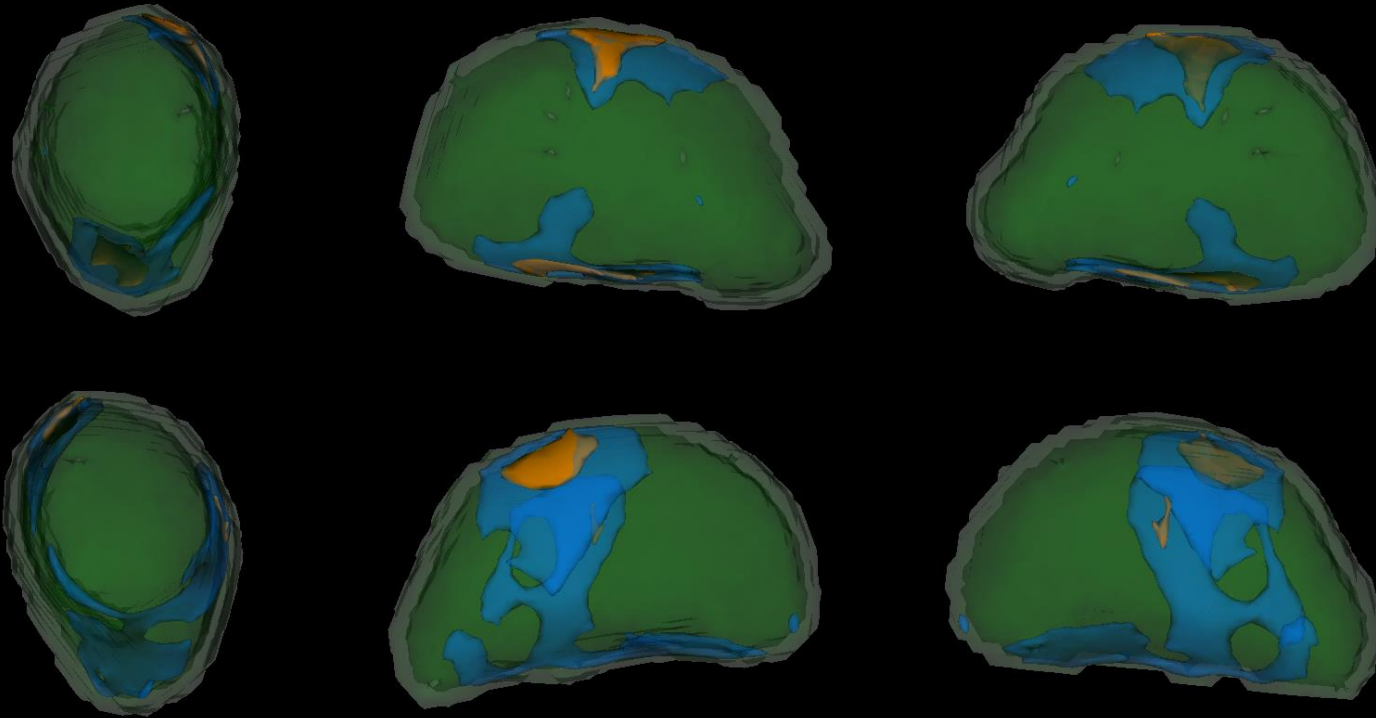


What does gluten do to your brain?

Dr Iain Croall



The
University
Of
Sheffield.



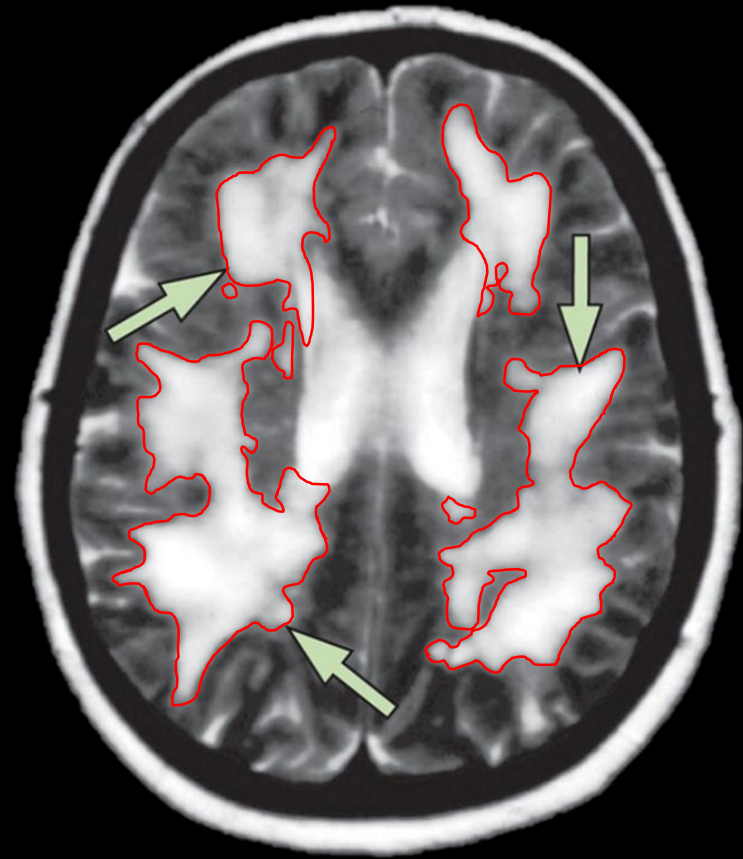
Gluten Ataxia



Gluten Ataxia



Gluten Encephalopathy

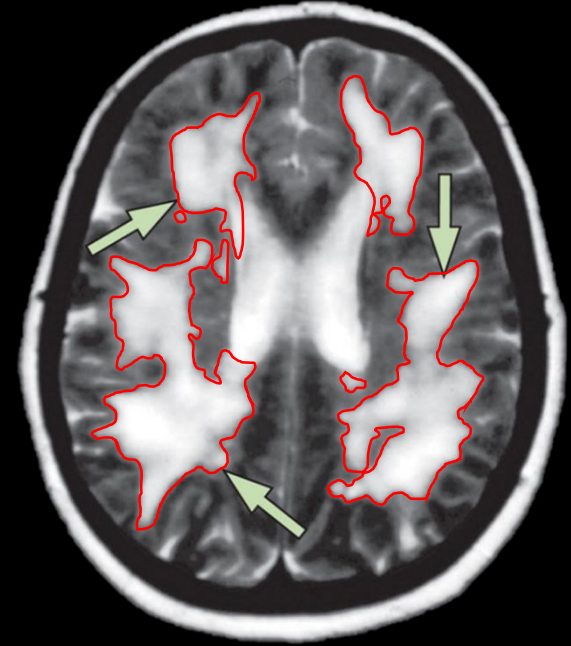




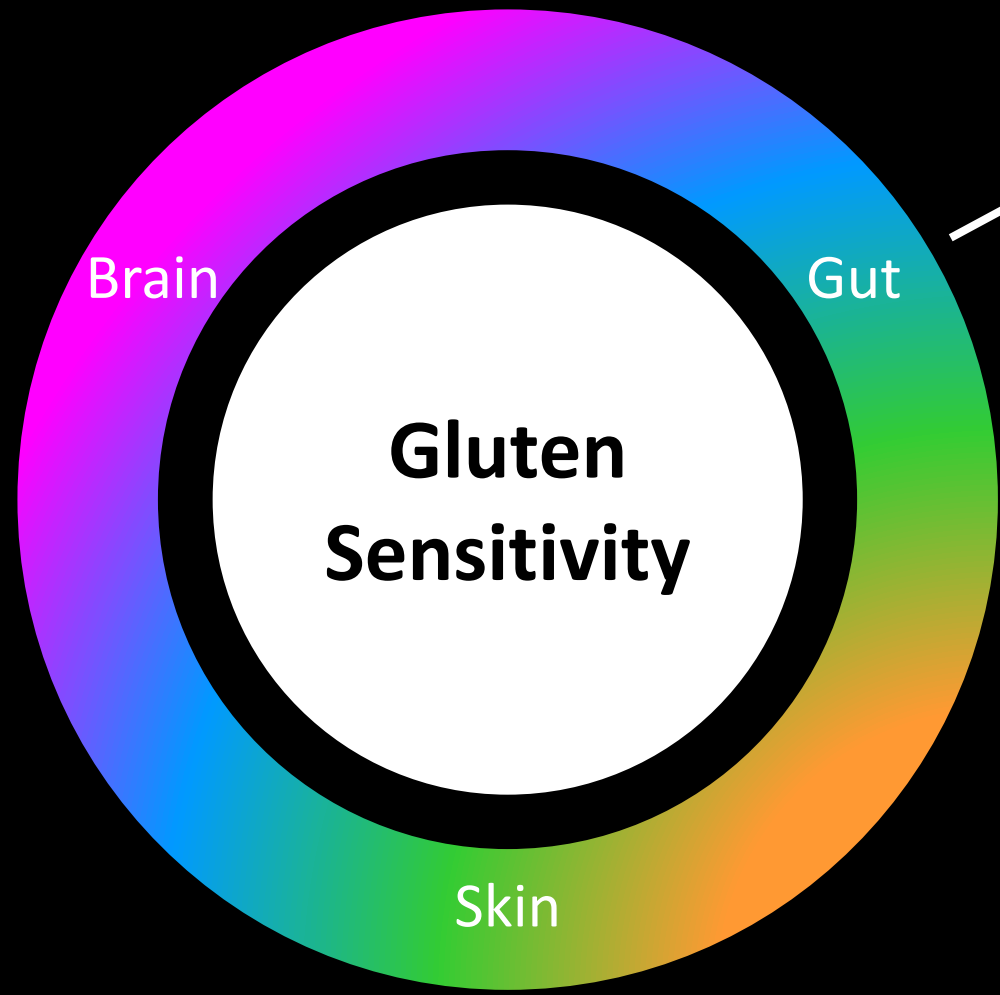
Cerebellar Involvement

- Movement
- Co-ordination
- Sensation
- TG6?

Cerebral white matter involvement



- Migraines
- Cognition
- “Foggy brain”



Clear enteropathy
= Coeliac Disease



**How pervasive are neurological problems
across the spectrum of gluten sensitivity?**

Coeliac disease – current literature

- In coeliac disease patients with neurological referrals; balance disturbances, headaches and sensory loss are common, with increased white matter lesions and brain atrophy compared to controls^{1,2}.
- Increased risk of vascular dementia³.
- Decreased cerebral blood flow⁴.
- Altered white matter microstructure⁵.
- Cognitive impairment compared to controls⁶. The improvement in cognitive scores after a year of gluten-free diet correlates with improvement in intestinal health⁷.

1. Currie et al. (2012), *J Neurol Neurosurg Psychiatry*, 83(12): 1216-1221

2. Briani et al. (2008), *J Neuroimmunol*, 195(1-2):171-175

3. Lebowitz et al. (2016), *J Alzheimers Dis*, 49(1):179-185

4. Addolorato et al. (2004), *Am. J. Med.*, 116(5):312-317

5. Della Nave et al. (2007), *Am. J. Neuroradiol.*, 28(3):479-485

6. Casella et al. (2012), *Dig. Liver Dis.*, 44(9):729-735

7. Lichtwark et al. (2014) *Ailment. Pharmacol. Ther.*, 40(2):160-170

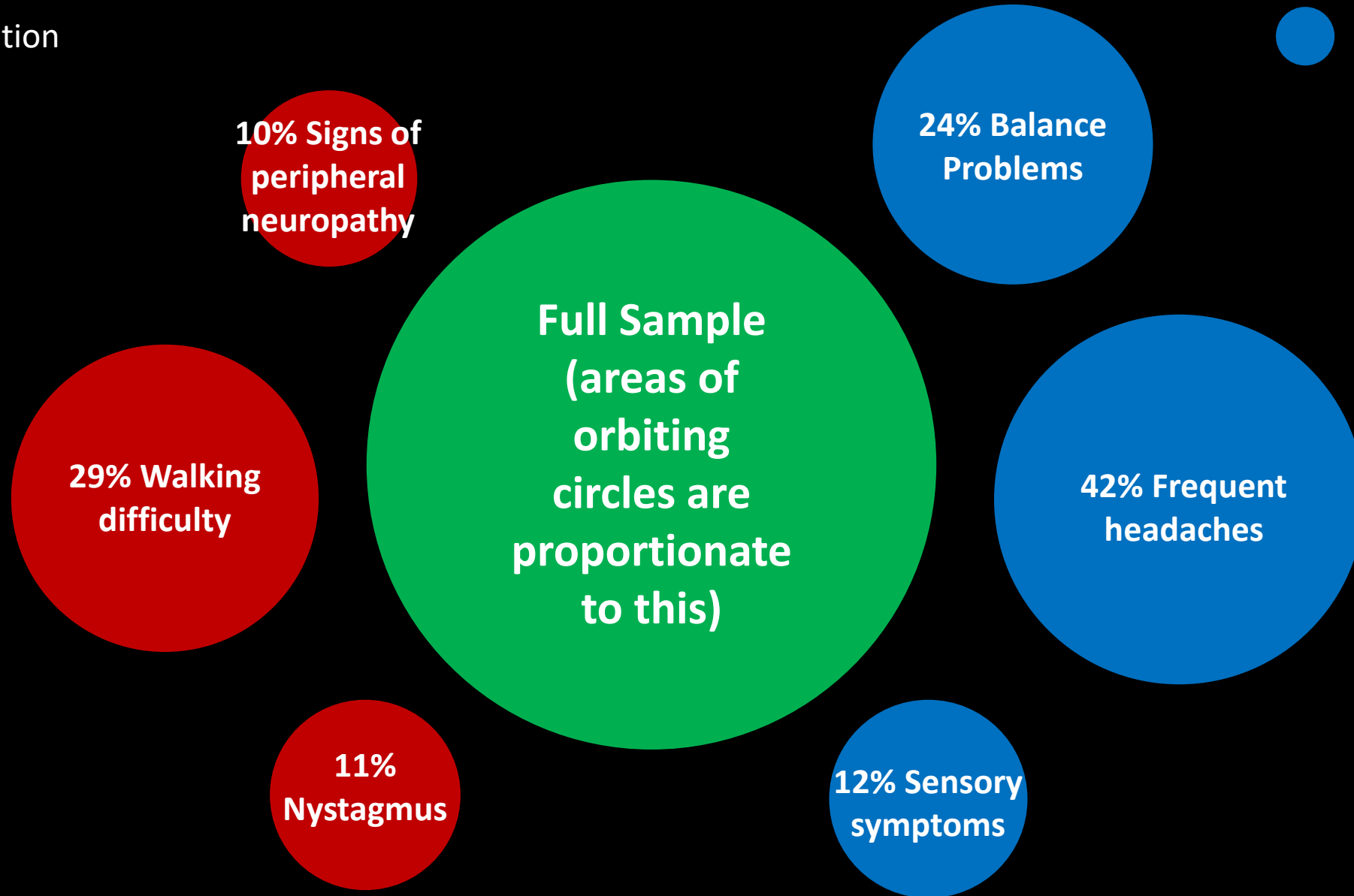
- 1. Foundations have been made in patients with neurological referrals – time to move onto “typical” presentations**
- 2. A number of key MRI methods have not yet been used in this research**

Experiment #1 - What is the neurological presentation of “typical” coeliac patients?

- 100 newly-diagnosed patients (via gastroenterology) consecutively enrolled.
- All subjects underwent:
 - Neurological examination
 - Blood sera testing for TG6
 - MRI scanning including:
 - Structural scans (T1W)
 - Spectroscopy scans to characterise cerebellar biochemistry

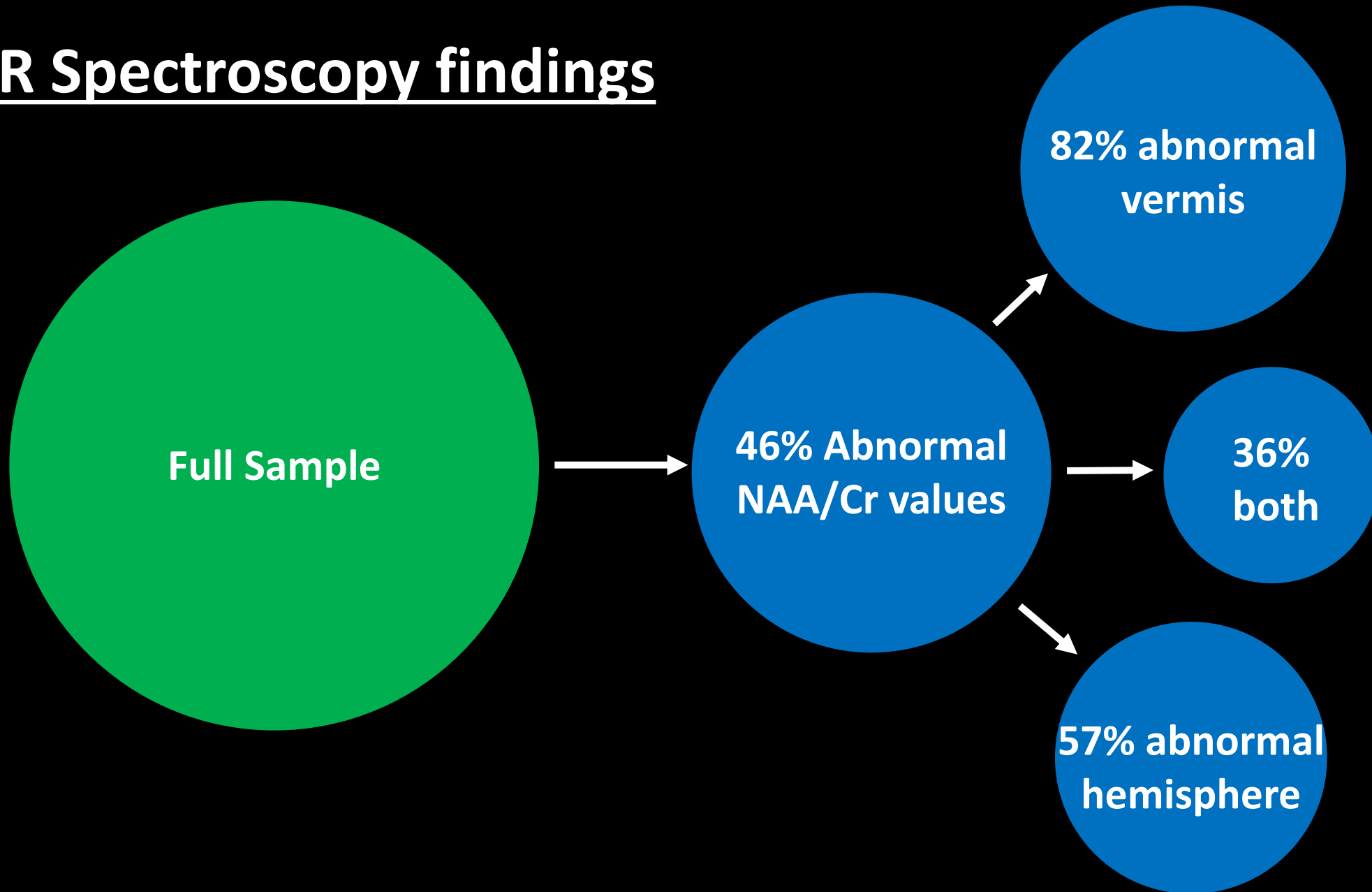
● = on examination

● = self-reported



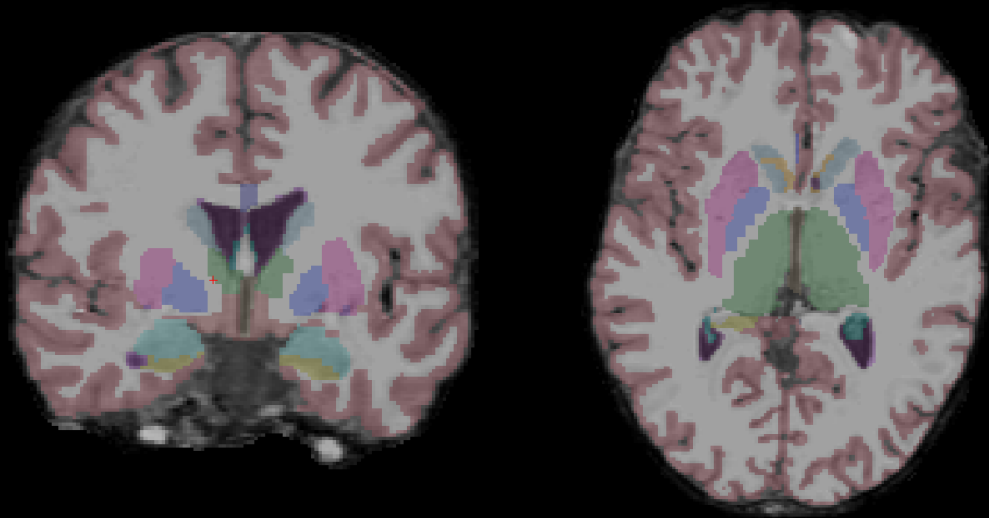
Excluding headaches, 50% had features of neurological dysfunction

MR Spectroscopy findings

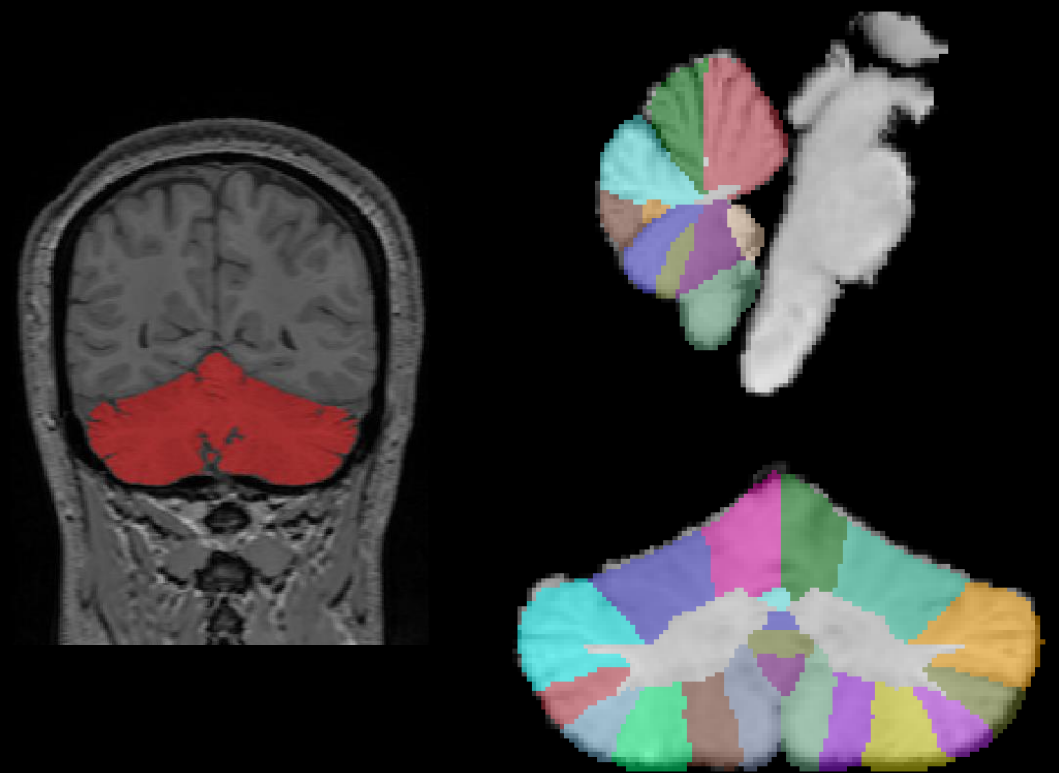


Brain Volumetry

Subcortical structures



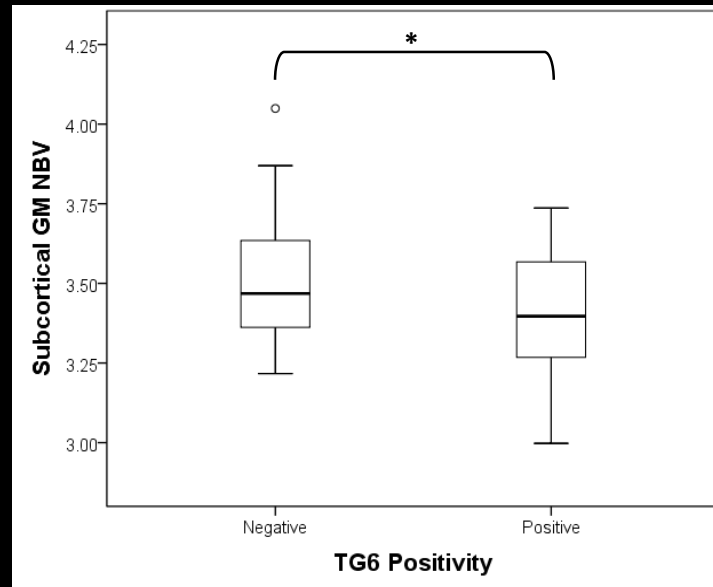
Cerebellum



Does TG6 positivity predict brain atrophy?

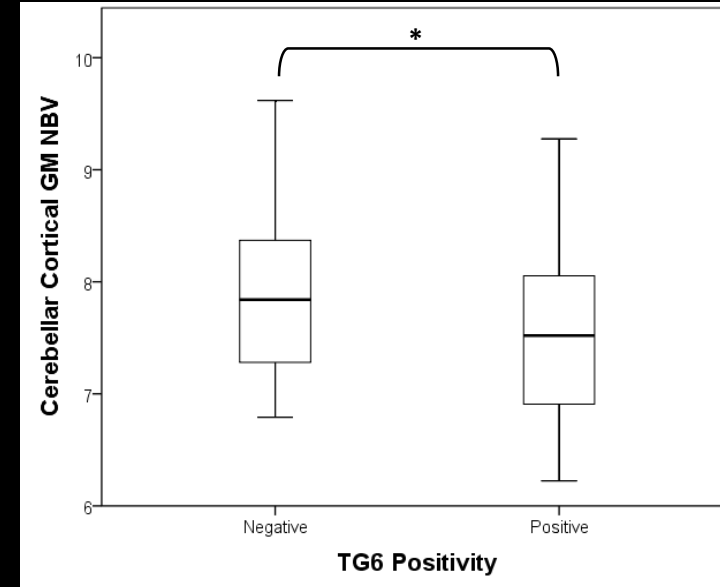
40% of subjects were TG6 positive

Cerebral Sub-Cortical GM



$p=0.016$

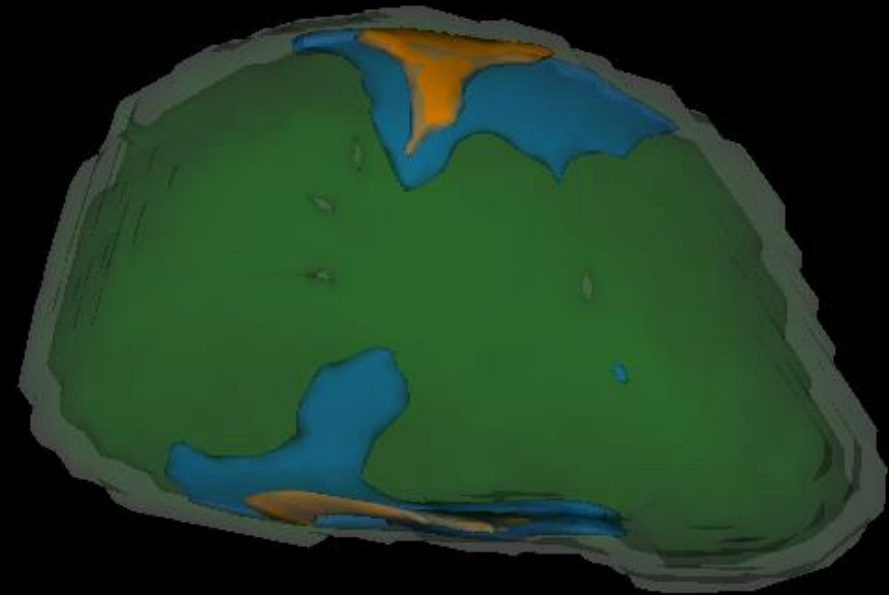
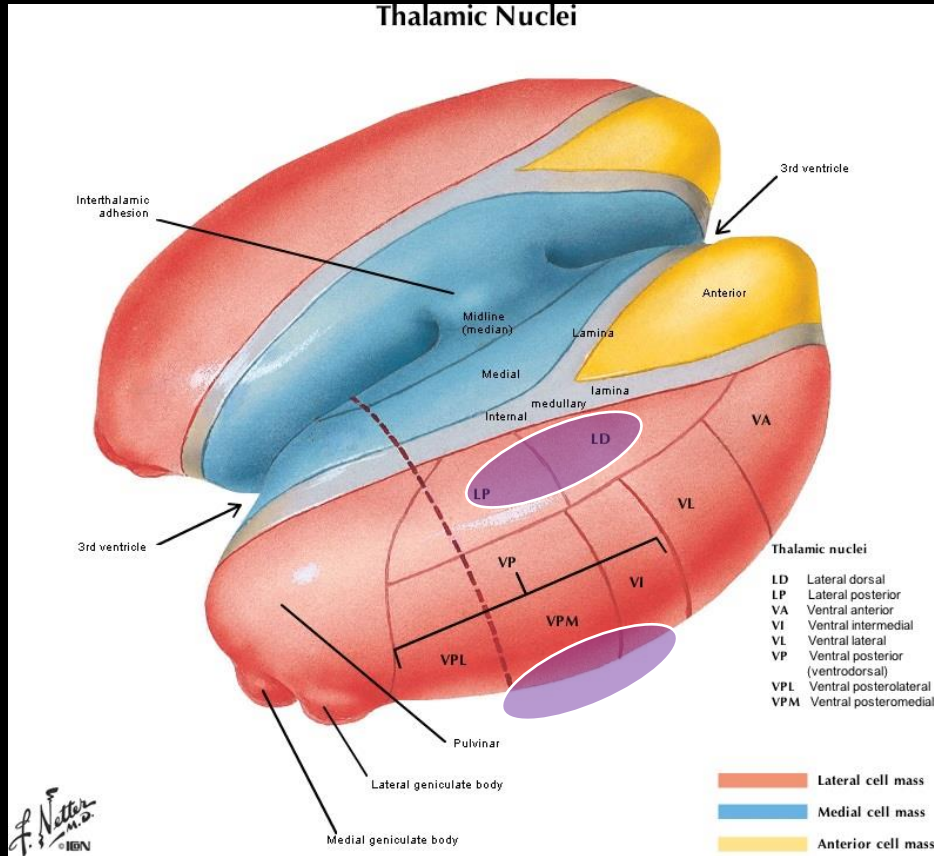
Cerebellar GM



$p=0.050$

Does TG6 positivity predict brain atrophy?

From Netter, F. (2010), *Atlas of Human Anatomy*



Motor and somatosensory

Experiment #2 - UK Biobank

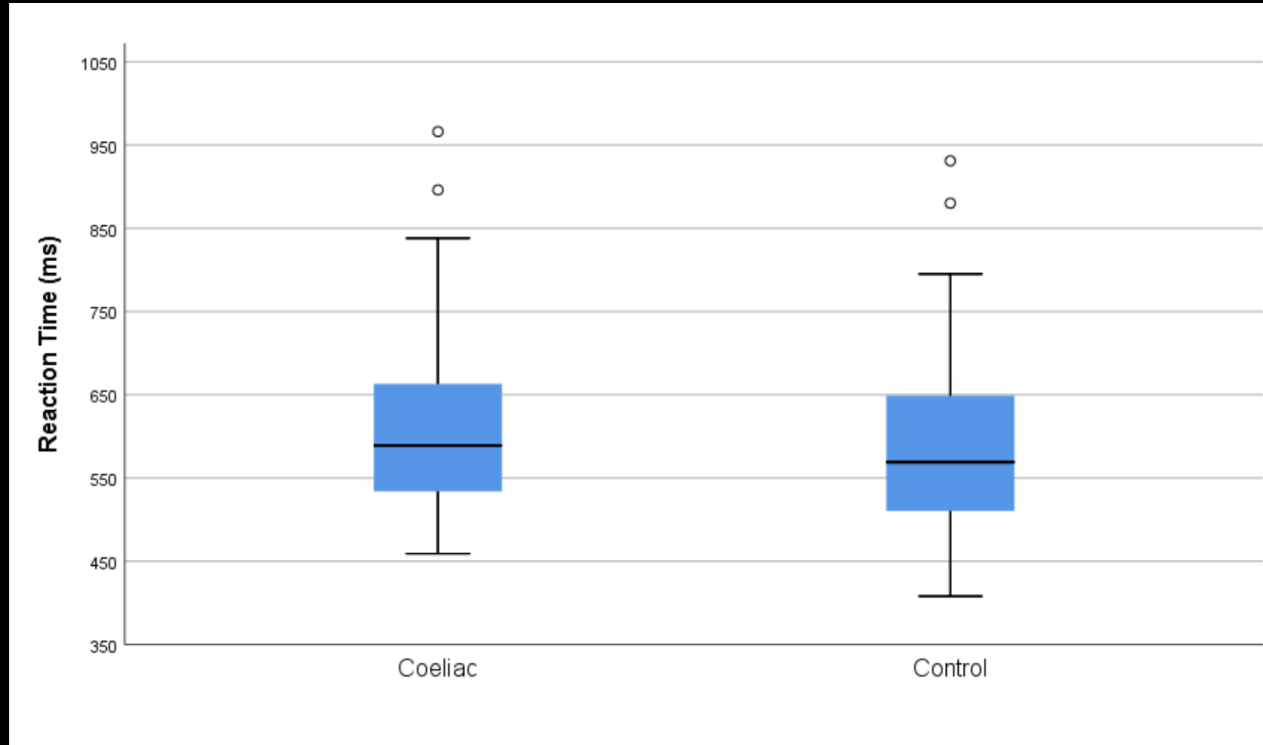
UK biobank is a “health resource” funded by the Wellcome Trust

More recently it has begun MRI scanning 100,000 of these (ongoing)

89 eligible volunteers with coeliac disease

Matched to controls on age, sex, highest level of education, BMI and diagnosis of hypertension

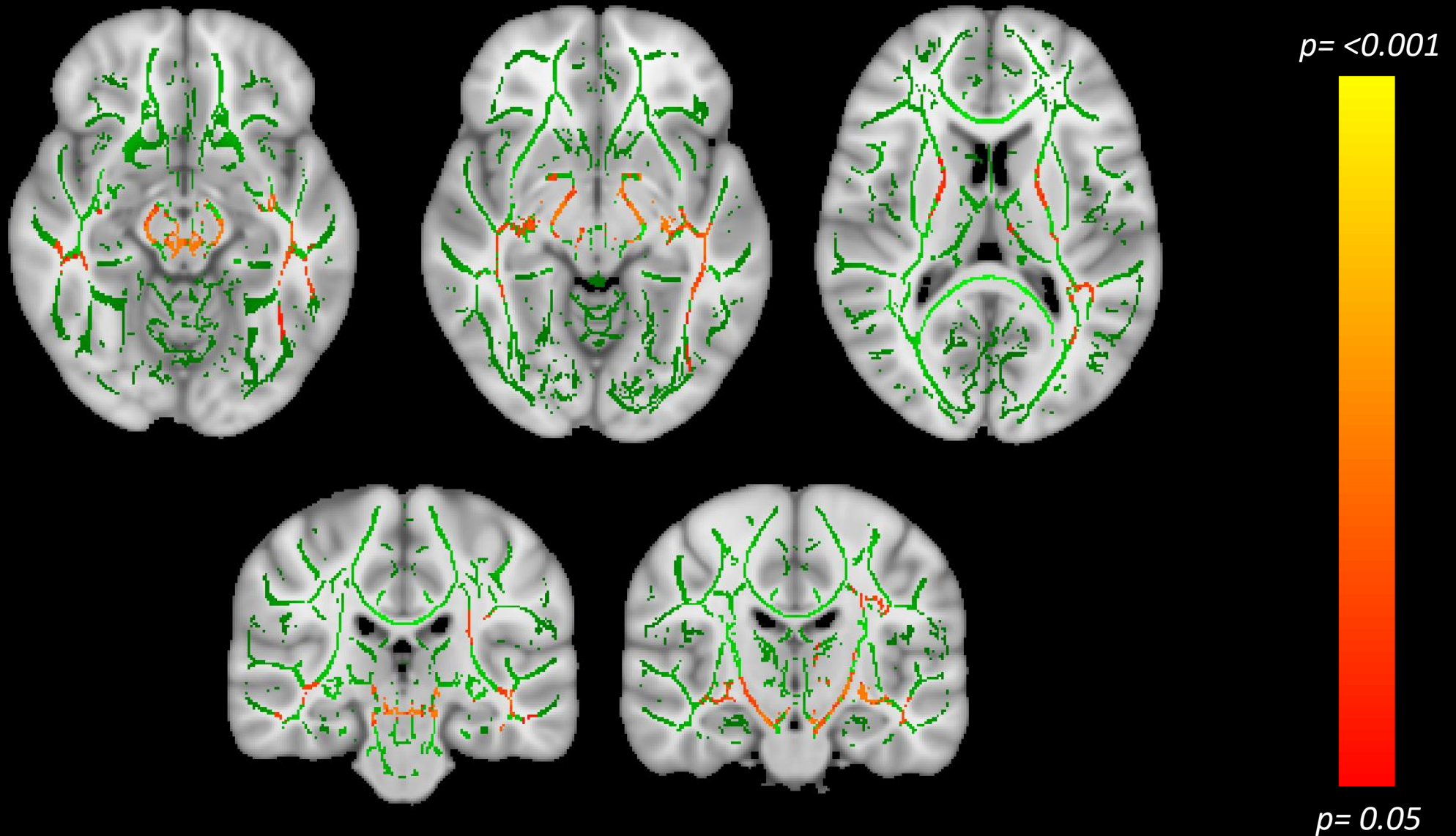
Preview #1 – Cognition and Mood



Reaction time sig. slower ($p=0.009$)

- “Ever felt worried, tense, or anxious for most of a month or longer?”
32.8% vs 13.8% ($p=0.005$)
- “Ever had prolonged loss of interest in normal activities?”
47.1% vs. 21.2%
- “Ever had prolonged feelings of sadness or depression?”
58.6% vs 43.8%

Preview #2 – Diffusion Tensor Imaging in Coeliac Patients



What about Non-Coeliac Gluten Sensitivity?

Neurological symptoms are indicated:

Aziz et al. 2014

- Headaches (22%)
- Confusion (5%)

Volta et al. 2014

- Headaches (54%)
- Brain fog (38%)

Postal Survey

118 patients with NCGS who had attended Prof. Sanders' Coeliac clinic returned a postal survey (221 approached).

Survey used tools from Coeliac research to investigate dietary adherence (CDAT) and quality of life (CSI).

Questions also characterised frequency / severity of neurological symptoms, and sleep quality.

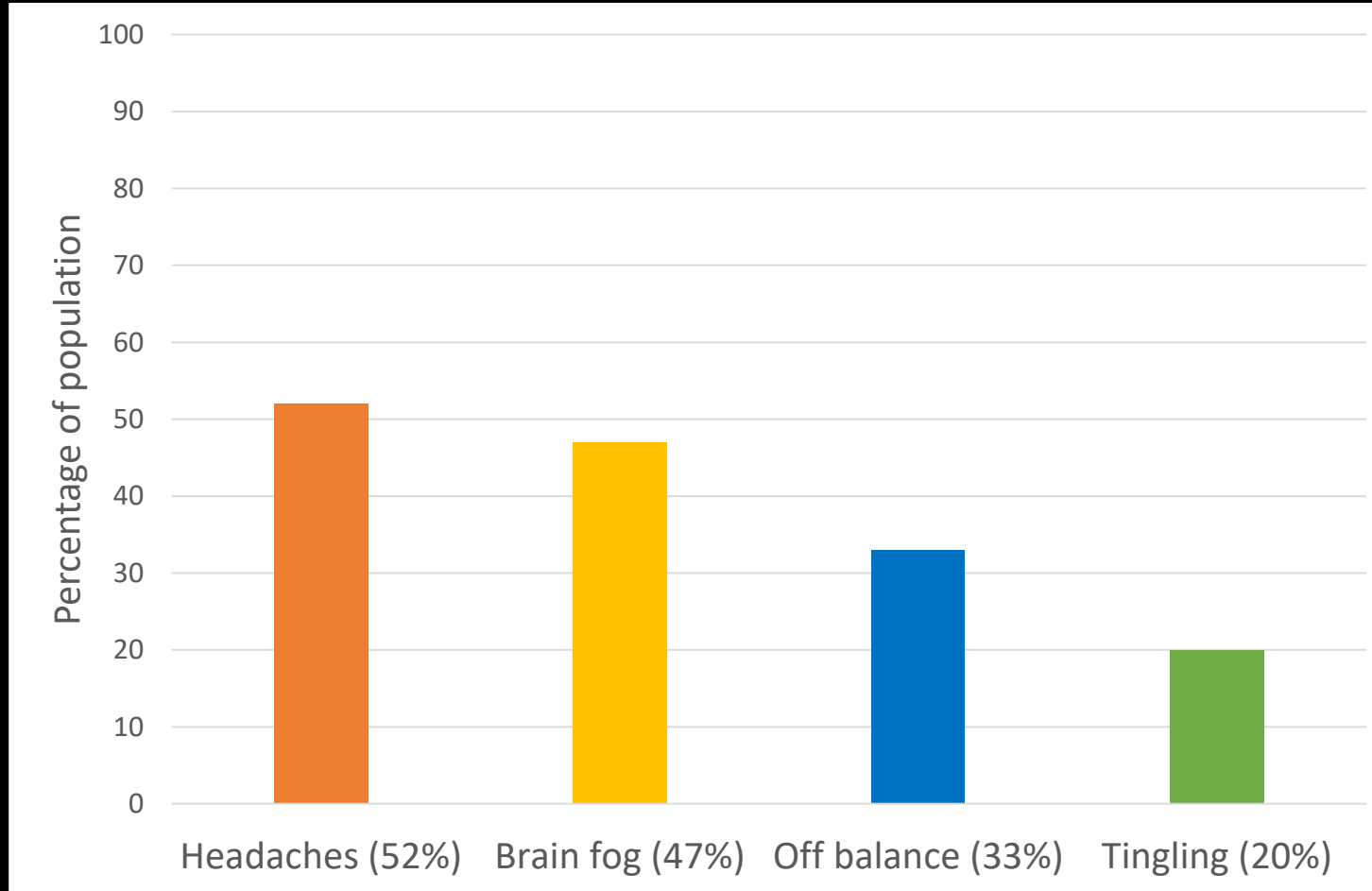
Postal Survey

43% described their diet as one where they attempted to eliminate gluten completely (17% made no restriction at all).

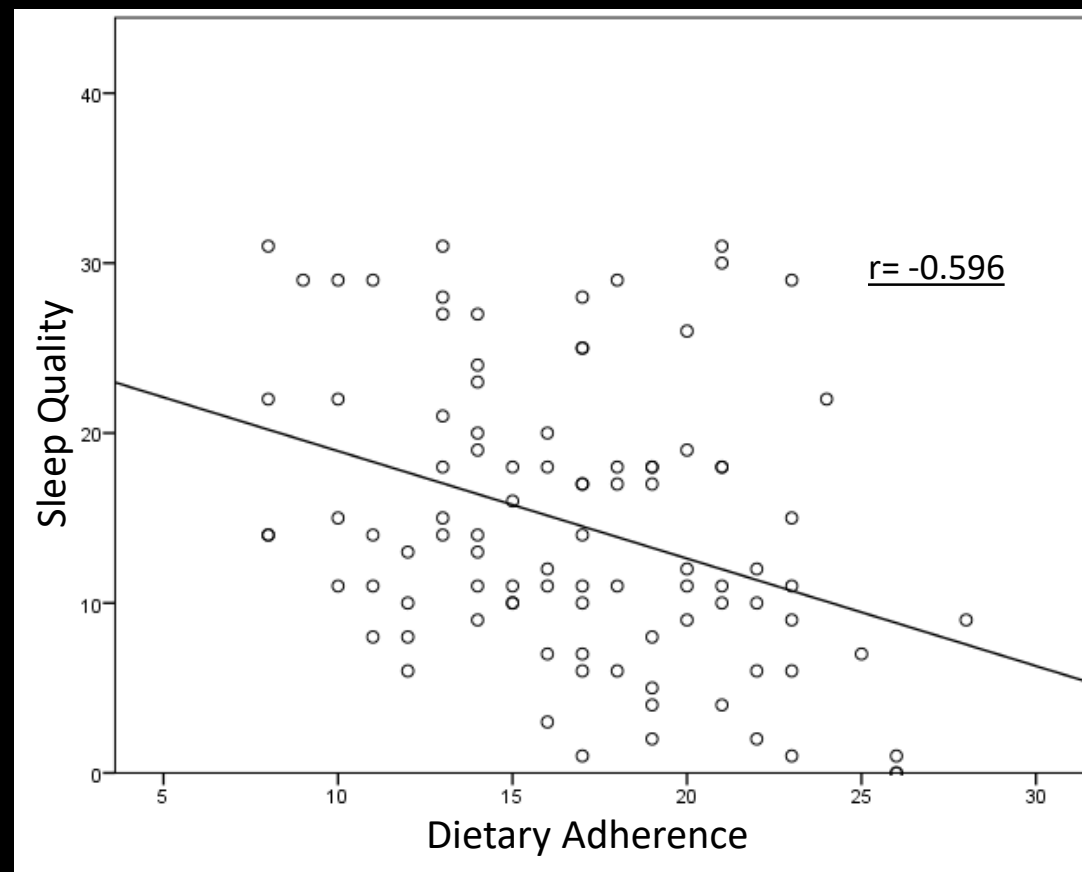
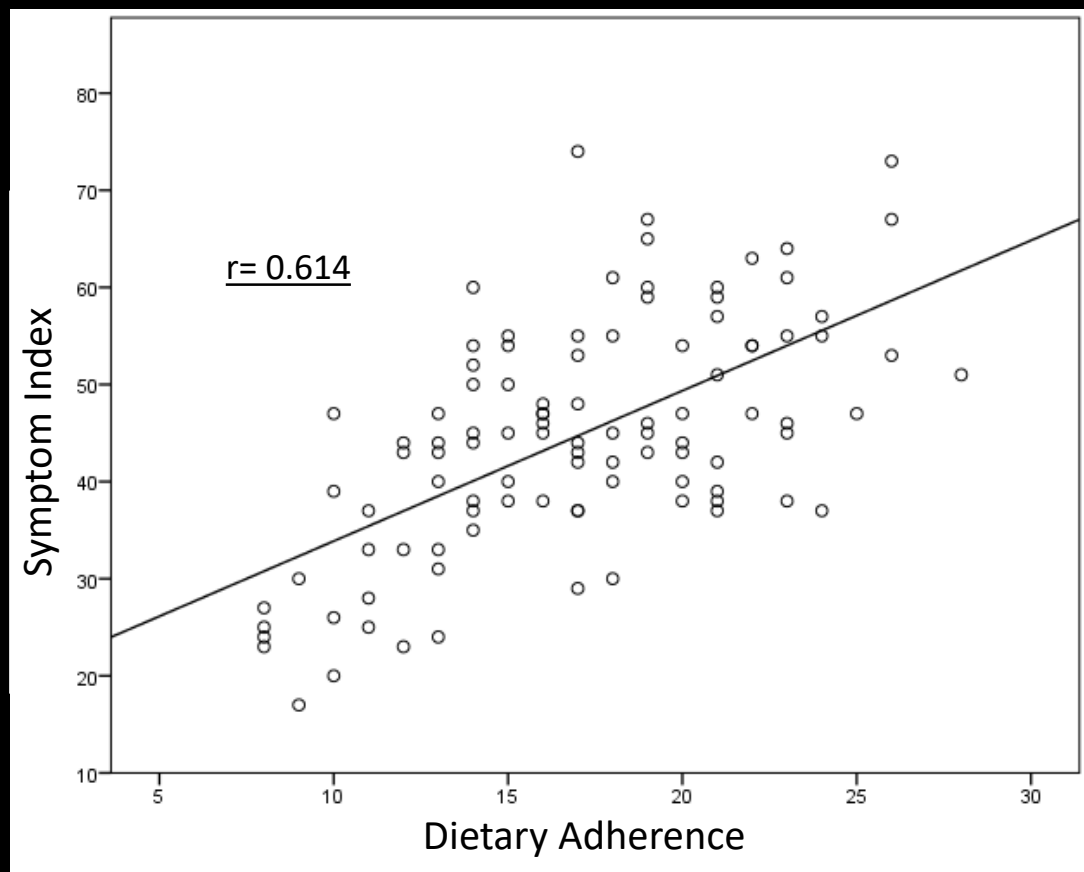
58% reported they had a reaction every time they ate gluten.

Median symptom onset was 90 minutes, with resolution at 48 hours.

Neurological symptoms are common in NCGS



Dietary adherence significantly linked to QoL and sleep

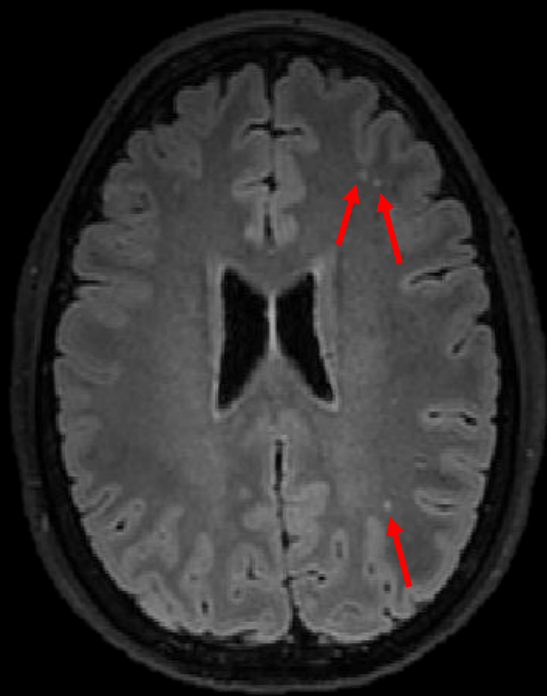


Each $p < 0.001$

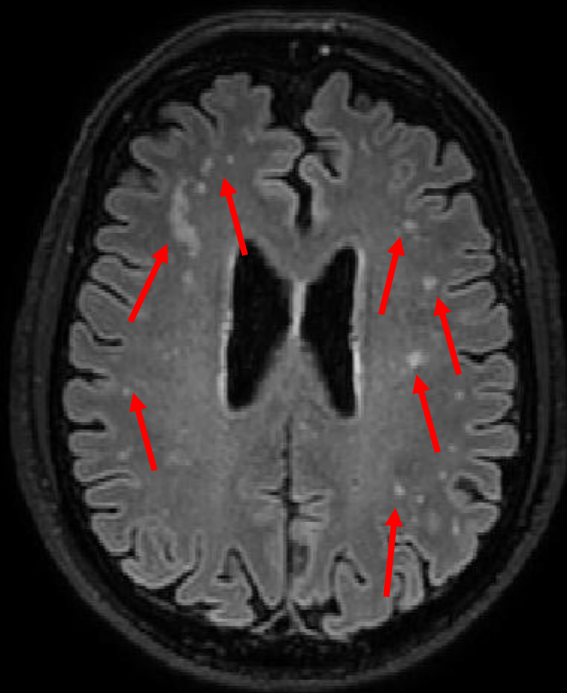
What about brain imaging?

Five responders who were on strict GFD were invited to a follow-up pilot study.

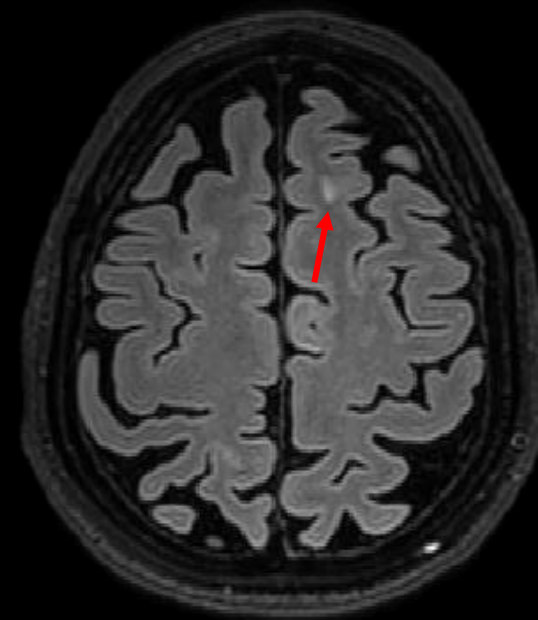
Brain imaging to characterise white matter pathology



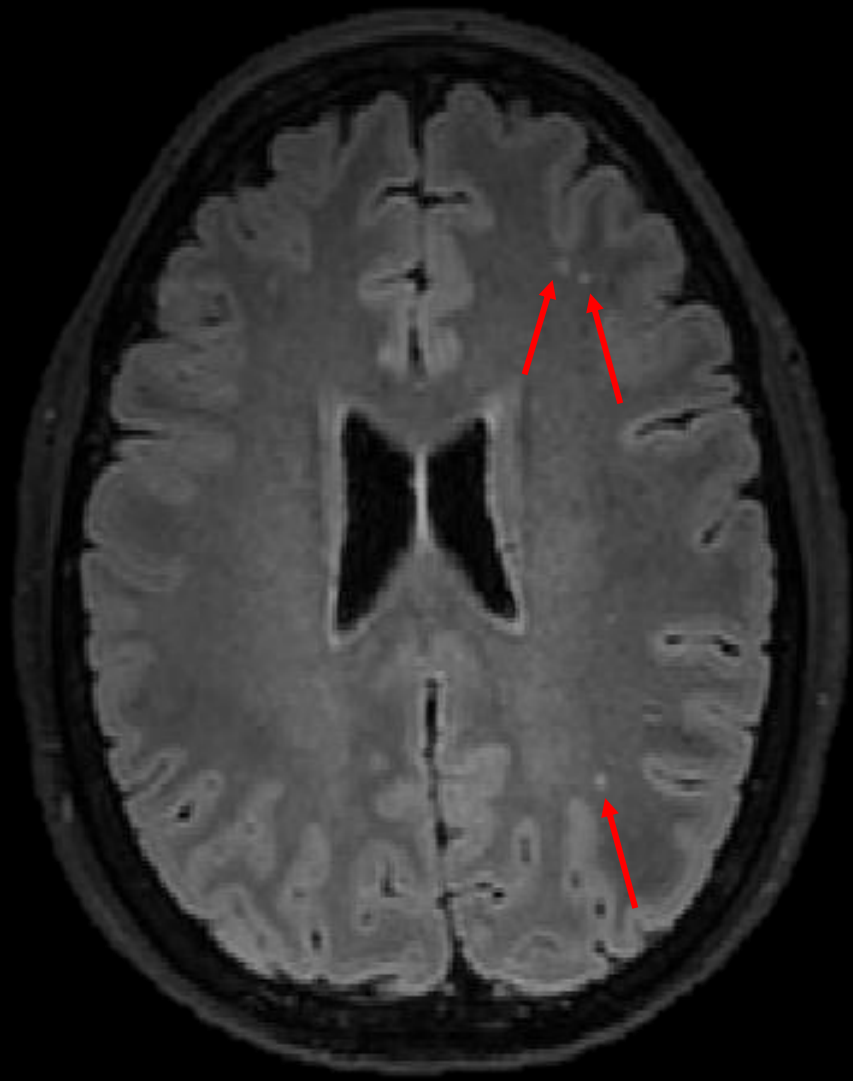
34 years



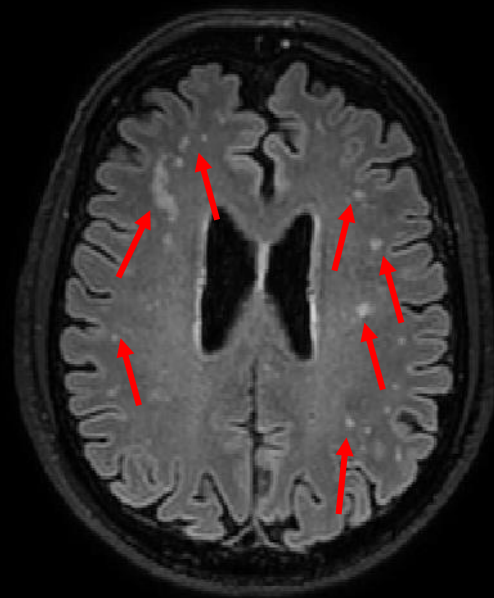
69 years



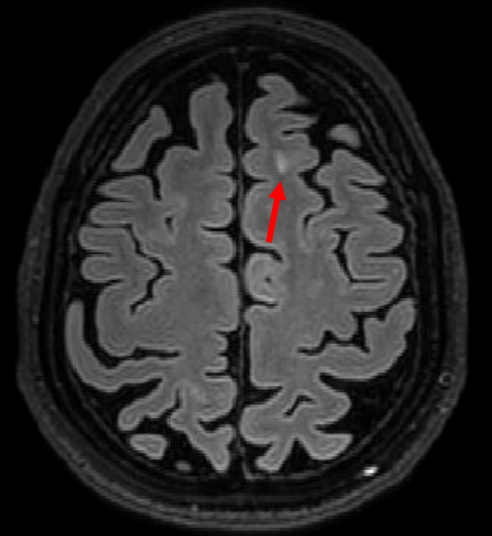
33 years



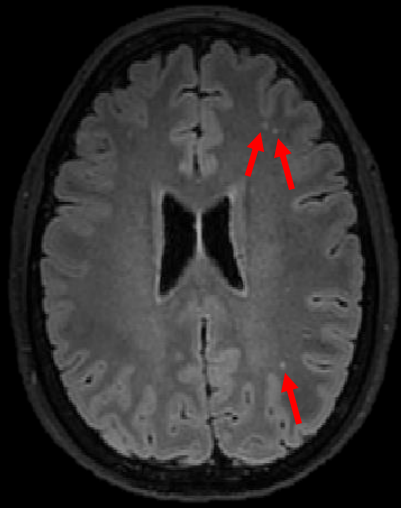
34 years



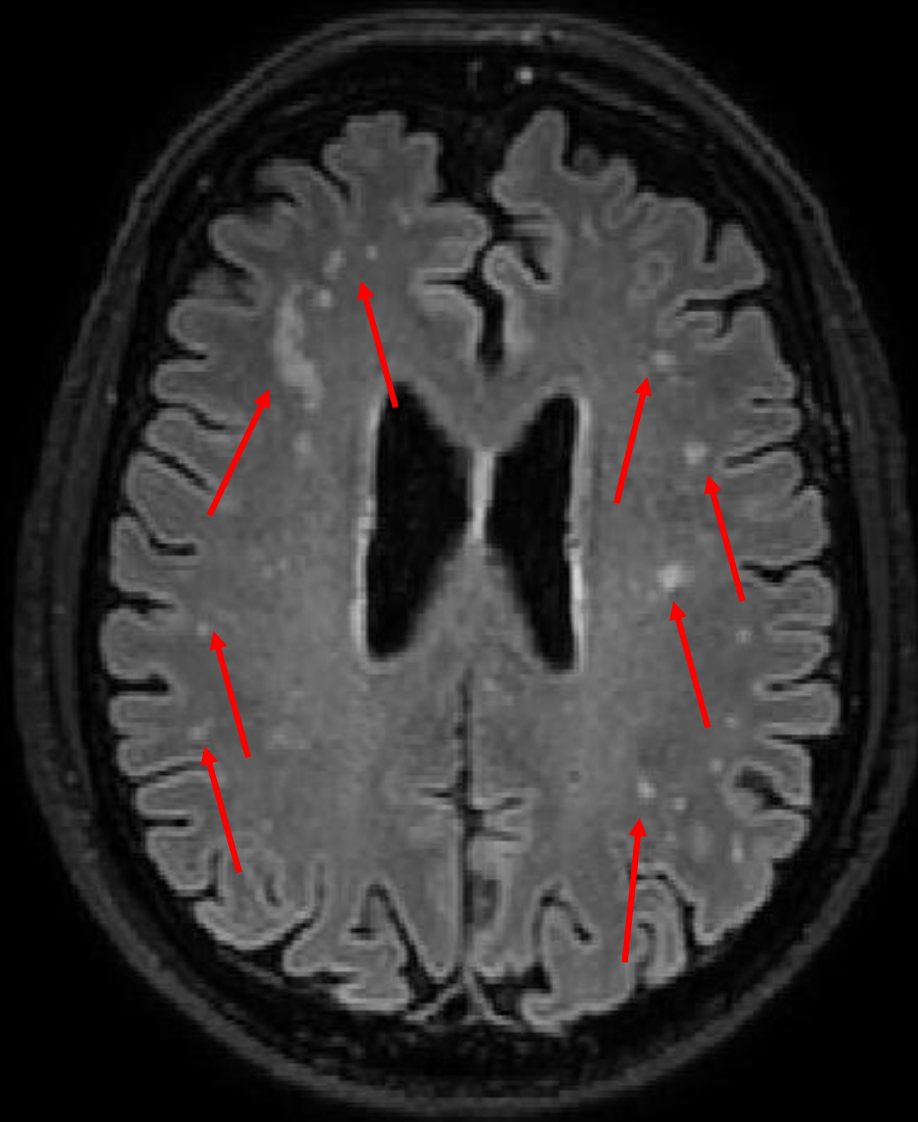
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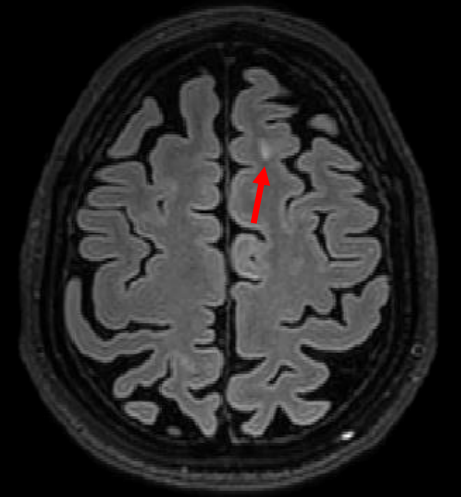
33 years



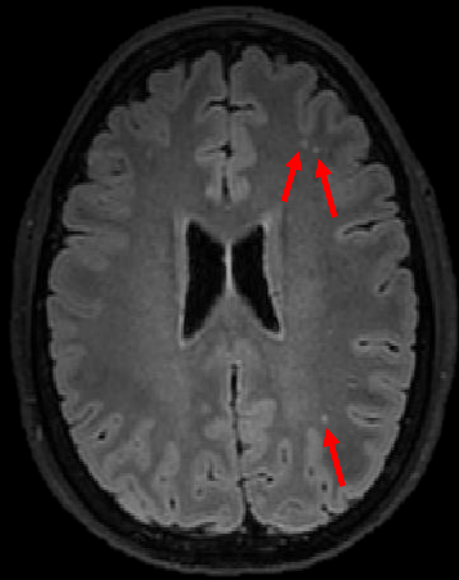
34 years



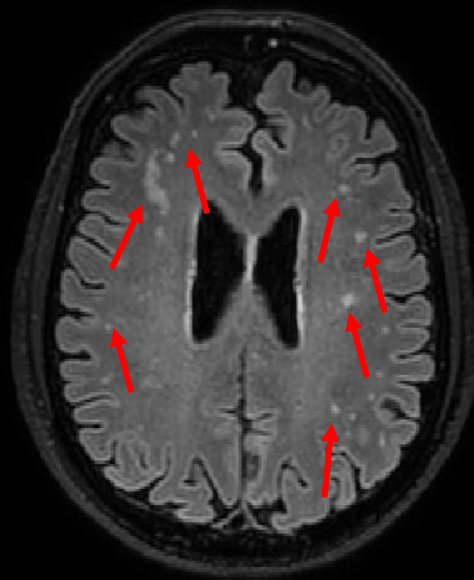
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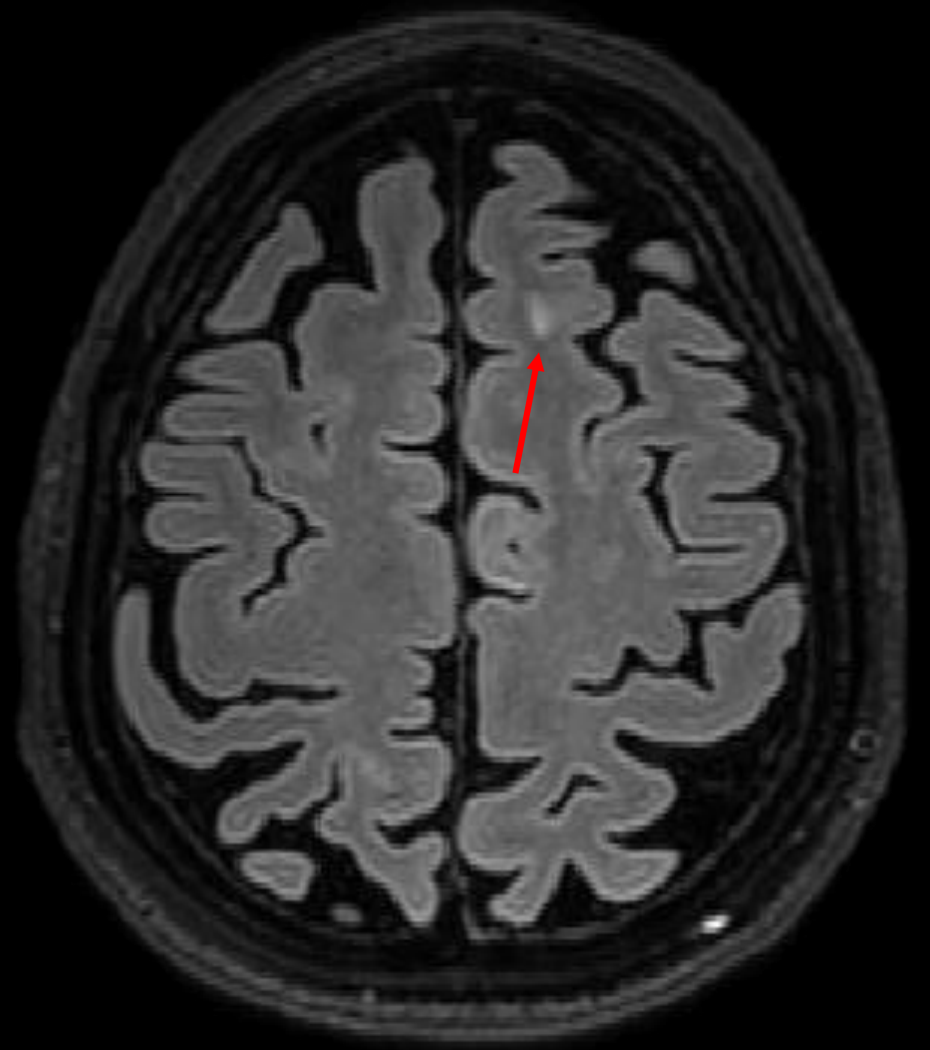
33 years



34 years



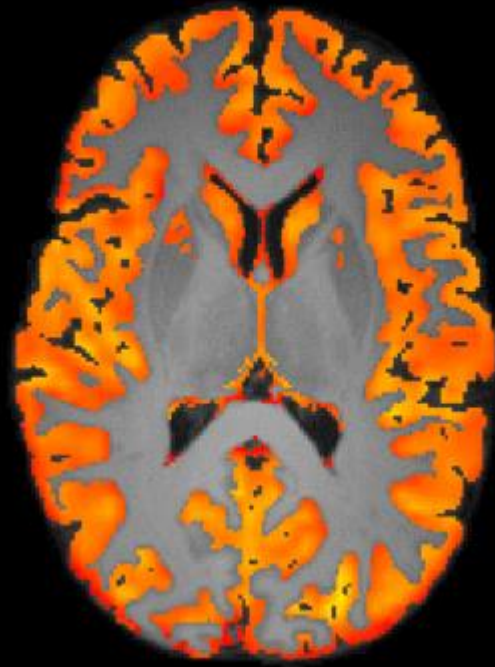
69 years



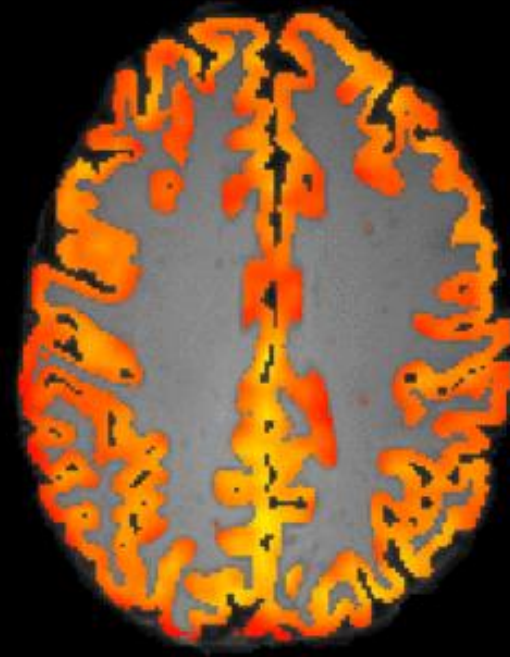
33 years

Blood flow increases by 14% in one subject after gluten

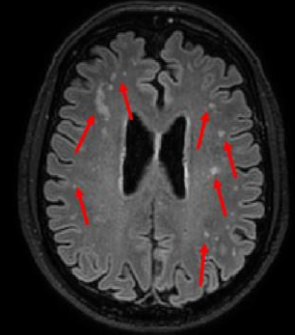
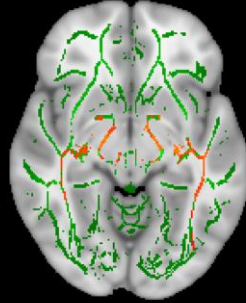
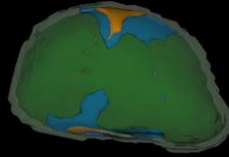
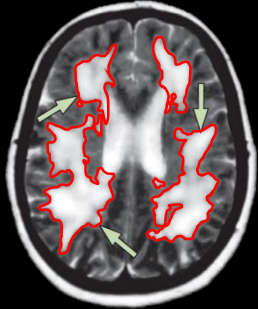
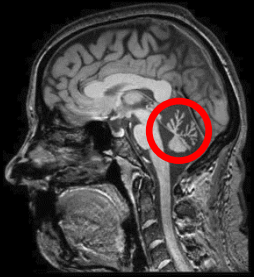
Pre-Gluten



Pre-Gluten



Tying it all together



Neurological Gluten Sensitivity

“Typical” Coeliac Disease

“Typical” NCGS

Cerebellar atrophy
White matter lesions

Movement/sensation
Cognitive deficits

TG6 involvement?

Prevalent neurological signs
Movement/sensation

Cognition and mood problems

TG6 positivity predicts cerebellar and
thalamic atrophy

Brainstem shows altered
microstructure

Dietary adherence
linked to quality of life
and sleep

Neurological signs are
common

White matter lesions?

Acknowledgements

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Anupam Rej

Pascale Aeschlimann

Daniel Aeschlimann



BRET

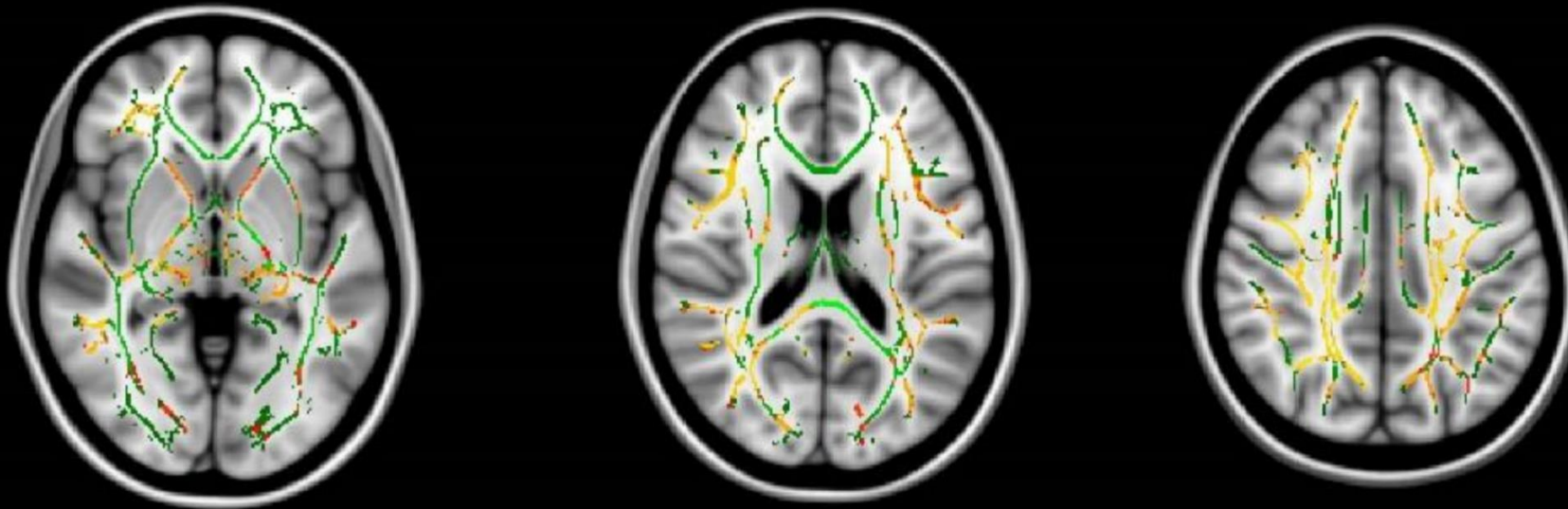
(Bardhan Research & Education Trust)

TG6

- 40% were TG6 positive
- TG6+ patients older than TG6-
 - TG6+ = 46.7(\pm 14.8) years
 - TG6- = 40.3(\pm 14.8) years
 - *t*-test $p=0.043$
- TG6+ patients were *not* more likely to suffer neurological symptoms (X^2 $p=0.152$)
- However those with balance symptoms and/or abnormal cerebellar MRS were more often TG6+
 - 74% of TG6+
 - 46% of TG6-
 - X^2 $p=0.007$

Diffusion Tensor Imaging

White matter DTI – detects changes in white matter not able to be seen on conventional imaging (Croall et al., 2014)



A Tract-Based Spatial Statistics analysis indicating white matter tract locations which are sig. altered in patients compared to controls

Outperforms other imaging markers at predicting patient outcome in vascular dementia (Croall et al., 2017)