Glutamate is elevated in presupplementary motor area in Parkinson's disease

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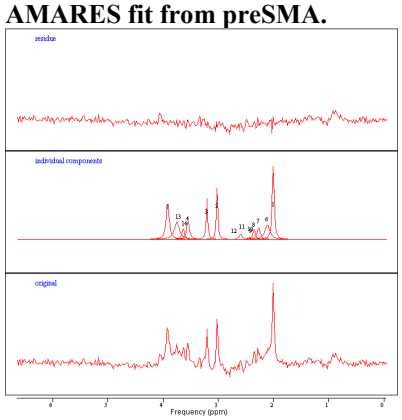
Introduction

Parkinsons' disease (PD) is a relentlessly progressive neurodegenerative disorder. Evidence suggests that PD-associated neuronal dysfunction occurs years before symptoms appear and clinical diagnosis is possible. Enlarged substantia nigra ultrasound hyperechogenicity (SN^+), present in 90% of PD patients, is showing promise as a method of identifying neurologically asymptomatic persons at risk of PD [1]. It is also apparent that compensatory changes in brain motor circuitry, including increased activation or novel area recruitment may help to mask symptom development. Here, we studied the pre-supplementary motor area (preSMA) of subjects with mild to moderate PD, neurologically normal SN^+ controls and neurologically normal (SN^-) controls using magnetic resonance spectroscopy to detect possible biomarkers of early disease or neural compensation.

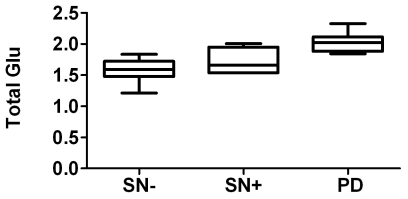
Fig. 1. Typical spectrum and AMARES fit from preSMA.



Methods

Subjects (8 SN^-, 55-62 y; 4 SN^+ 51-61 y; 8 PD 56-63 y) were scanned at 3T (Philips Achieva TX) using an 8 channel head coil. A 2cm^3 VOI was positioned in the left preSMA and a 1H MR spectrum acquired using the PRESS sequence (TR = 2s, TE = 32 ms, 32 scans) along with a water reference. Spectra were processed in the time domain using the AMARES and QUEST algorithms of jMRUI (vs 3 and 4 (build 162), respectively) and compared to the water resonance. Subjects also underwent ultrasound to determine SN hyperechogenicity and motor and neurological assessment. Statistical significance was tested using Kruskal Wallis non-parametric ANOVA followed by a Mann-Whitney U test where significance was indicated. Correlations were tested using the Spearman rank test in Graphpad Prism (v 5).

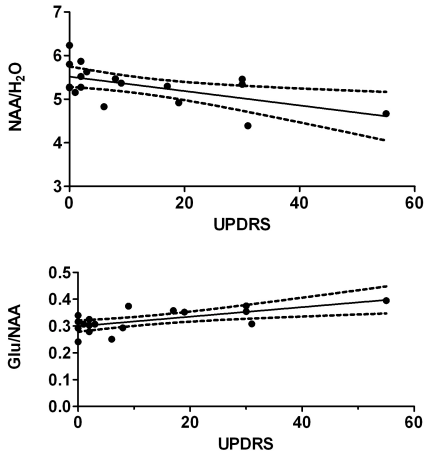
Fig. 2. Total Glu/H_2O pre-SMA. Box and whisker (10-90%)



Results

Levels of glutamate were significantly elevated in PD (Fig. 2) compared to SN- controls (P = 0.0007) but not compared to SN+ (P = 0.054) . There were no significant differences in NAA, choline and creatine peaks, nor *myo*inositol although some involvement of NAA in motor ability was indicated by the correlation of NAA with the Parkinson's motor severity scale UPDRS (P = 0.011). Accordingly, a more robust correlation (Fig. 3) was found between Glu/NAA and UPDRS (P = 0.0081; ρ_s = 0.60) and between Glu/Cre and UPDRS (P = 0.038; ρ_s = 0.48). Additionally, Cre and NAA correlated (P = 0.032, ρ_s = 0.48) but neither showed any correlation with Cho.

Fig. 3. Relationship of UPDRS to Glu/NAA and NAA. Dotted lines = 90% CIs.



Discussion

We detected a significant *increase* in glutamate levels in the PreSMA, which, along with Cre and NAA levels, was related to decreased motor function. Previously lower NA/Cre has been reported in preSMA in an older PD cohort (70 y) at 1.5T with a trend to correlation with the UPDRS [2]. We suggest that increased preSMA activity may predate decreased NAA but whether this is a compensatory mechanism awaits further investigation.

References

1. Berg, D, Seppi, K, Behnke, S et al., *Enlarged Substantia Nigra Hyperechogenicity and Risk for Parkinson Disease A 37-Month 3-Center Study of 1847 Older Persons.* Archives of Neurology, 2011. **68**: 932-937.
2. Camicioli, R, Hanstock, C, Bouchard, T et al., *Pre-supplementary motor are changes are found in Parkinson's disease using magnetic resonance spectroscopy.* Neurology, 2006. **66**: A112-A113.