

Advances in ageing and dementia in people with learning disabilities

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Outline

- Context
 - Diagnosis
 - Presentation and prevalence of dementia in people with ID
 - Understanding brain mechanisms and developing treatments
- Neurodevelopmental syndromes
 - Down's syndrome
 - Prader-Willi Syndrome
 - Tuberous sclerosis
- Service developments
 - What services are needed
 - The importance of social care
 - Interventions

The challenge of diagnosing dementia

The application of established diagnostic criteria to a population with pre-existing cognitive and functional impairments and disabilities and additional co-morbidities

Diagnostic criteria for dementia

A. The development of multiple cognitive deficits manifest by both:

1. Memory impairment (new information)
2. One or more of the following cognitive disturbances:
 - a) Apraxia (inability to undertake complex tasks)
 - b) Agnosia (inability to recognise or identify objects)
 - c) Disturbance in executive function (e.g. planning etc)

B. Significant impairment in function

C. Gradual onset and declining course - several **possible causes**

The importance of establishing change from baseline

- Previous information on function (Life story books etc)
- Screening and diagnostic assessment (DSQ, TSI, DMR, DSDS)
- Retrospective diagnostic assessment (CAMDEX informant interview)
- Longitudinal cognitive and functional assessments

Dementia in people with ID (without DS)

- N = 222 (60 years or older)
- ICD-10 RDC criteria
- DSM-IV (dementia and sub-groups e.g. vascular)
- DC-LD (Royal College Psychiatrists)
- NINCDS-ADRDA criteria for Alzheimer's disease
- Lewy body criteria
- Fronto-temporal dementia criteria

Two stage epidemiological study of dementia (Becoming Older with LD – BOLD Study) Prevalence of dementia in ID using different diagnostic criteria
Strydom et al 2007 BJ Psych 191, 150

Dementia in people with LD (without DS)

Strydom et al 2007

- 222 people with LD 60 years or older
- 60 screened positive
- 29/60 positive for at least one set of diagnostic criteria
- 29/222 (13%) +ve for dementia

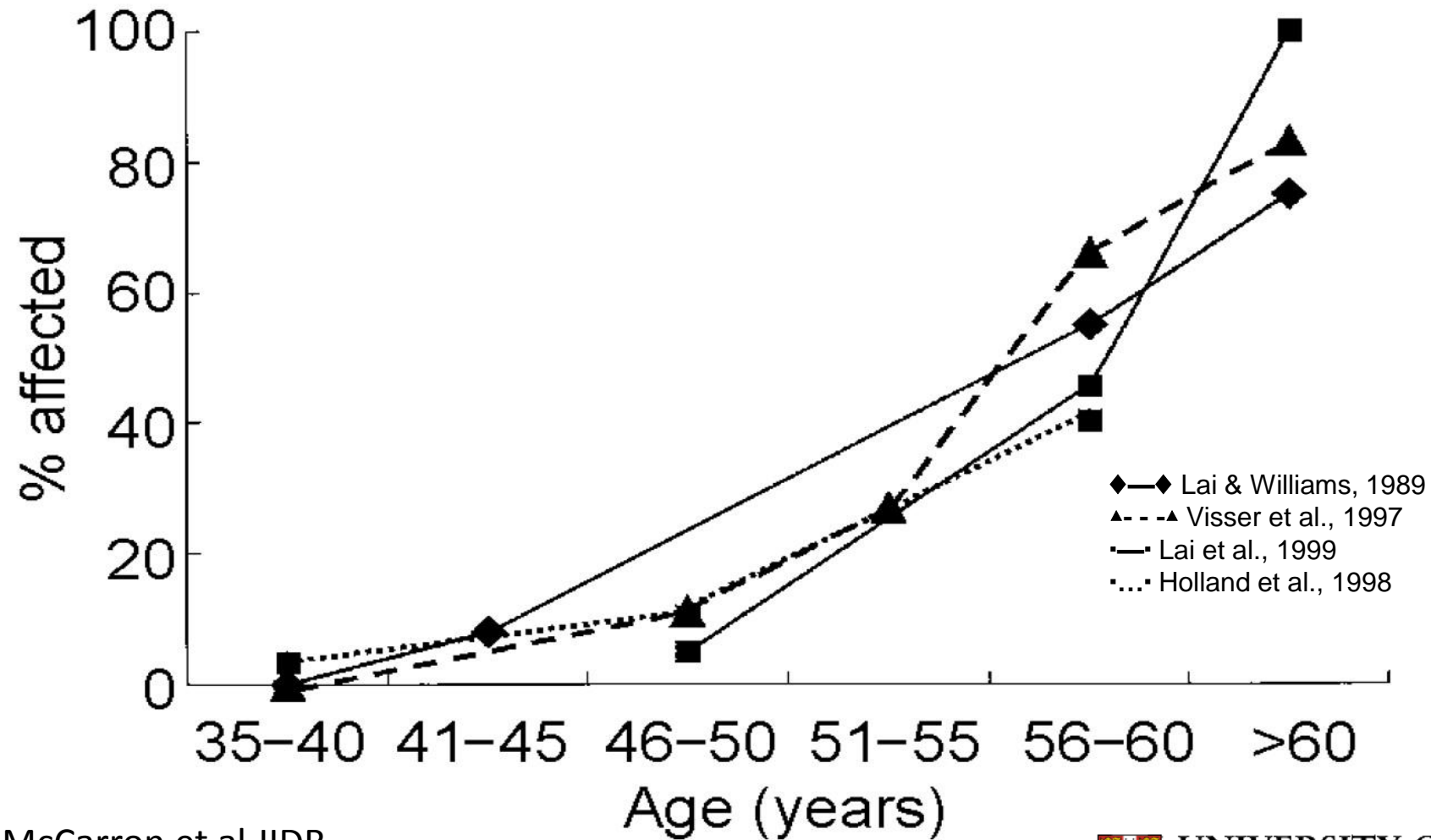
- Alzheimer's; Lewy body; fronto-temporal dementias

- Presenting symptoms (N=26)
 - General loss of function (13/26)
 - Behavioural and emotional change (4/26)
 - Reported deterioration in memory (rare) (2/26)

The special case of people with Down's syndrome

- Unique risk for dementia due to Alzheimer's disease
- Evidence of premature ageing
- Amyloid cascade hypothesis
- Recent advances
 - Availability of combined MRI/PET scanning (Pittsburgh Compound B)
 - Importance of biomarkers for dementia
 - Potential for preventative treatment

Age-specific risk of dementia in people with Down syndrome



See recent study McCarron et al JIDR – rates of dementia reach 97% aged 50+

Schupf, N et al; BJP 2002;180:405-410



Images courtesy of the UK DSA



From clinical studies to prevention

Clinical

An understanding of the presentation and course of dementia in people with DS and the ability to make an accurate diagnosis.

Basic neuroscience and molecular biology

New technologies now enable the investigation of the underlying brain mechanisms that result in brain cell death and dementia

Partnerships

Clinicians, researchers, people with DS and their families and others who support them are all essential partners if treatments are to be developed and tested - people with DS value being part of research

‘Together’

www.youtube.com/watch?v=pB7iqWUXQIM&feature=youtu.be

Ageing in people with Down syndrome: a research journey

- Observations from the early 1900's of brain related changes similar to those first described by Alzheimer
- Although life expectancy has improved still less than that found in the typically developing population
- Increased risk of age-related illnesses earlier in life
 - Skin changes
 - Sensory impairments
 - Thyroid disorders
 - Menopause
 - Physical exercise and obesity
 - Dementia (Alzheimer's disease)

Physical activity of people with DS – evidence for an age-related abnormality of function

152 people with ID aged 12 to 70 years (79 people with DS)

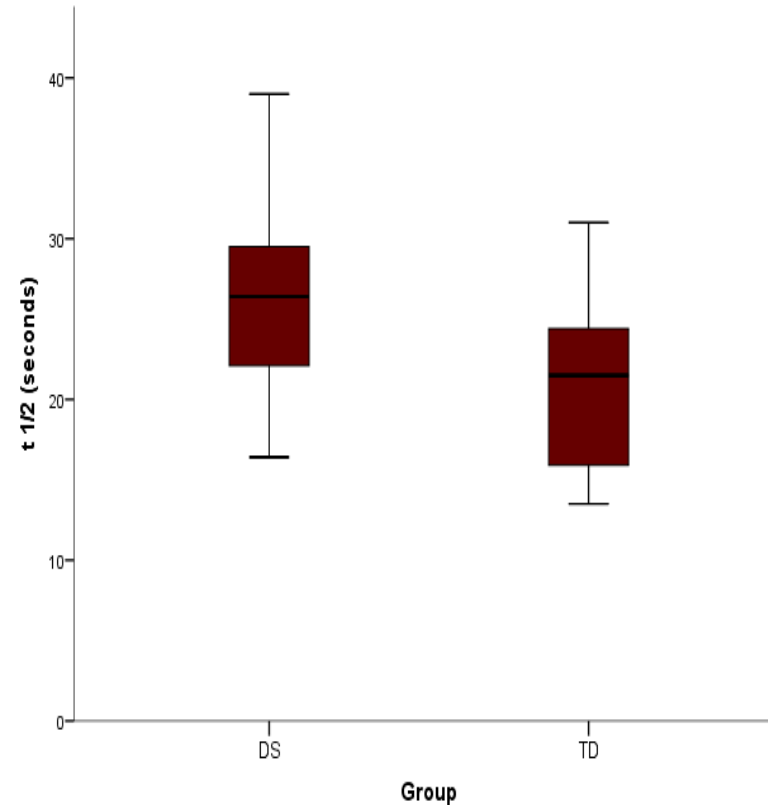
Physical activity levels were measured using an accelerometer (Actigraph GT1M) worn for 7 days

Findings

- No individuals with ID met current UK Government recommended levels of physical activity
- People with DS engaged in significantly less physical activity than people with ID not due to DS
- Levels of activity in people with DS were lower with increasing age than people with ID not due to DS

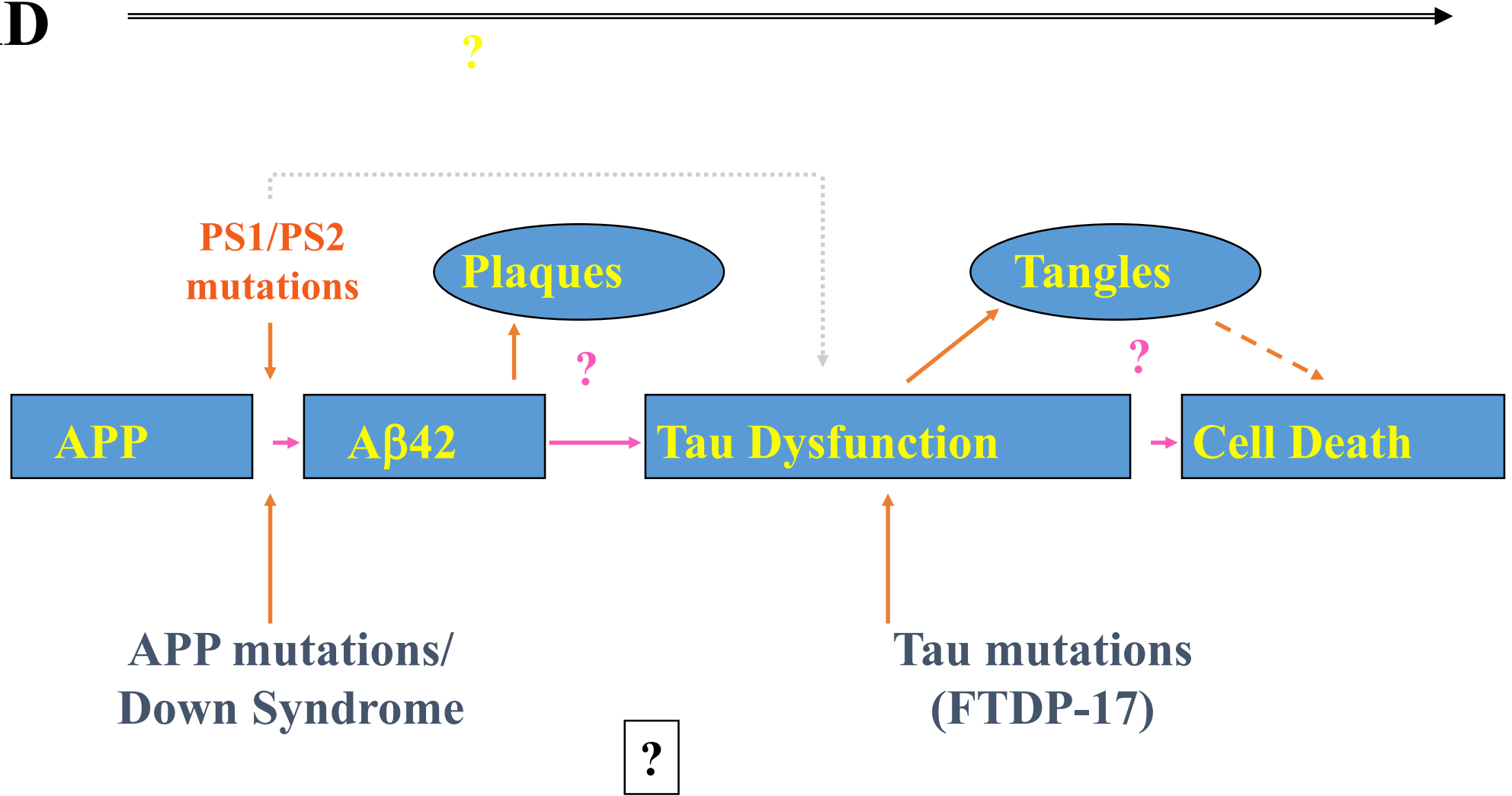
Mitochondrial function in people with DS

Using a form of imaging, magnetic resonance spectroscopy (MRS), the time taken for energy levels in muscle to recover (phosphocreatine recovery time) after physical activity was measured. People with DS had a slower recovery time than in a control group of similar age and fitness.



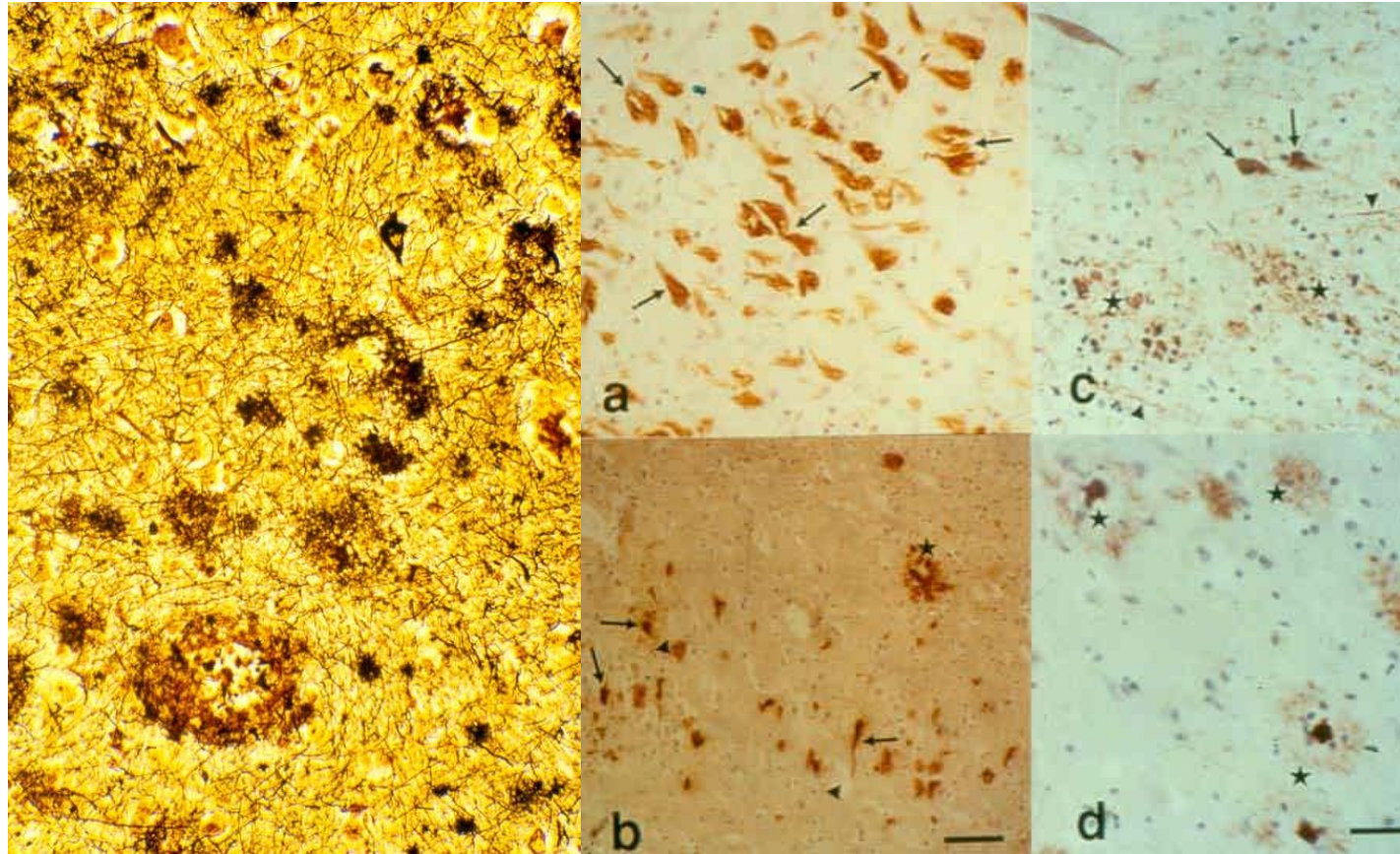
Phillips et al (2013) Defective Mitochondrial Function In Vivo in Skeletal Muscle in Adults with Down's Syndrome: A 31P-MRS Study. *PLoS ONE*, 8(12): e84031. doi:10.1371/journal.pone.0084031

AD



AD: the Amyloid cascade Hypothesis Hardy and Higgins, 1992

Down syndrome: Neuropathological Hallmarks



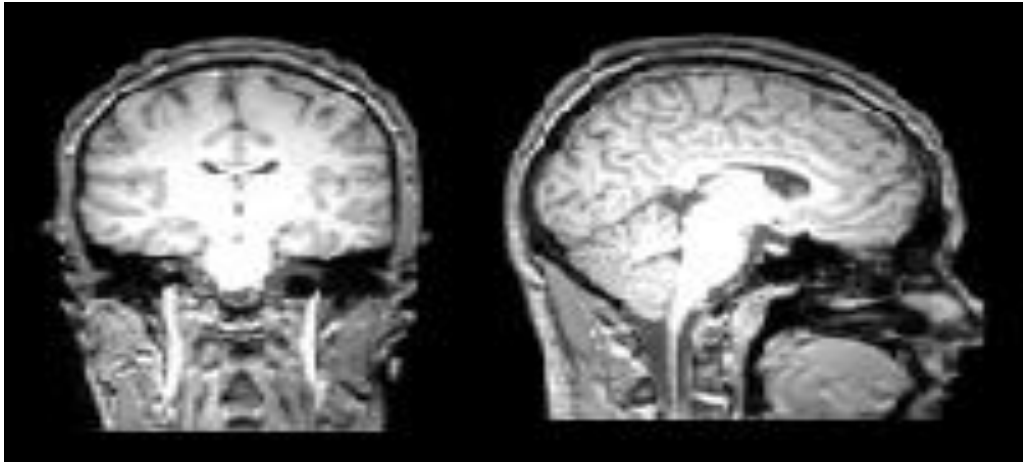
First reported by Struwe et al 1920



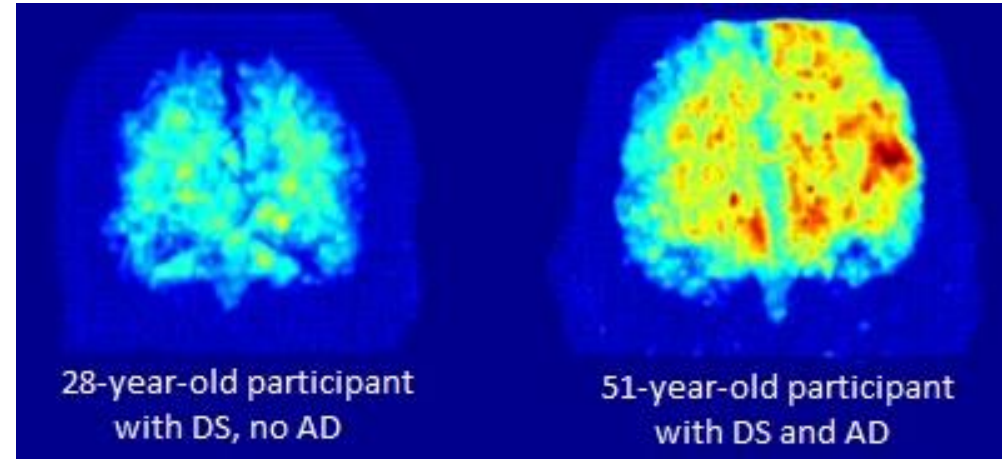
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The use of neuroimaging

MRI
Structure



PET
Amyloid



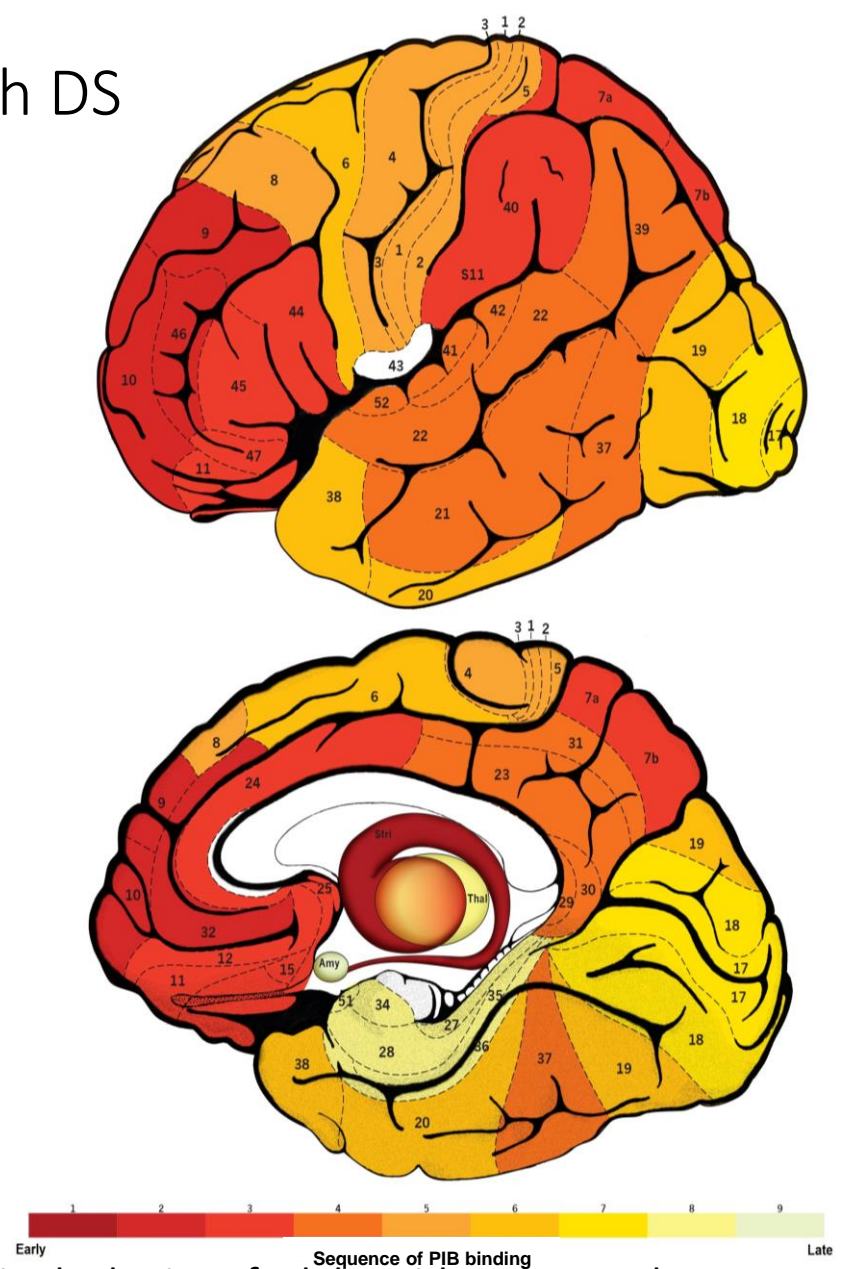
What is the relationship between brain amyloid accumulation, the loss of brain tissue and the development of dementia (Alzheimer's disease)?

Sequence of PIB binding in adults with DS

Nine stages of PIB binding were identified:

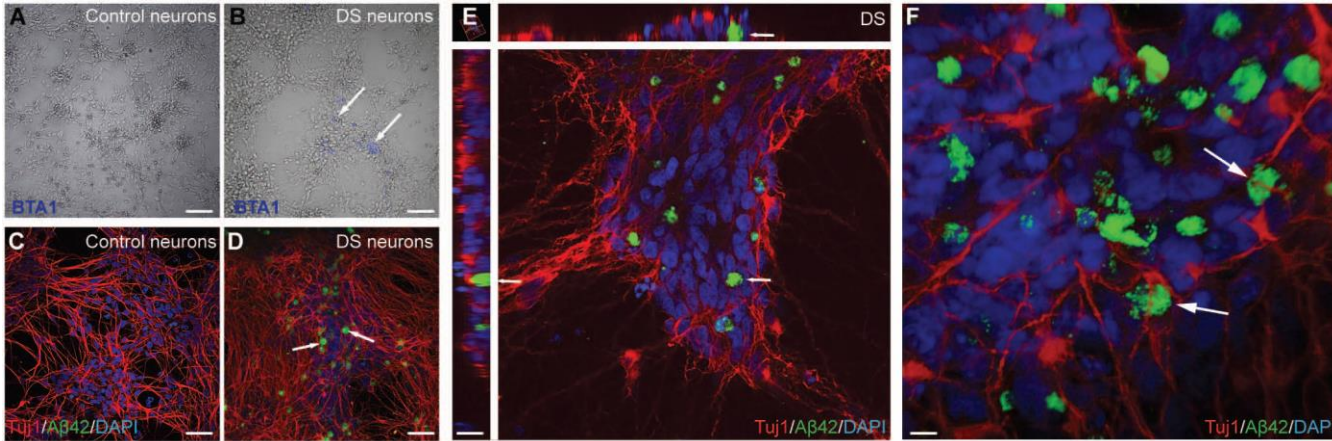
- (1) striatum
- (2) dorsal prefrontal and anterior cingulate cortex
- (3) ventral prefrontal cortex and areas of the parietal lobe including the superior parietal lobule
- (4) most of the lateral temporal cortex and the rest of the parietal lobe
- (5) sensory and motor areas
- (6) associative visual and pre-motor cortex, and the rest of the temporal lobe
- (7) occipital lobe
- (8) thalamus and the medial temporal lobe
- (9) amygdala.

None of the participants were PIB positive in the hippocampus.

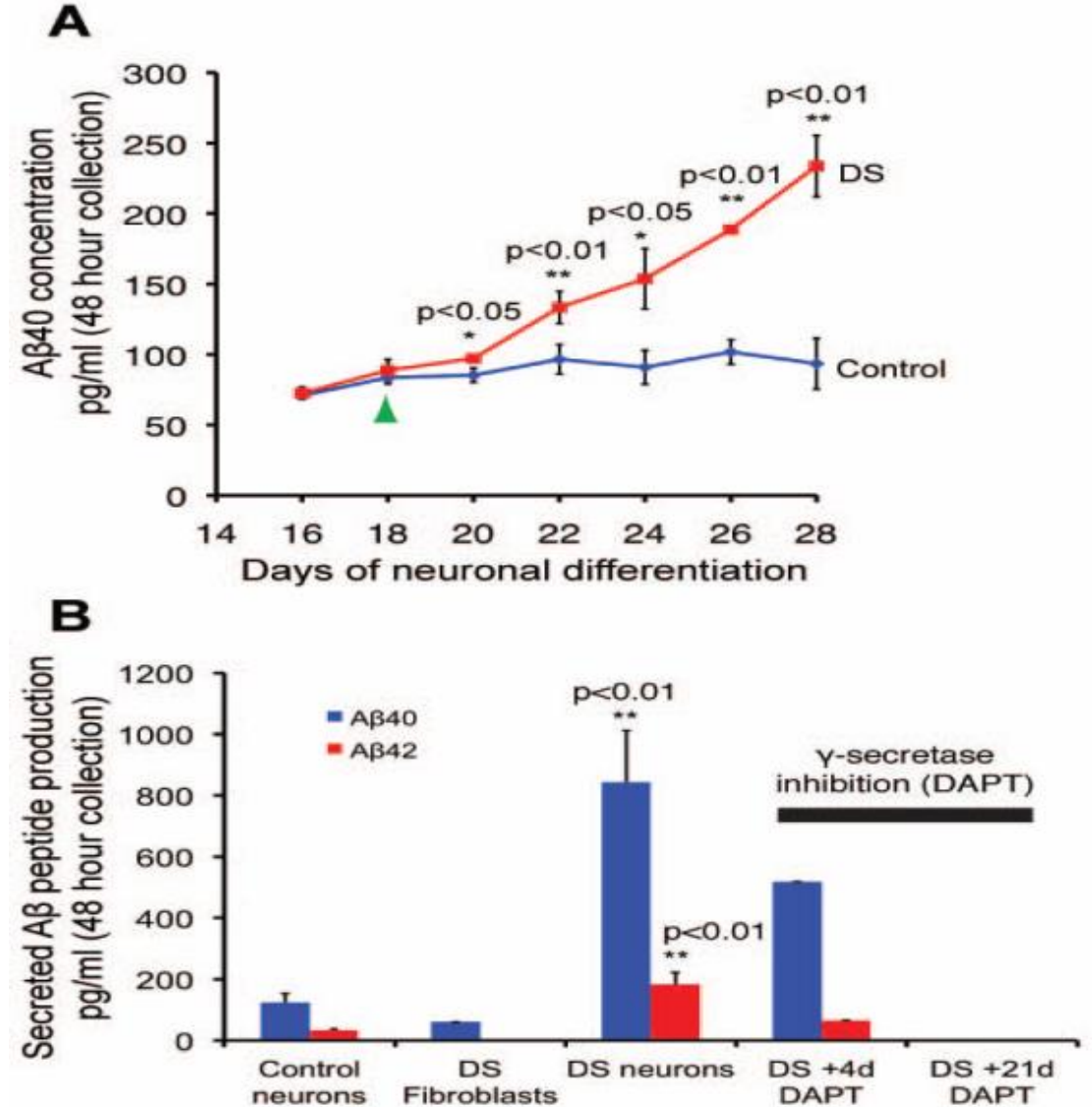


Annus et al (2016). The pattern of amyloid accumulation in the brains of adults with Down syndrome. *Alzheimer's & Dementia*, 12(5), 538-545.

Expression and localisation of APP protein (green)



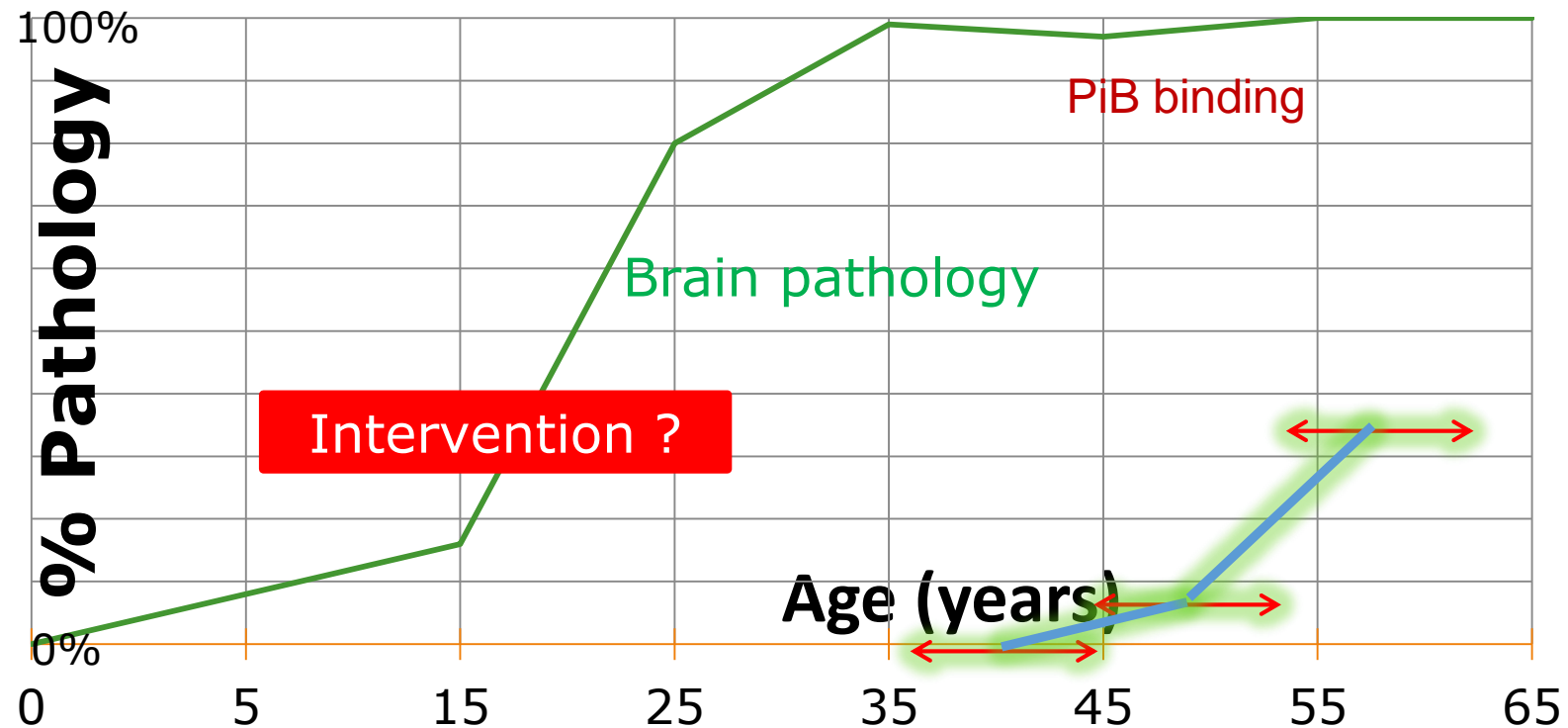
A human stem cell model of early AD pathology in DS
 Yichen Shi et al. Sci Transl Med (2012)
 DOI: 10.1126/scitransmed.3003771



Looking ahead in DS

Neuropathology versus age in Down's syndrome

(approximated from Mann et al., 1989)



Apoptosing retinal cells as a proxy marker of amyloid deposition

Rafii et al., 2015 showed amyloid-beta plaques in the retina of people with DS

Amyloid-beta is neurotoxic in plaque form and can induce apoptosis (Elmore, 2007)

Apoptosis

- *Increased rates of apoptosis are seen in degenerative diseases*
- *Toxicity can induce apoptosis and has a trigger effect in surrounding cells*

Decreased phagocytic function has been reported in DS (Barkin et al., 1980)

Ineffective clearing of apoptotic cells in the retina could lead to increased thickness



Rafii et al., (2015) retinal image from a person with DS demonstrating positive amyloid plaques

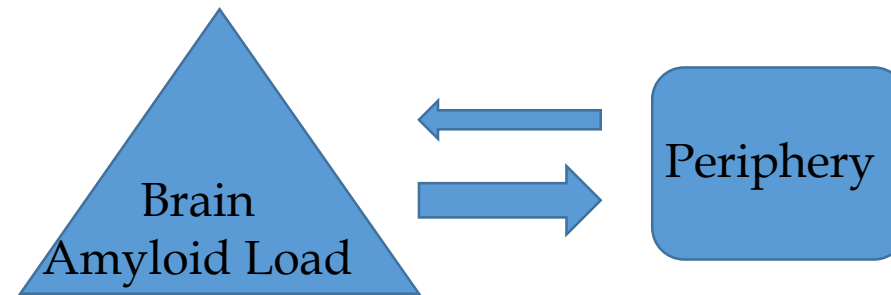
The challenge of 'prevention' trials

The importance of biomarkers

- Any substance, structure, or process, that can be measured in the body or its products and influence or predict the incidence of outcome or disease
- Clinical and proxy outcome measures
 - EEG (MMN)
 - Retina (A β thickness and apoptosis)
 - Physical activity and mitochondrial function (MRS muscle)
 - Brain Predicted Age
 - CSF A β
 - Neuroimaging (A β binding, structural change, connectivity)
 - Cognitive decline
 - Dementia

Treatments acting on amyloid and/or its pathway

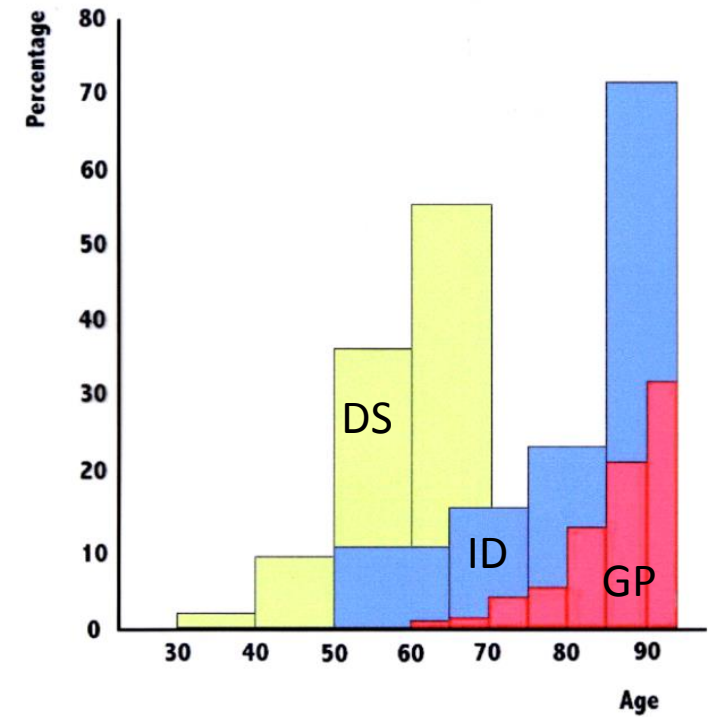
- B-secretase and γ -secretase inhibitors (reduce production of toxic $A\beta$)
- Active and passive immunization against $A\beta_{42}$
- Antibodies
 - Solanezumab
 - Gantenerumab
 - Crenezumab
 - Aducanumab



- Anti-inflammatory agents (NSAID)
- Statins

So far...

- Increased age-related prevalence rate of dementia in older people with ID
- Presentation may be atypical
- Different clinical criteria may differ in sensitivity
- Patterns of presentation and course meet criteria for different causes of dementia



Research questions?

Does the non-specific effect of pre-existing ID predispose to a future risk of dementia?

Reserve capacity

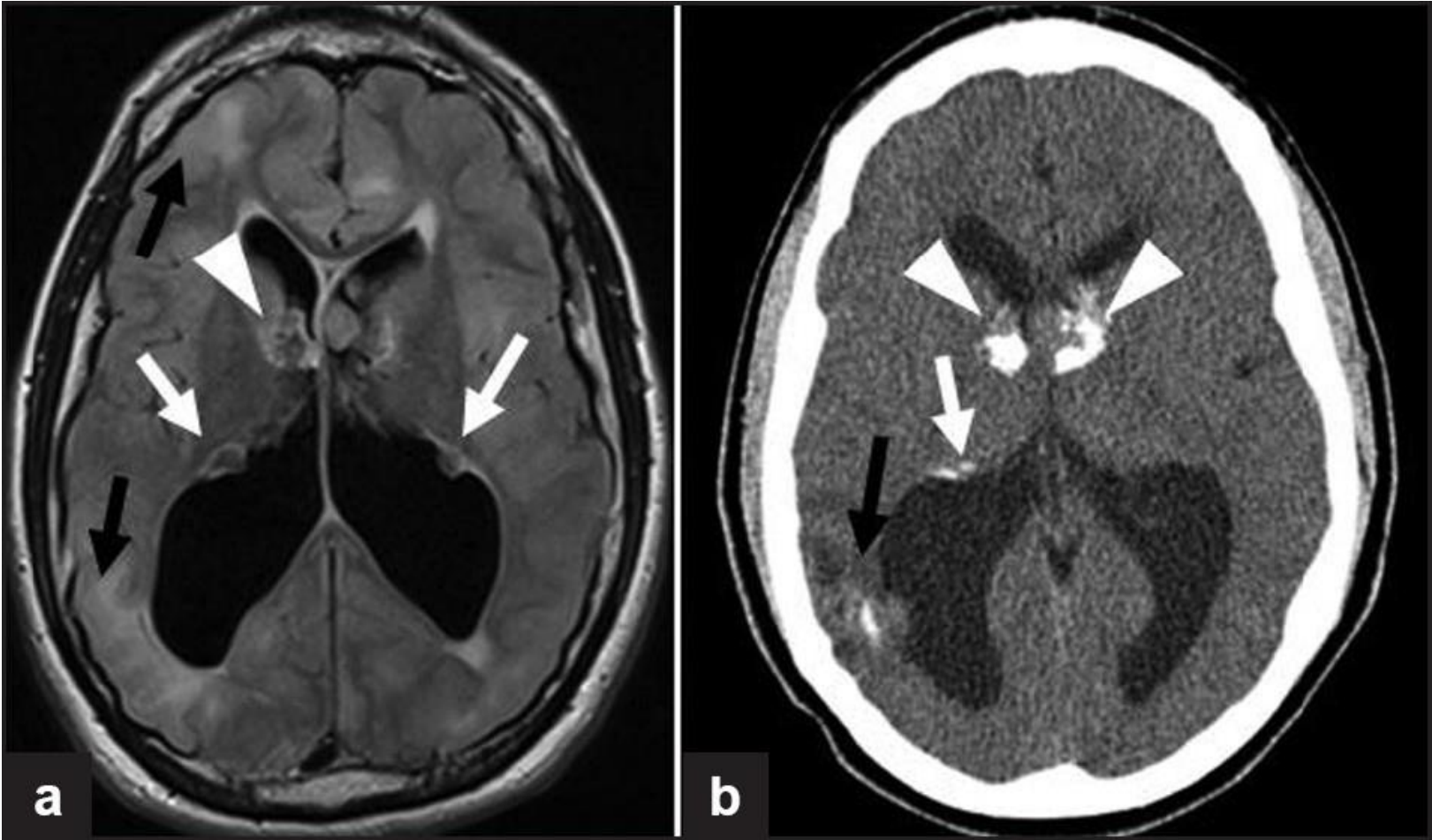
Does atypical development increase risk of subsequent 'dementia related brain changes' (cf ABI)?

Do adults with other neurodevelopmental syndromes have syndrome specific prevalence risks for dementia – PWS, TS, Sanfilippo, Williams, Retts?

Decline in people with TS

- Changing brain pathology
 - Increase in tuber size
 - Development of hydrocephalus
 - Brain malignancy
- Severe renal failure (not recognised)
- Use of mTOR inhibitors (rapamycin)

Tuberous sclerosis



Ageing in PWS

- Reduced life expectancy
- High risk of psychosis in those with mUPD
- ? Evidence of cognitive decline in older (aged 40+) with mUPD or the equivalent.
 - Diagnostic challenge
 - Relationship to the propensity to psychotic illness
 - Role of relative GH and sex hormone deficiencies

Larson et al 2016

Future clinical challenges

- The central role of social care in supporting a healthy life style and in the detection and treatment of age-related illness such as dementia
- Access to services that enable the early and accurate diagnosis of the cause of apparent functional decline in people with ID
 - Cognitive and functional screening
 - Differential diagnosis
 - Post diagnosis support (Dementia and people with LD – BPS and Royal College Psychiatrists 2009)
- Better understanding of age-related risks of dementia within the heterogeneity of the ID population-service planning
- Policies and practice fit for purpose
- Services that can respond to changing need in this population

Some key clinical issues in the support of people with ID and dementia...

- Health
 - Reliable diagnosis of dementia (differential diagnosis)
 - Characterisation of changing cognitive and functional abilities
 - Diagnosis and treatment of comorbid physical and mental ill-health
 - Dementia specific treatments
- Family or social care environment
 - Philosophy of care (sound understanding of dementia)
 - Modifications of the physical environment
 - Respond to changing communication needs
 - Emotional support (including to the family)
- Other common issues
 - Pain
 - Sleep
 - Decision-making
 - End of life care (maintenance of dignity)

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Together

<https://www.youtube.com/watch?v=pB7iqWUXQIM&feature=youtu.be>