



The
University
Of
Sheffield.

Cognitive deficit and white matter changes in celiac disease

Nigel Hoggard

 **ICDS2022** SORRENTO

Financial disclosures

- I have previously received research funding from GE medical systems and Philips Medical systems

The neurological perspective of gluten sensitivity and CD ...1994

Does cryptic gluten sensitivity play a part in neurological illness?

M Hadjivassiliou, A Gibson, G A B Davies-Jones, A J Lobo, T J Stephenson, A Milford-Ward

Summary

Background Antigliadin antibodies are a marker of untreated coeliac disease but can also be found in individuals with normal small-bowel mucosa. Because neurological dysfunction is a known complication of coeliac disease we have investigated the frequency of antigliadin antibodies, as a measure of cryptic gluten sensitivity, and coeliac disease in neurological patients.

patients from group 1 revealed histological evidence of coeliac disease in nine (35%), non-specific duodenitis in ten (38%), and no lesion in seven (26%) individuals.

Interpretation Our data suggest that gluten sensitivity is common in patients with neurological disease of unknown cause and may have aetiological significance.

Lancet 1996; **347**: 369–71



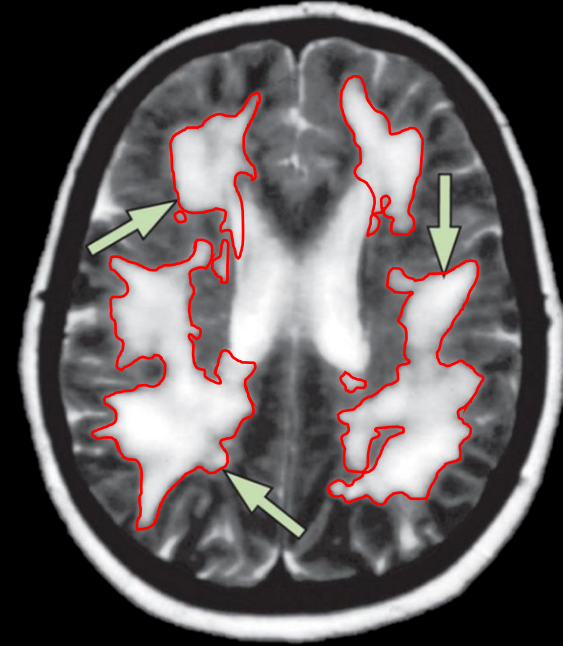
The
University
Of
Sheffield.



Cerebellar Involvement

- Movement
- Co-ordination
- Sensation

Cerebral white matter involvement



- Migraines
- Cognition
- “Foggy brain”

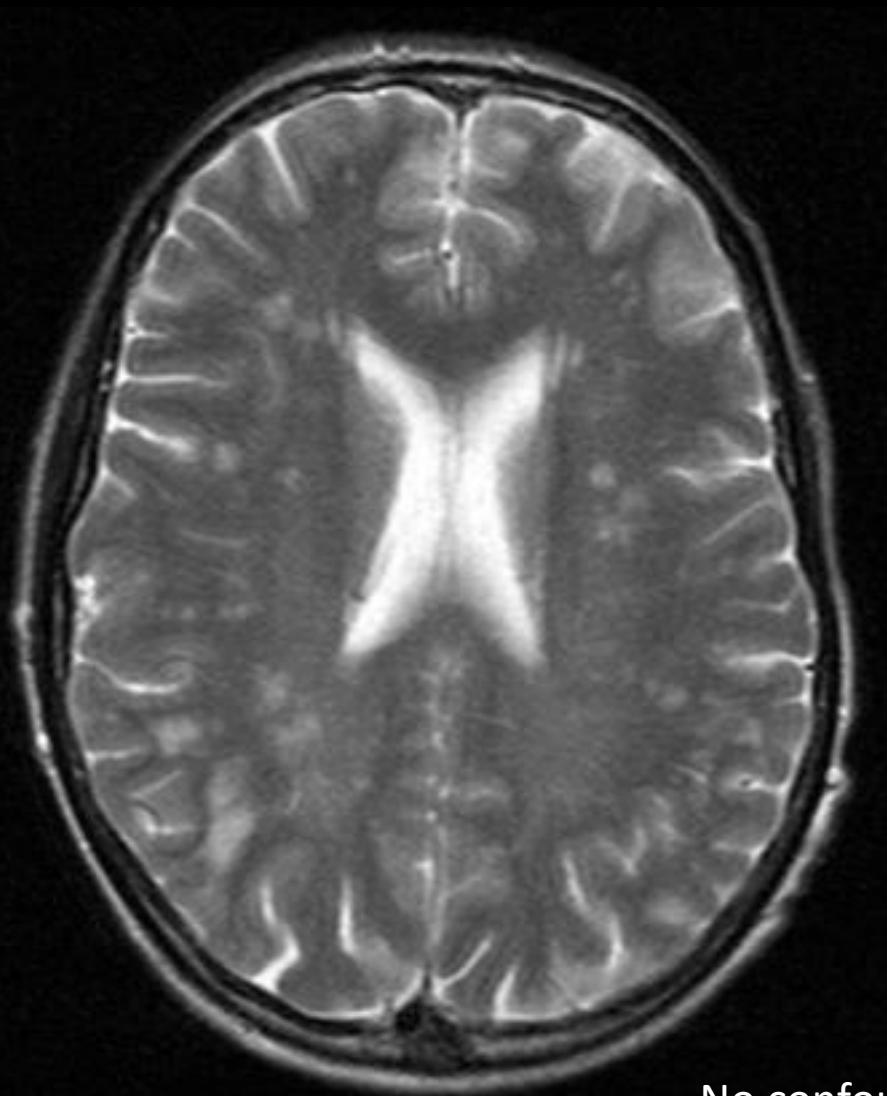
Gluten encephalopathy: symptoms

- Episodic often severe and intractable headaches
 - can mimic migraine
- Patients often also complain of slow mentation “foggy brain” and may have significant cognitive deficits
- Headache and cognitive difficulties improve on gluten-free diet
- Often have abnormal MRI brain



The
University
Of
Sheffield.

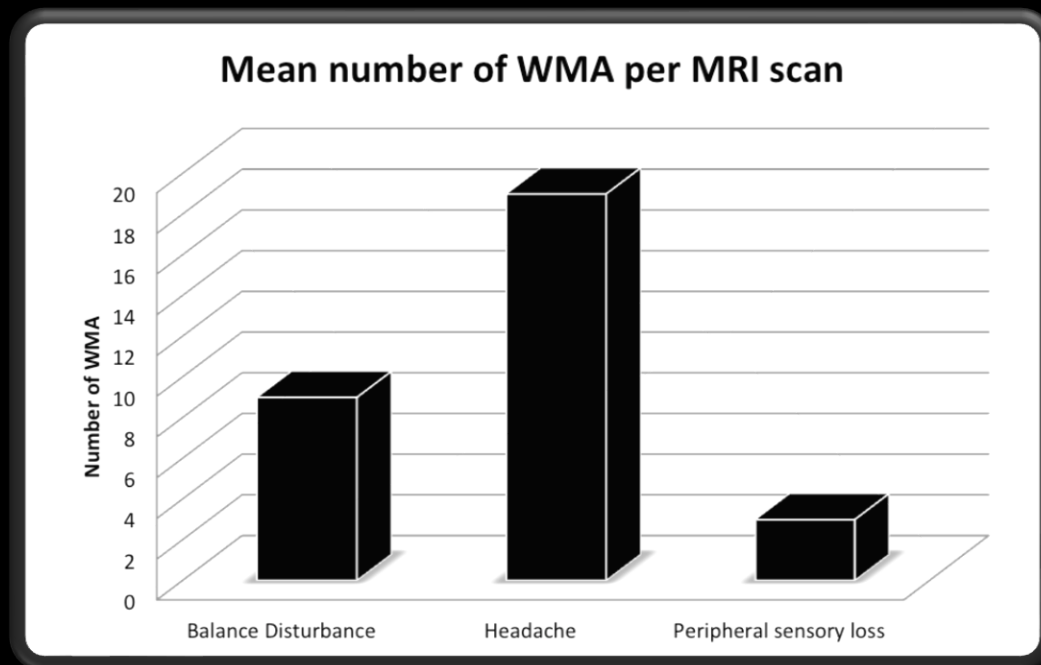
2 years, no gluten-free diet



Mid 60's female
No confounding neurological diseases
No vascular risk factors

White matter disease seen in gluten sensitivity

White Matter Abnormalities (WMA)



Subgroup	Incidence of WMA (%)
Balance Disturbance	53
Headache	66.6
Peripheral Sensory Loss	25



The
University
Of
Sheffield.

The neurological iceberg

**classical coeliac
disease**

**coeliac disease
presenting with
neurological
manifestations**

**gluten sensitivity
without CD but
with
gastrointestinal
symptoms**

**gluten sensitivity
without CD
presenting with
neurological
manifestations**



The
University
Of
Sheffield.

The brain health iceberg

classical coeliac disease

coeliac disease presenting with
neurological manifestations

gluten sensitivity without CD but
with gastrointestinal symptoms

gluten sensitivity without CD with
impaired brain health

Understanding the significance of white matter disease

WMH are very common in older individuals and regarded as typical signs of 'small vessel disease'.

Symptoms of WMH develop insidiously, such as

- Cognitive impairment/ Doubles the risk of dementia
- Depression
- Associated with triple the risk of stroke
- Increases the risk of death

Debette S, Markus HS. *The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.*



Understanding the significance of white matter disease

When severe also associated with

- Gait abnormalities
- Falls
- Adds to frailty
- Doubles risk of nursing home care over 3 years



The
University
Of
Sheffield.

**Question - Can we see these
sorts of findings in other people's data?**



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

Initially collected healthcare data on 500,000 participants

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

Independently-collected data; diagnoses will be representative of “typical” celiac disease

Biobank data

Volunteers with celiac disease identified:

(N=104)

- Otherwise healthy
- Was not taking “psychoactive” medication at the time of data collection
- Also had brain imaging data available

Cases matched in a 1:2 ratio to healthy controls on:

(N=198)

- Age
- Sex
- B.M.I.
- Highest level of education
- Diagnosis of hypertension

Methods

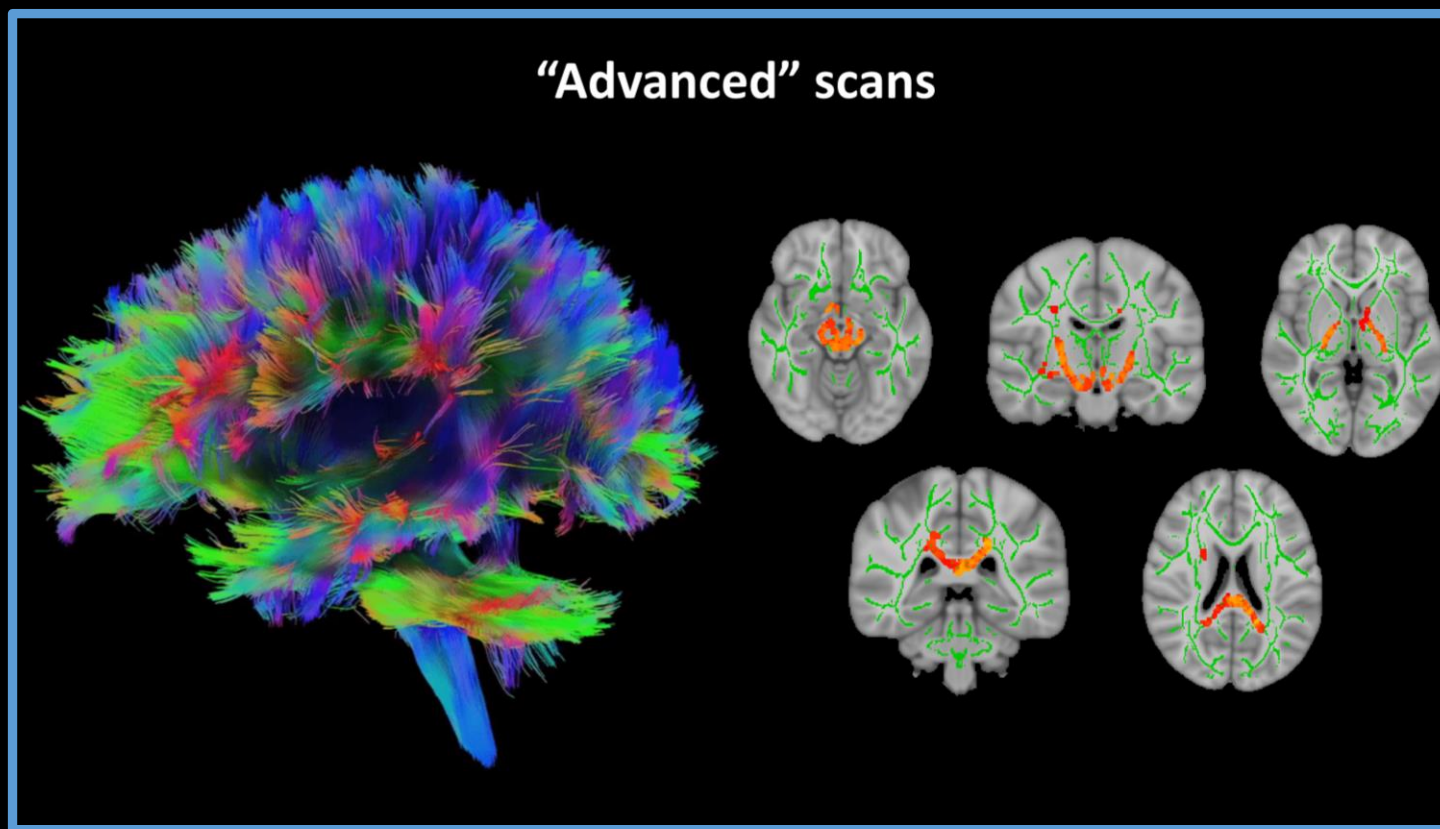
Case vs control analyses:

- Key scores from 5 cognitive tests
- Responses given to 6 multiple-choice questions exploring aspects of mental health
- Brain imaging analyses...

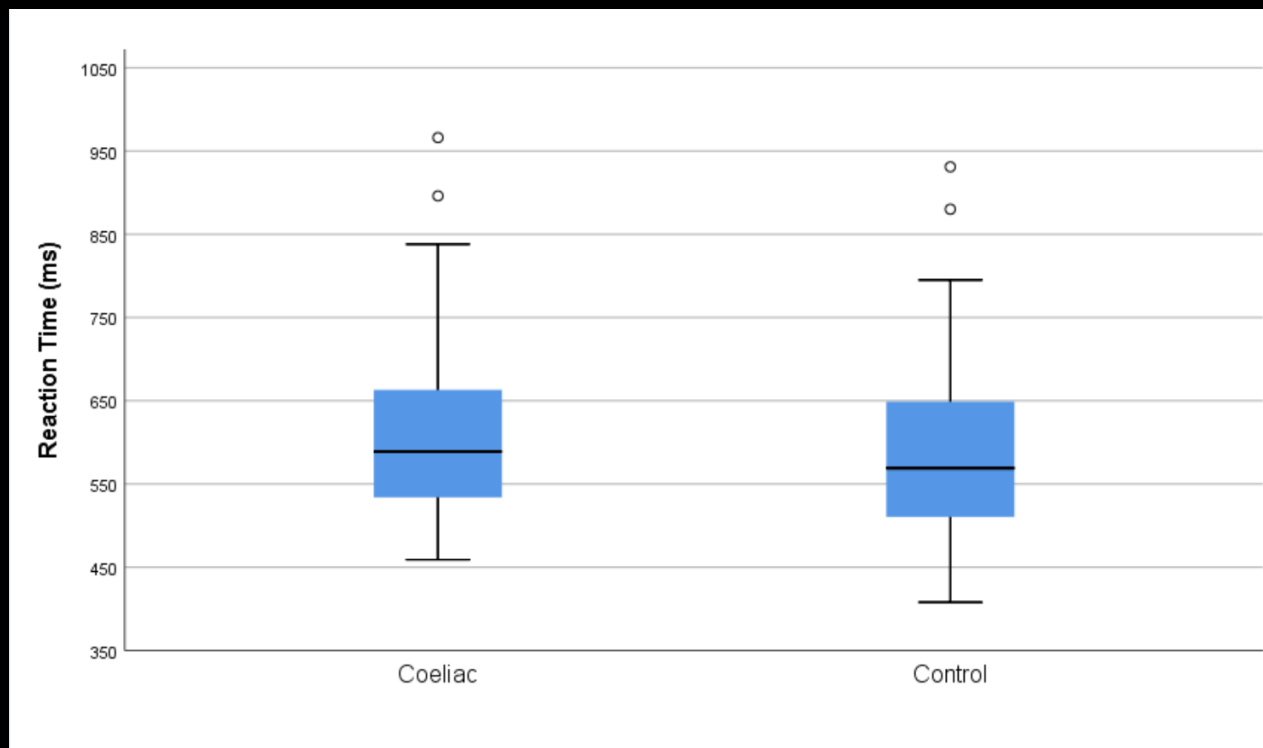
Methods

Case vs control analyses:

- Key scores from 5 cognitive tests
- Responses given to 6 multiple-choice questions exploring aspects of mental health
- Brain imaging analyses...



Results – Cognition and Mood



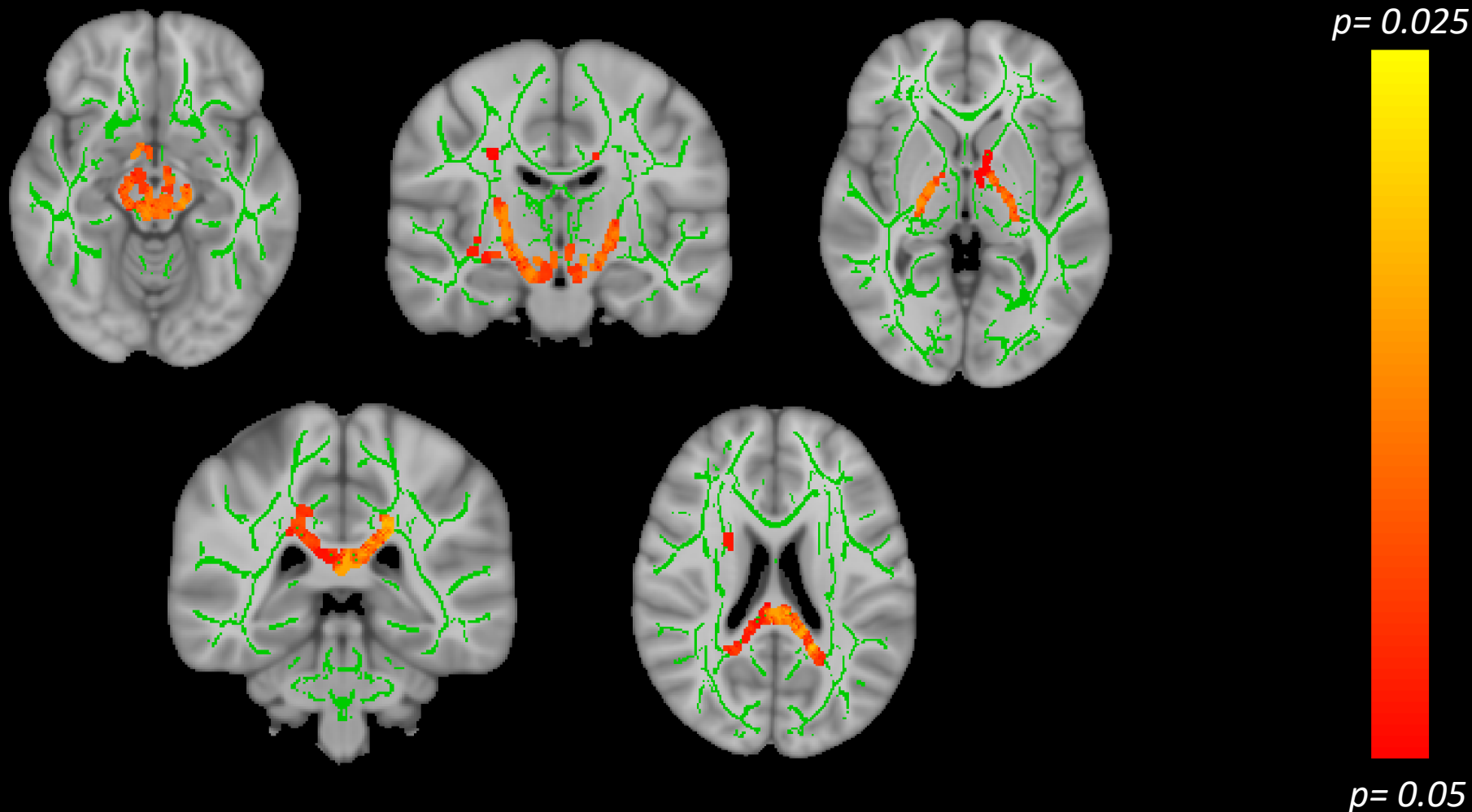
Reaction time sig. slower ($p=0.004$)

- “Ever felt worried, tense, or anxious for most of a month or longer?”
31.5% vs 18.0% ($p=0.025$)
- “Ever had prolonged feelings of sadness or depression?”
58.4% vs. 41.4% ($p=0.015$)
- “Ever contemplated self-harm?”
19.5% vs 9.0% ($p=0.025$)
- Coeliac patients sig. more likely to be “unhappy” with their own health.
($p=0.010$)



The
University
Of
Sheffield.

Results – White matter changes in patients with celiac disease





Cognitive Deficit and White Matter Changes in Persons With Celiac Disease: A Population-Based Study



Iain D. Croall,^{1,4} David S. Sanders,² Marios Hadjivassiliou,³ and Nigel Hoggard^{1,4}

¹University of Sheffield, Academic Unit of Radiology, Royal Hallamshire Hospital, Sheffield, United Kingdom; ²Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom; ³Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom; and ⁴University of Sheffield, Institute for in silico Medicine (INSIGNEO), Sheffield, United Kingdom

See editorial on page 2043.



The
University
Of
Sheffield.

Question

**How come I don't see it in my patients?
....Or just how frequent are symptoms in
patients with celiac disease?**

BRET



Neurologic Deficits in Patients With Newly Diagnosed Celiac Disease Are Frequent and Linked With Autoimmunity to Transglutaminase 6

Marios Hadjivassiliou ¹, Iain D Croall ², Panagiotis Zis ³, Ptolemaios G Sarrigiannis ³,
David S Sanders ⁴, Pascale Aeschlimann ⁵, Richard A Grünewald ³, Paul A Armitage ²,
Daniel Connolly ², Daniel Aeschlimann ⁵, Nigel Hoggard ²

- 100 newly-diagnosed patients (via gastroenterology) consecutively enrolled.
- All subjects underwent:
 - Neurological examination
 - Blood sera testing for TG6
 - MRI scanning including structural T1-weighted imaging
- Characterisation of this cohort

 = on examination

10% Signs of
peripheral
neuropathy

24% Balance
Problems

 = self-reported

29% Walking
difficulty

Full Sample
(areas of
orbiting
circles are
proportionate
to this)

42% Frequent
headaches

11%
Nystagmus

12% Sensory
symptoms

Excluding headaches, 50% had features of neurological dysfunction

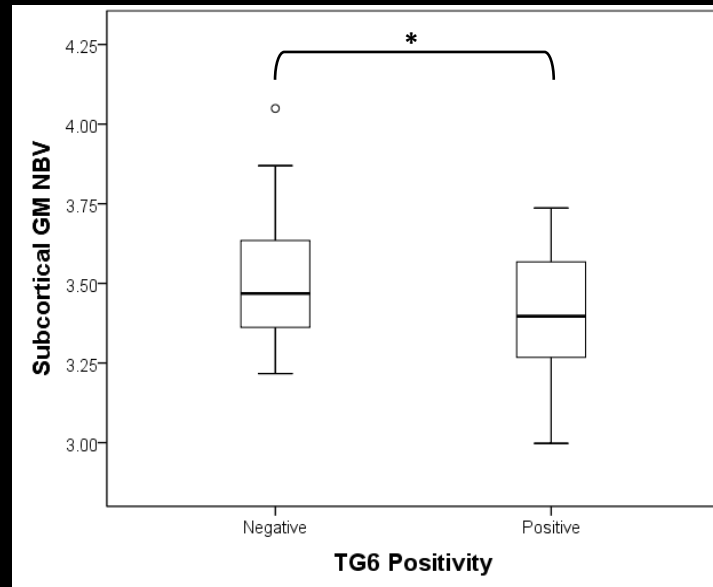


Does TG6 positivity predict brain volume loss?

40% of subjects were TG6 positive

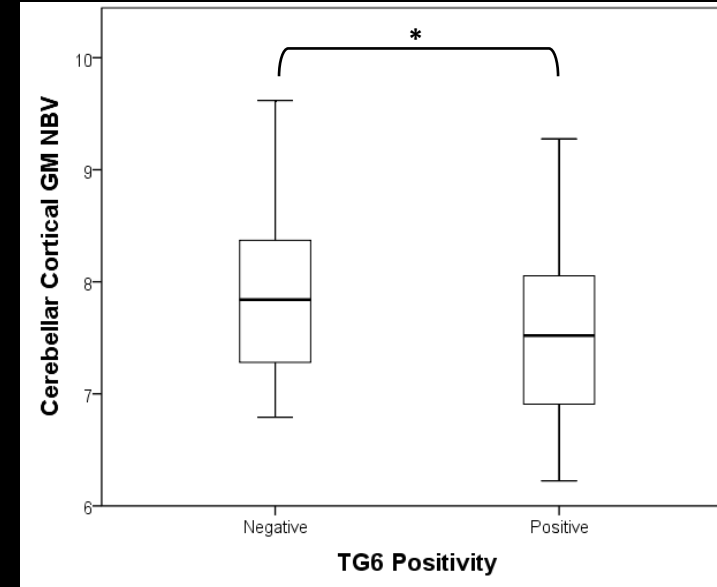
Really the thalamus

Cerebral Sub-Cortical GM



$p=0.016$

Cerebellar GM



$p=0.050$



The
University
Of
Sheffield.

Question: Does the gluten-free diet help?

Neurological Evaluation of Patients with Newly Diagnosed Coeliac Disease Presenting to Gastroenterologists: A 7-Year Follow-Up Study

Marios Hadjivassiliou ¹, Iain D Croall ² ³, Richard A Grünewald ¹, Nick Trott ⁴, David S Sanders ⁵, Nigel Hoggard ² ³

- 30 of these patients re-attended for follow-up measurements 7 years later
- All subjects underwent:
 - Neurological examination
 - Blood sera testing
 - Structural MRI scanning

Exactly half of the cohort had achieved negativity of all gluten-related antibodies at follow-up (TG2, TG6, EMA, gliadin)

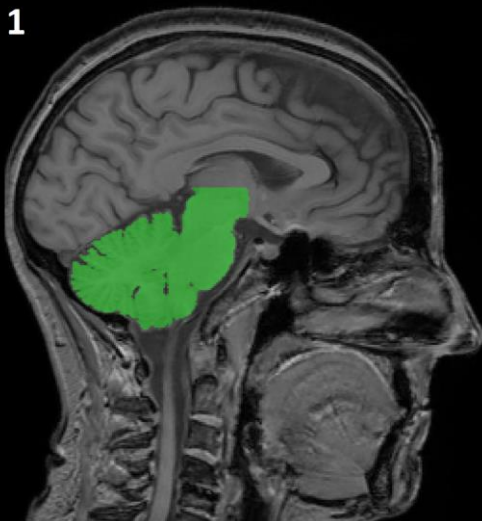
		Symptom	% at baseline	% 7 years later
Self-reported	{	Frequent headaches	47%	20%
		Balance problems	27%	47%
		Sensory symptoms	10%	10%
On examination	{	Gait ataxia	33%	57%
		Nystagmus	10%	7%
		Myoclonic tremor	3%	3%
		Loss of sensation in feet	0%	13%



The
University
Of
Sheffield.

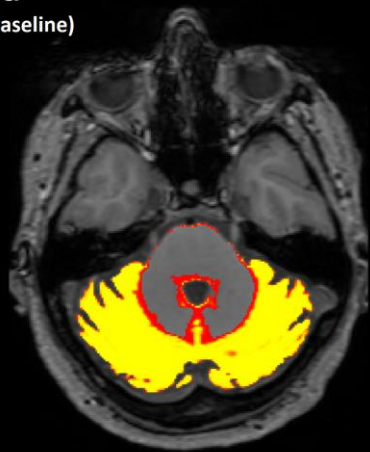
Rate of cerebellar atrophy greater in those who are still positive for gluten antibodies

1



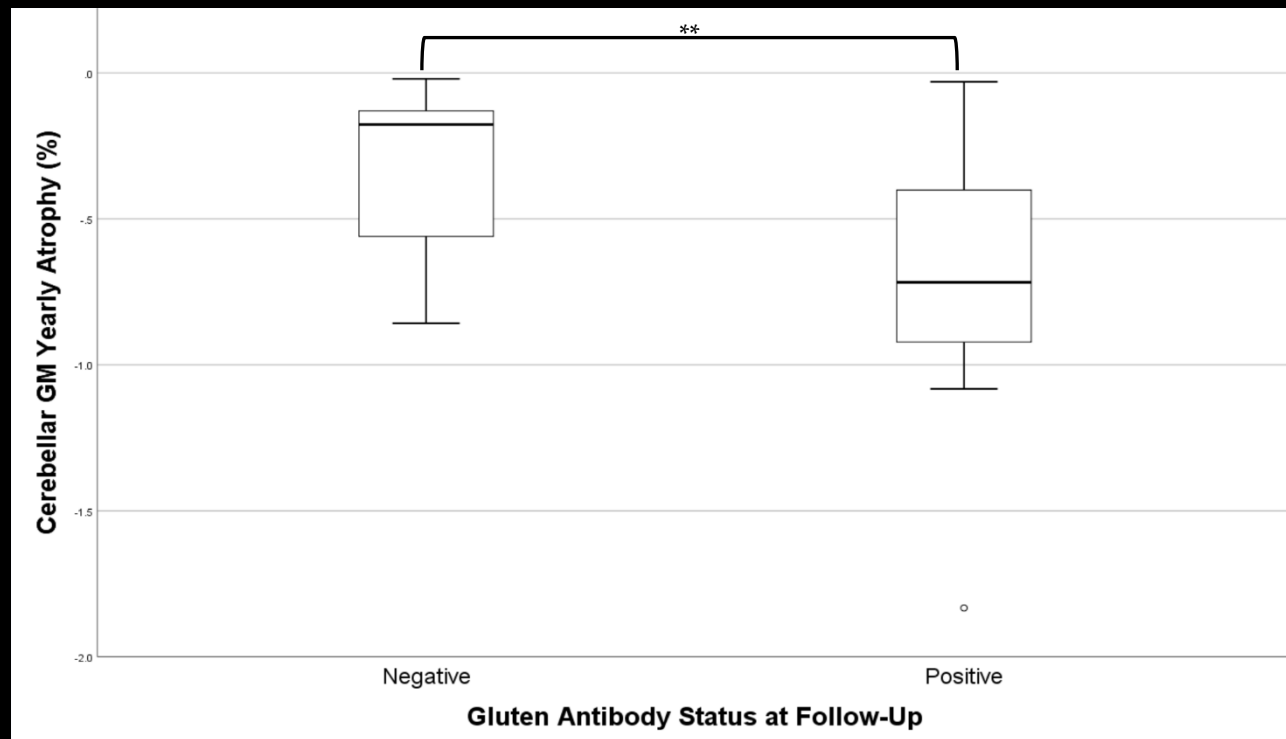
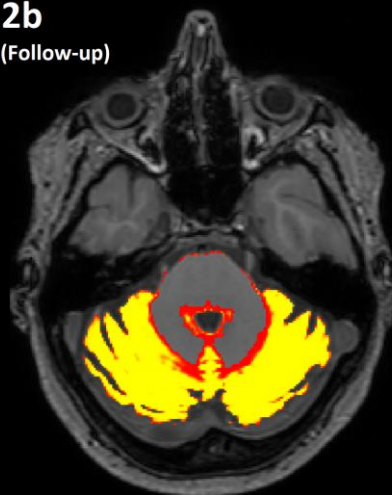
2a

(Baseline)



2b

(Follow-up)



Independent t-test, $p=0.007$,
Yearly rate of atrophy = -0.73% vs -0.32%
Groups not significantly different in age

What about WMD and asymptomatic gliadin positive people

- If anti-gliadin antibodies are so common (10 to 12% of population).....Is there an increased risk of WMD for patients with antibodies and no symptoms?
- Answer coming next year!



Bringing it all together...

- Brain and cognitive changes are detectable in patients with celiac disease using independent, population data. This is happening in your patients too!
- Patients with CD may have a wide variety of symptoms including headache, brain fog, sensory symptoms and coordination problems
- There is some evidence that a strict gluten-free diet slows or prevents progression of deterioration of brain health; more, better-powered research is underway to properly determine this...

Beyond Celiac & University of Sheffield Collaboration

We will combine the clinical data of >1000 patients with neurological problems related to gluten sensitivity with new cognitive, mood and quality of life measurements...

How much does the gluten-free diet help stop further progression of these problems?

What other factors determine how well a patient progresses over time?

How do these problems, and treatment, impact a patient's quality of life?

Acknowledgments



Prof. Marios Hadjivassiliou



Dr Iain Croall



Prof. David Sanders



Dr Paul Armitage

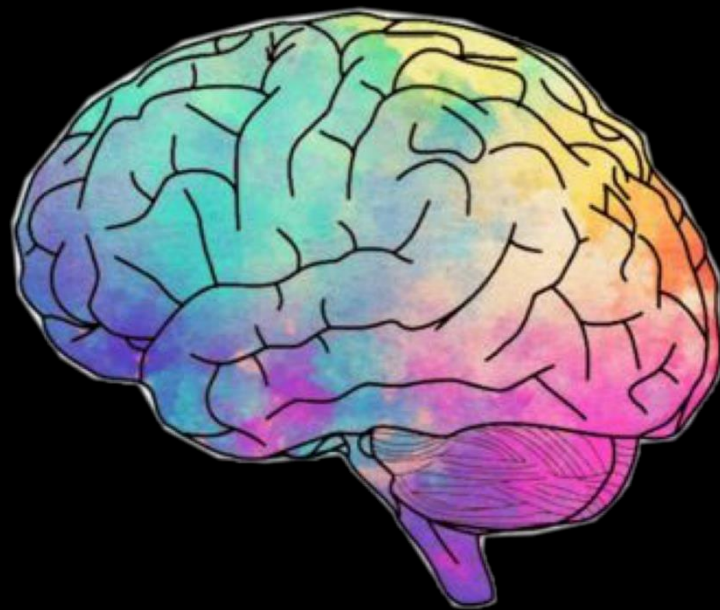
Leanne Armstrong, Jan Burrows, Dave Capener, Stuart Currie, Mat Clark, Priya Shanmugarajah, Iain Wilkinson & Paul Griffiths





The
University
Of
Sheffield.

Thank you!



Gluten Ataxia /
Encephalopathy

TG6?



Brain

Gut

Celiac Disease
(clear enteropathy)

TG2



**Gluten
Sensitivity**

Skin



Dermatitis Herpetiformis

TG3

