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The cerebral metabolic topography of spinocerebellar ataxia type 3

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ABSTRACT

Introduction: We aimed to uncover the pattern of network-level changes in neuronal function in Spinocerebellar ataxia type 3 (SCA3).

Methods: 17 genetically-confirmed SCA3 patients and 16 controls underwent structural MRI and static resting-state [^{18}F]-Fluoro-deoxyglucose Positron Emission Tomography (FDG-PET) imaging. A SCA3-related pattern (SCA3-RP) was identified using a multivariate method (scaled subprofile model and principal component analysis (SSM PCA)). Participants were evaluated with the Scale for Assessment and Rating of Ataxia (SARA) and with neuropsychological examination including tests for language, executive dysfunction, memory, and information processing speed. The relationships between SCA3-RP expression and clinical scores were explored. Voxel based morphology (VBM) was applied on MRI-T1 images to assess possible correlations between FDG reduction and grey matter atrophy.

Results: The SCA3-RP disclosed relative hypometabolism of the cerebellum, caudate nucleus and posterior parietal cortex, and relatively increased metabolism in somatosensory areas and the limbic system. This topography, which was not explained by regional atrophy, correlated significantly with ataxia (SARA) scores ($\rho = 0.72$; $P = 0.001$). SCA3 patients showed significant deficits in executive function and information processing speed, but only letter fluency correlated with SCA3-RP expression ($\rho = 0.51$; $P = 0.04$, uncorrected for multiple comparisons).

Conclusion: The SCA3 metabolic profile reflects network-level alterations which are primarily associated with the motor features of the disease. Striatum decreases additional to cerebellar hypometabolism underscores an intrinsic extrapyramidal involvement in SCA3. Cerebellar-posterior parietal hypometabolism together with anterior parietal (sensory) cortex hypermetabolism may reflect a shift from impaired feedforward to compensatory feedback processing in higher-order motor control. The demonstrated SCA3-RP provides basic insight in cerebral network changes in this disease.

1. Introduction

Spinocerebellar ataxia type 3 (SCA3, previously coined Machado-Joseph disease) is a neurodegenerative disease caused by trinucleotide (CAG) repeat expansion in exon 10 of the ATXN3 gene on chromosome 14 (p32). The cerebellum is most severely affected, with ataxia as key feature, but patients may also develop pyramidal and extra-pyramidal signs, neuropathy and oculomotor dysfunction (Riess et al., 2008), as well as cognitive problems (Braga-Neto et al., 2014).

Pathology in variable brain structures (including the cerebellum, brainstem, thalamus, basal ganglia, and cerebral cortex) (Seidel et al., 2012; Rub et al., 2008; Rub et al., 2013) may explain the variety of symptoms, although dysfunction may also arise from functional disconnection from the cerebellum. Imaging cerebral metabolism with [^{18}F]-Fluoro-deoxyglucose Positron Emission Tomography (FDG-PET) enables assessment of distributed cerebral dysfunction (Reivich et al., 1979). The obtained FDG-PET (as well as perfusion SPECT) data are commonly analyzed with univariate models which have consistently demonstrated cerebellar hypo-activity, but showed variable results regarding the involvement of extra-cerebellar structures such as the

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brainstem (Soong et al., 1997; Soong and Liu, 1998; Wullner et al., 2005; Wang et al., 2007), thalamus (Wullner et al., 2005), lentiform nucleus (Wang et al., 2007), limbic lobe (Wang et al., 2007; Braga-Neto et al., 2012a), and occipital cortex (Soong et al., 1997; Soong and Liu, 1998; Braga-Neto et al., 2012a).

While univariate approaches treat every region (voxel) individually, multivariate analysis enables assessment of network-level alterations. With the scaled subprofile model with principal component analysis (SSM PCA) (Spetsieris and Eidelberg, 2011) disease-specific patterns have been identified in several neurodegenerative disorders (Meles et al., 2017; Niethammer and Eidelberg, 2012).

Here, we studied FDG-PET data of SCA3 patients with SSM PCA to gain insight into the pattern of changed neuronal activity in this disease. To understand the relation with symptoms, correlations between expression of the SCA3 metabolic pattern and clinical parameters were analyzed. Moreover, to assess whether the metabolic pattern reflects network-level activity changes beyond regional atrophy due to neuronal cell-loss, we additionally performed a voxel-based morphometry (VBM) analysis on structural MRI data to compare FDG uptake with grey matter loss.

2. Methods

2.1. Participants

We included 17 genetically-confirmed SCA3 patients. Inclusion criteria were age 18–65 years and absence of other neurological disorders. In addition, we studied 16 age, gender and education-matched healthy controls. Healthy controls did not have a history of neurological disease, nor a family history of cerebellar disorders. Severity of ataxia was assessed in both groups by an experienced neurologist (HPHK, JJdV) with the Scale for Assessment and Rating of Ataxia (SARA) (Schmitz-Hubsch et al., 2006).

Neuropsychological tests selected for this study were based on previously published results in SCA3 patients (Braga-Neto et al., 2014). These tests evaluated language (Semantic Fluency), memory (Dutch version of the Rey Auditory Verbal Learning Test; RAVLT), and executive (Letter Fluency) domains. Information processing speed was measured with the Symbol Digits Modalities test (SDMT). Affective symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS).

The study was approved by the Ethics Committee of the University Medical Center Groningen (NL45036.042.13). Voluntary written informed consent was obtained from each subject after verbal and written explanation of the study, in accordance with the Declaration of Helsinki.

2.2. Image acquisition

Static FDG-PET scanning was performed on a Siemens Biograph mCT-64 PET/CT camera (Siemens, Munich, Germany) in a three-dimensional mode, 30 min after intravenous injection of 200 MBq of ^{18}F-FDG, with a frame-duration of 5 min. A low-dose computed tomography transmission scan was performed for attenuation correction. Images were reconstructed with OSEM3D, including point-spread function and time-of-flight modeling (3 iterations/21 subsets, matrix 400) and smoothed with a Gaussian 2 mm full-width at half-maximum filter. Central nervous system depressants were discontinued in all subjects for at least 24 h before FDG-PET scanning. This included clonazepam, which was used by three patients. One patient used levodopa at the time of the study, which was not discontinued. FDG uptake and image acquisition were performed in a resting state with the subject's eyes closed in a dimly lit room with minimal auditory stimulation.

MRI-T1 images were acquired for registration purposes. Subjects were scanned at a Philips Achieva 3.0T MRI scanner (Philips, Best, The Netherlands) with a 32-channel head coil. A 3D T1 TFE image was acquired for each subject using the following parameters: 160 sagittal slices without gap, FOV (ap × rl × fh) 256 × 160 × 256 mm, acquired matrix 256 × 256, voxel size 1 × 1 × 1 mm, repetition time 7.8 ms, echo time 3.6 ms and flip angle 8 degrees for a total scan duration of 10 min and 14 s.

2.3. Image registration

Prior to the SSM PCA analysis, the PET images of all subjects needed to be in registration. First, from the T1 images the brains were extracted from the rest of the head using FreeSurfer (Segonne et al., 2004; FreeSurfer, 2012) (version 5.3, with default parameters, running on Ubuntu 12.04.5 LTS), resulting in a brain mask per subject. Tools from the FSL (Smith et al., 2004) toolbox (version 5.0.8, running under Ubuntu 10.04 LTS) were used for subsequent registration. Using FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002), the PET images were registered to the brain mask produced by FreeSurfer (i.e. intra-subject registration), and the transformation parameters were stored. Here, default parameters were used except for the cost and search-cost options (set to normalized mutual information) and the degrees of freedom (6, i.e. allowing for rotations and translations). The MRI data were registered to the MNI 2 mm template provided with FSL by first using FLIRT to register the subject's brain mask linearly with the MNI 2 mm brain image (using default parameters). The resulting transformation parameters were used as a starting estimate for the nonlinear registration of the subject's T1 image with the MNI 2 mm head volume using FNIRT (Andersson et al., 2007) (using default parameters, as stored in the T1_2_MNI152_2mm.cnf file supplied with FSL). The linear transformation parameters resulting from registering the PET image to the brain mask and the nonlinear transformation parameters resulting from registering the T1 image to the MNI volume were combined (to minimize the number of interpolation steps) and applied to the PET images. Finally, these images were smoothed with an 8 mm full-width at half-maximum filter Gaussian kernel and stored for subsequent analyses.

2.4. Identification of the SCA3-RP

We applied an automated algorithm written in-house, based on the SSM PCA method of Spetsieris et al. (2015), implemented in Matlab (version 2012b; MathWorks, Natick, MA). First, a 35% threshold of the whole-brain intensity maximum was applied to each individual FDG-PET image to remove out-of-brain voxels; these were multiplicatively combined to create one common mask that included only non-zero values for all subjects. This mask was applied to all images. Masked images were log-transformed and subject mean and group mean were removed, resulting in a Subject Residual Profile per subject. Principal component analysis (PCA) was applied in voxel space, and the principal components explaining the top 50% of the total variance were selected for further analysis.

For each subject, a score was calculated for each principal component, by projecting the Subject Residual Profile on each principal component. Components that gave maximum discrimination between controls and SCA 3 patients (based on these scores) were identified with a stepwise logistic regression procedure, using the lowest Akaike information criterion of the model as a selection criterion. If more than one component was identified, then these components were linearly combined to form one pattern. Each component in this pattern was weighted by the coefficient obtained from the logistic regression model. The final pattern was termed the SCA3 related pattern (SCA3-RP).

2.5. Validation of the SCA3-RP

A previously identified pattern can be used to quantify the FDG-PET scans of new subjects. In this procedure, an individual's scan is projected onto the pattern, resulting in a single score (Spetsieris et al.,