen, Germany). In accordance with the protocol, a series of high-resolution T1-weighted images was obtained using a volumetric 3D spoiled gradient recall sequence. These images were acquired with the following parameters: TR/TE = 2200 ms/3.2 ms, FOV = 256 x 256 mm^2, matrix size = 256 x 256, and slice thickness = 1 mm (Abdul Wahab et al. 2022). This step was essential for registering the functional images to the Montreal Neurological Institute (MNI) template brain.

Subsequently, a 10-minute rs-fMRI scan was conducted, during which participants were instructed to lie flat with their eyes closed throughout the session. Gradient-echo echo-planar imaging (GRE-EPI) was employed as the pulse sequence for the scan. Functional T2* weighted images were acquired using the following parameters: repetition time (TR)/time-to-echo (TE) = 3000 ms/29 ms, flip angle = 75°, field-of-view (FOV) = 240 mm x 240 mm, data matrix = 64 x 64, slice thickness = 3.5 mm, slice gap = 1.05 mm, voxel size = 3.75 x 3.75 x 3.75 mm and number of scans/time point = 200. To mitigate magnetic saturation effects, the first ten scans were treated as dummy and discarded according to the blood oxygenation level dependent (BOLD) imaging protocol (Abdul Wahab et al. 2022).

Data Pre-processing

The rs-fMRI data were analysed using MATLAB (R2022a) (Mathworks Inc., Natick, MA, USA) and statistical parametric mapping (SPM) version 12 (Wellcome Centre for Human Neuroimaging. University College London, London, United Kingdom) (Ashburner 2012). Before pre-processing, a random check of the functional images was performed for each measurement to identify and exclude any noise or artifact caused by magnetic field distortion.

Pre-processing began with slice timing correction, followed by motion correction using a six-parameter affine transformation during the realignment process. Data with excessive motion (i.e., displacement exceeding 2 mm) was discarded. Subsequently, the mean image from each scan series was co-registered to a template with standard anatomical space (the EPI template provided by the MNI), followed by normalisation using a 12-parameter affine transformation. Finally, the images were smoothed using an 8-mm full-width at half-maximum (FW-HM) Gaussian kernel (Abdul Wahab et al. 2022).

Functional Connectivity

Following pre-processing of the fMRI data, region-of-interest (ROI) time courses were extracted using the Data Processing & Analysis of Brain Imaging (DPABI) toolbox (Institute of Psychology, Chinese Academy of Sciences, Beijing, China) (Yan et al. 2016), with ROI selected from the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer N./Neurofunctional Imaging Group (GIN-CNRS), Caen, France) (Tzourio-Mazoyer et al. 2002). Specifically, Crus I of the cerebellum was chosen as the seed region due to its early degeneration in SCA3 (Rezende et al. 2018), and its known connectivity with the FPN and DMN (Buckner et al. 2011; Reineberg et al. 2015).

Group differences in FC between Crus I and specific cerebral networks (i.e., FPN and DMN), as well as the remaining 115 AAL regions, were examined. The regions comprising the FPN and DMN were outlined in Figure 1. FC between Crus I and contralateral FPN/DMN regions were analysed, given the cerebellum's contralateral connections to cerebral regions (Pieterman et al. 2017).

Statistical Analysis

In this study, variance analysis was employed to assess the FC of the rs-fMRI data, with larger variances indicating lower FC (Sadiq et al. 2022). First, Pearson's correlation coefficients (*r*) were calculated between the BOLD signals of Crus

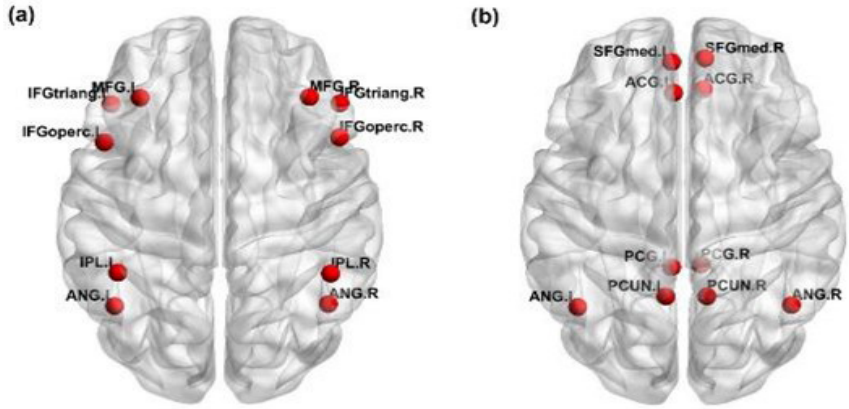

FIGURE 1: Brain areas of the (a) frontoparietal network and (b) default-mode network based on Automated Anatomical Labelling. MFG: Middle frontal gyrus; IFGoperc: Inferior frontal gyrus opercularis; IFGtriang: Inferior Frontal gyrus triangularis; IPL: Inferior parietal lobe; ANG: Angular gyrus; SFGmed: Superior medial frontal gyrus; ACG: Anterior cingulate gyrus; PCG: Posterior cingulate gyrus; PCUN: Precuneus. For variance analysis of functional connectivity, '.L' and '.R' represented the left and right hemisphere, respectively

I and the other 115 ROIs for each individual participant. Subsequently, the variance of *r* was computed for each correlation pair (e.g., Crus I vs. each ROI), separately for the HC and individuals with SCA3 groups.

For specific networks (i.e., FPN/DMN), the mean variance of FC between Crus I and selected ROIs (n*r* = 5) were calculated. For whole-brain analysis (Crus I and the other 115 ROIs, n*r* = 115), the mean of the 115 variance values were calculated for each group. Independent t-tests were then conducted to compare mean variances between groups at an alpha level of 0.05. To address multiple comparisons, a Bonferroni correction was applied in the secondary analysis, adjusting the alpha level to 0.004 due to 12 t-tests performed (Napierala 2012).

Effect sizes were computed using Bonett's δ, which accounted for potential non-normality and skewness in small samples (Bonett 2008). Bonett's δ values of 0.20, 0.50 and 0.80 indicated small, moderate and large effect sizes, respectively (Cohen 2013). Post-hoc power analyses were performed for all significant findings. An overview of the entire data processing workflow was shown in Figure 2.

RESULTS

A total of 14 HC and 14 individuals with SCA3 underwent fMRI scans. All participants were right-handed. There were no significant differences in the sociodemographic variables between the HC and individuals with SCA3 ($p > 0.05$) (Table 1).

Table 2 presented the variances in FC between Crus I and: (i) the FPN; (ii) the DMN; and (iii) the remaining 115 ROIs, for both HC and individuals with SCA3. The variances of FC between Crus I-FPN were significantly larger in the SCA3 group compared to HC, with both hemispheres demonstrating large effect sizes ($p < 0.004$).

Within-group comparisons in SCA3 group revealed that the variance of FC between Crus I(R)-FPN(L) was significantly larger than its contralateral counterpart, with a large effect size [$t(4) = 7.688$, $p = 0.002$, $\delta = 4.37$, Power = 100%]. In contrast, no significant hemispheric difference was observed in the HC group [$t(4) = 1.715$, $p = 0.162$] (Figure 3a).

Similarly, the variances of FC between Crus I-DMN were significantly larger in the SCA3 group than in HC, with both hemispheres again showing large effect sizes ($p < 0.05$). However, these differences were not statistically significant

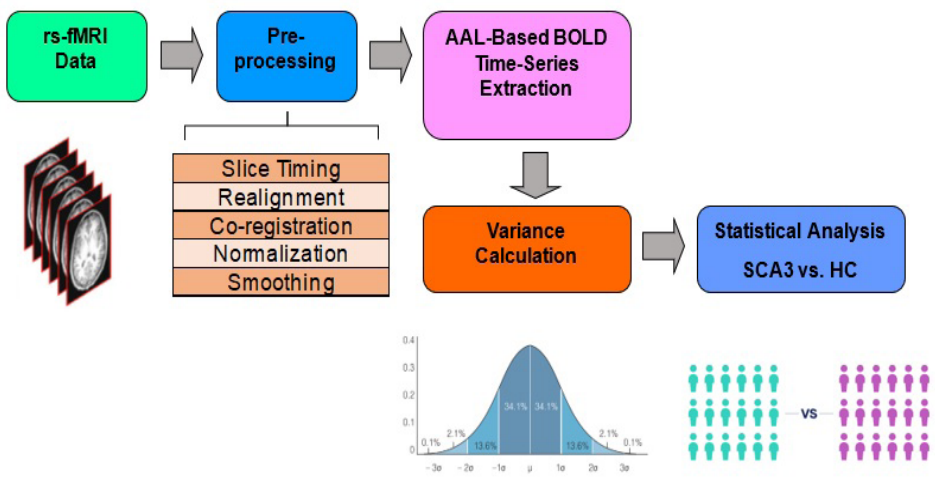

FIGURE 2: The overview of rs-fMRI data acquisition, processing and statistical analysis

after Bonferroni correction ($p > 0.004$) (Table 2). Within-group analysis showed a significantly larger variance in Crus I(R)-DMN(L) compared to its contralateral counterpart in the SCA3 group, with a large effect size [$t(4) = 8.599$, $p = 0.001$, $\delta = 1.87$, Power = 100%]. No significant hemispheric difference was observed in HC [$t(4) = 0.571$, $p = 0.599$] (Figure 3b).

For non-specific connectivity, variances were significantly larger in SCA3 group compared to HC, regardless of hemisphere, with large effect sizes ($p < 0.004$). Within the SCA3 group, FC variance between Crus I(R)-non-specific was significantly larger than its contralateral counterpart, also demonstrating a large effect size [$t(114) = 11.655$, $p < 0.001$, $\delta = 1.19$, Power = 99.8%]. A similar finding was observed in the HC group with a small effect size [$t(114) = 5.517$, $p <$

TABLE 2: Mean and SD of variances in the FC between SCA3 vs HC

Variances [Mean (SD)]	HC	SCA3	t-test value	p-value	Bonett's δ	Post-hoc power analysis
FPN						
Crus I (L)	0.0341 (0.0053)	0.1086 (0.0227)	3.596	0.001	4.52	100%
Crus I (R)	0.0739 (0.0102)	0.1916 (0.0144)	19.438	< 0.001	9.43	100%
DMN						
Crus I (L)	0.0383 (0.0134)	0.1032 (0.0359)	5.387	0.006	2.40	100%
Crus I (R)	0.0455 (0.0219)	0.1778 (0.0435)	5.791	0.004	3.84	100%
Non-specific						
Crus I (L)	0.0414 (0.0239)	0.0889 (0.0437)	12.571	< 0.001	1.35	100%
Crus I (R)	0.0514 (0.0261)	0.1623 (0.0755)	15.938	< 0.001	1.96	100%

L: Left; R: Right; CI: Confidence interval; DMN: Default mode network; FC: Functional connectivity; FPN: Frontoparietal network; HC: Healthy comparisons; SCA3: Spinocerebellar ataxia type 3; SD: Standard deviation

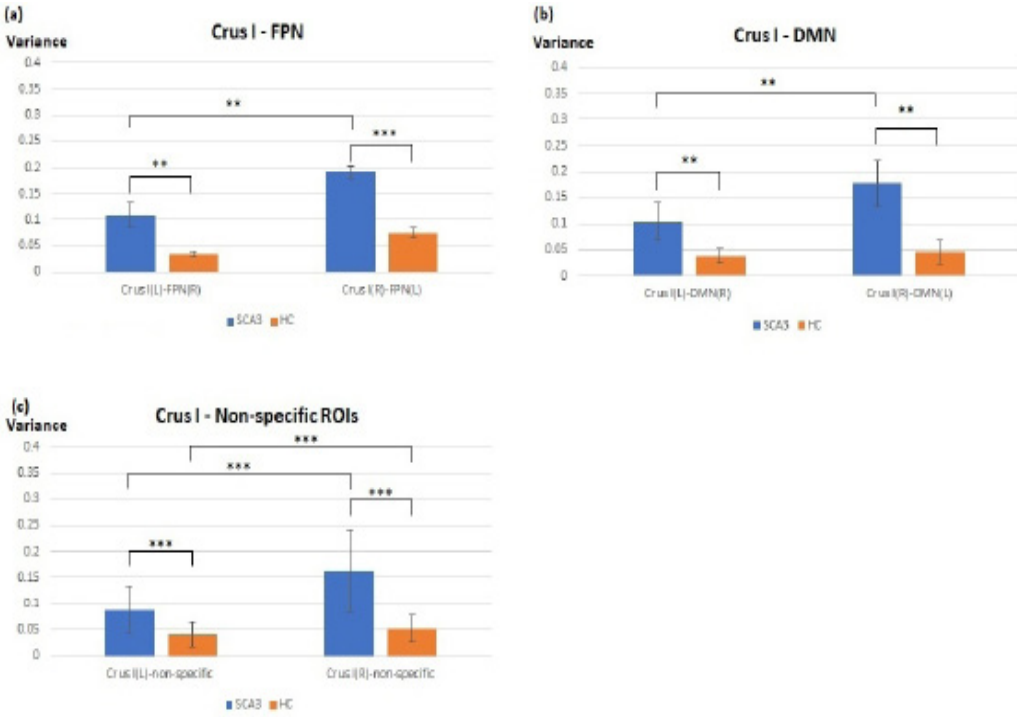

FIGURE 3: (a) Bar chart of mean variances of FC between Crus I–FPN (SCA3 vs. HC); (b) Bar chart of mean variances of FC between Crus I–DMN (SCA3 vs. HC); (c) Bar chart of mean variances of FC between Crus I–non-specific ROIs (SCA3 vs. HC). Error bars represented standard deviations. x-axis represented brain networks. Asterisks represented significant differences. (DMN: Default mode network; FC: Functional connectivity; FPN: Frontoparietal network; HC: Healthy comparisons; SCA3: Spinocerebellar ataxia type 3; ROI: Region-of-interest (*p<0.05, **p<0.01, ***p<0.001)

0.001, δ = 0.40, Power = 17.9%] (Figure 3c).

Overall, post-hoc power analysis revealed 100% power for all significant findings, except for the within-group comparison for HC for non-specific connectivity.

DISCUSSION

Overall, FC was lower in individuals with SCA3 compared to HC, particularly between Crus I–FPN. This difference was most pronounced between the right Crus I and the left FPN. Conversely, no hemispheric difference was observed in the HC group. These findings are discussed in terms of network specificity and hemispheric lateralisation.

Network Specificity

The effect of network specificity highlights the functional relevance of Crus I within distinct networks (FPN: δ = 4.52–9.43 vs. DMN: n.s. vs. non-specific: δ = 1.35–1.96). Crus I, located in the posterior cerebellum, plays a crucial role in executive function processing (Buckner et al. 2011). Its FC with the FPN is crucial for optimal executive performance. The cerebellum regulates behaviours around a homeostatic baseline through unconscious processes (Schmahmann et al. 2019), and diminished FC between Crus I–FPN may contribute to executive dysfunction in SCA3 through two inter-related mechanisms.

First, executive function impairment arises from frontal lobe atrophy (Yap et al. 2022a).

Second, cerebellar atrophy further compromises the regulation of executive function (Klinke et al. 2010). The combined effects of cerebellar and frontal lobe atrophy likely contribute to the observed reduction in Crus I-FPN connectivity in individuals with SCA3 (Yap et al. 2022a). However, it is important to note that FC alone cannot fully explain these observations, given the potential role of functional reorganisation. This study did not examine the corresponding structural changes (i.e., volumetric analysis or voxel-based morphometry), which are needed to establish a definitive relationship.

The absence of significant group differences in Crus I-DMN connectivity suggests reduced specificity for cognitive processing in this network compared to Crus I-FPN. Notably, the significance of intrinsic activity in the resting brain remains unclear and has been subjected to debate (Morcom & Fletcher 2007). The definition of the resting brain or the DMN is not universally accepted and has faced criticism (Fair et al. 2008). Some studies argue that the ROIs within the DMN may not be functionally connected but instead share vascular coupling of large arteries and veins, making them sensitive to oxygenation changes rather than neural activity (Buckner et al. 2008). Therefore, a significant finding at the alpha level of 0.05 may reflect vascular coupling rather than true FC.

Compared to the FPN, the lower effect sizes observed in non-specific FC between Crus I and 115 other ROIs are consistent with expectations. Specifically, the inclusion of functionally unrelated ROIs (i.e., those within the DMN) may dilute the meaningful loss of FC between Crus I and more relevant networks, such as the FPN. Non-specific FC thus serves as an effective baseline comparison for evaluating network-specific alterations. Nevertheless, the significant group differences in non-specific FC suggest that neurodegeneration in SCA3 simultaneously affects multiple brain regions, including those implicated in the CCAS and motor coordination (Bodranghien et al. 2016).

Hemispheric Lateralisation

The effect of hemispheric lateralisation highlights the functional relevance of the left cerebral hemisphere in the neurodegeneration process of SCA3. The right Crus I connects contralaterally to the left cerebral hemisphere, and vice versa (Pieterman et al. 2017), suggesting that the FC involving the left cerebral hemisphere is disproportionately affected in SCA3. Similarly, neurodegenerative disorders such as Alzheimer's disease exhibit asymmetrical vulnerability, implicating the left hemisphere (Lubben et al. 2021). This finding suggests that, like other neurodegenerative diseases, SCA3 may also exhibit hemispheric asymmetry, though it remains understudied.

Supporting this observation, the absence of hemispheric differences in FPN and DMN connectivity among HC implies that this hemispheric lateralisation is specific to neurodegeneration. In contrast, significant hemispheric differences in non-specific FC within HC may be partially explained by gender distribution (male = 11, female = 3), although with low power. Power research suggests that males tend to have higher FC in right-hemisphere networks and lower FC in left hemispheric networks (Tian et al. 2011).

Several factors may contribute to this asymmetrical vulnerability in SCA3. First, the limb dominance theory from amyotrophic lateral sclerosis research proposes that overutilisation of the dominant limb may increase oxidative stress in the corresponding contralateral hemisphere (Devine et al. 2014; Lubben et al. 2021; Turner et al. 2011). In line with this, all individuals with SCA3 in this study were right-handed, which may explain the greater FC reduction involving the left hemisphere. To confirm this hypothesis, future studies should examine clinical measures that compare performance between HC and individuals with SCA3. For example, we anticipate a greater decline in dominant-hand function over time in individuals with SCA3, as measured by tasks that differentiate motor vs. non-motor demands [e.g., dominant vs. non-

dominant on ataxia severity (Schmitz-Hübsch et al. 2008); motor-dependent Trail Making Test vs. non-motor dependent Wisconsin Card Sorting Test on shifting (Yap et al. 2022b)]. Similarly, we expect that left hemisphere-dominated cognitive functions, as measured through verbal tasks, may show greater decline in SCA3 (i.e., verbal Digit Span vs. nonverbal Spatial Span) (Yap et al. 2022b).

Alternatively, assuming equal hemispheric vulnerability, the observed differences may be explained by the inhibitory hypothesis derived from aging and Alzheimer's disease studies (Cox et al. 2015; Yap et al. 2017). To preserve the integrity of functional networks such as the FPN, the dominant left PFC typically suppresses activity in the non-dominant right PFC for optimal performance (Oliver et al. 2019). However, atrophy in the left PFC may compromise this transcallosal inhibition, leading to increased recruitment of the right PFC as a compensatory mechanism (Cox et al. 2015; Yap et al. 2017). This cortical reorganisation may reflect a functional adaptation in response to neurodegeneration.

Implications

Overall, FC between Crus I and cerebral networks was lower in individuals with SCA3. Additionally, network specificity and hemisphere lateralisation appear to play important roles. Among the FCs studied, the connection between Crus I(R)–FPN(L) was the most impaired in SCA3, likely due to its functional relevance. This disruption aligns with the core executive function impairments commonly observed in individuals with SCA3 (Yap et al. 2022b). Changes in FC may provide an avenue for future studies exploring imaging biomarkers in SCA3, particularly when paired with longitudinal monitoring of executive function decline.

In contrast, although FC between Crus I and non-specific ROIs was also significantly lower in SCA3, this finding may lack of clear functional relevance. This is further supported by larger standard deviations (i.e., lower reliability) observed in both HC and individuals with SCA3 groups compared to the FPN. Given that cognitive decline in SCA3 typically does not resemble dementia and may involve cortical reorganisation, we propose that FC between Crus I-FPN, alongside related executive function changes, could represent a meaningful target for future disease-modifying interventions.

Strengths and Limitations

This study represents the first investigation into the FC of cerebellar-cerebral networks in SCA3. First, we compared the FC of networks between HC and individuals with SCA3 using an established network (i.e., FPN) alongside a baseline comparison (i.e., non-specific ROIs). Second, we employed the Bonferroni method to correct for multiple comparisons (Napierala 2012). Finally, the mean scale for the assessment and rating of ataxia (SARA) scores for individuals with SCA3 fell within the mild-moderate range (SARA: 3-20) (Maas et al. 2022), suggesting that confounding factors commonly associated with later stages of disease progression were unlikely to influence the observed FC changes. For example, disease severity influences functional impairment and quality of life in SCA3, which in turn increases the risk of depression over time (Cecchin et al. 2007). As depression is associated with FPN and executive dysfunctions (Tan et al. 2021), it could confound our findings. Consistently, no participant met the clinical criteria for depression at the time of data collection.

The main limitation of this study is its small sample size, particularly for an rs-fMRI study (Szucs & Ioannidis 2020). Specifically, we included 14 HC and 14 individuals with SCA3, meeting the minimum threshold for MRI studies (n = 12) (Szucs & Ioannidis 2020). The limited sample size is attributable to several factors: (i) the rarity of SCA3; (ii) claustrophobia among potential participants; and (iii) reluctance to participate during the COVID-19 pandemic. Additionally, there was gender imbalance in the HC group (Male/Female = 11/3), which may have introduced gender-related effects in FC analysis (Tian et al. 2011).

Moreover, although the Bonferroni method minimises the risk of false positives in the context of multiple comparisons, it may also increase the risk of Type II errors, leading to exclusion of some true effects (Napierala 2012). However, given that we observed significant group differences in FC between HC and individuals with SCA3, the risk of Type II error in these findings is minimal. This is further supported by post-hoc power analysis, which showed 100% power for all significant findings, indicating the observed effect sizes are likely reflective of true group differences. In contrast, the lower power observed in within-group comparisons among HC using non-specific connectivity suggests that statistical significance in that context may lack clinical significance, aligning with the theories of asymmetric vulnerabilities (Devine et al. 2014; Lubben et al. 2021; Turner et al. 2011).

Nevertheless, to substantiate these findings, future research with a larger sample size would be beneficial, offering increased statistical power and enabling subgroup analyses to explore differences in cerebellar-cerebral connectivity between mild-moderate and severe SCA3. Additionally, future studies should incorporate objective neuropsychological testing to evaluate corresponding group differences in cognitive performance.

CONCLUSION

In this study, we compared the FC between the cerebellum and cerebral networks in HC and individuals with SCA3. Significant group differences were observed in the FC between Crus I and cerebral networks. These differences were particularly pronounced in the connectivity with the Left FPN, underscoring the roles of network specificity and hemisphere lateralisation SCA3-related neurodegeneration. These findings support further validation of FC as a potential imaging biomarker. Future studies with larger sample sizes may offer greater statistical power and allow for subgroup analyses to explore FC differences across varying levels of disease severity.

Author contributions: Conceptualisation: NMI, SA, HAM, NY, SAMM; Methodology, data analysis: KHY, AS, TBT, HAM, NY, SAMM; Data collection: KHY, SA, SHMD, HNA, NMI; Manuscript-original draft: KHY, AS; Manuscript-review and editing: TBT, HAM, NY, SA, SAMM, NMI. All authors have approved the final manuscript.

Conflict of interest: The authors declare no conflicts of interest.

Funding: This study was funded by Dana Impak Perdana Grant (DIP-2019-007) received by NMI from Universiti Kebangsaan Malaysia.

Acknowledgement: The authors express their appreciation to the staffs from MRI lab, Department of Radiology, Hospital Canselor Tuanku Muhriz for their help in data acquisition, and patients from different parts of the peninsular Malaysia who participated in the study. The authors also acknowledges the support of Ministry of Higher Education under HICoE scheme to Centre of Signal and Imaging Research (CISIR), Universiti Teknologi PETRONAS.

Ethical statement: Ethical approval was obtained from the Faculty of Medicine, Universiti Kebangsaan Malaysia Research Ethics Committee (JEP-2019-826).

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