Williams syndrome

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Outline

- Introduce my PhD research with adults with Williams syndrome
- Adults 35+ years
- Behavioural and neuroimaging research

Focus of my PhD

- Work with older adults with WS

- We know much more about younger groups (children, adolescents, young adults)

- But we know very little in general about the ageing process with increasing age in WS

Access to participants

- Many older adults with WS are undiagnosed
- UK – currently ~100 members of the WSF over 40 years of age
- Research into the ageing process in WS problematic due to low numbers, logistics and funding required to visit these individuals

Theoretical / applied research

- My work is theoretical
- Lab-based (though was mainly conducted in the participants' homes)
- Rather than in day-to-day settings
- Need to understand the processes (behavioural and neuropsychological) that underpin every day behaviours
- Initial research investigated premature cognitive ageing
- Subsequent studies focussed more on attention and inhibition

Is there evidence for premature ageing in WS?

- Physical characteristics indicative early onset of ageing
  - cataracts, skin ageing, early greying of hair
- Motor control problems associated with ageing process in typically developing older adults
- Early onset of Alzheimer's Disease <u>not</u> associated with WS (unlike Down syndrome)
- Two studies found decline in memory occurred chronologically earlier in WS compared with both typically developing adults and those with mild learning difficulties
- But no other research published with evidence for premature cognitive ageing in WS

Gaps in the literature

- Older adults with WS are included research, but paradigm specific, rather than focussing on ageing process
- How best to research ageing in WS?
- Look at specific memory processes affected by the typically developing ageing process
- Conduct similar experiments in order to see how individuals with WS perform

Associative memory

- 'Binding' independent pieces of information into one coherent representation
  - real life e.g. remember last time saw friend's mum was in the supermarket
  - lab based task – make associations between stimuli
    - e.g. horse/cart; lemon/orange; tree/chair; spoon/lamp
- Recollection – need to remember items in context with each other
- Familiarity – can 'know' the item without encoding
- Distinct brain distribution in activity
  - familiarity – frontal
  - recollection - centro-parietal

Associative memory, typical ageing, & WS

- AM – known to decline with older age in typically developing adults
- Item recognition (familiarity) - relatively spared
- Recollection places greater demands on attentional processes and episodic memory, problematic in WS
- WS – difficulties in 'binding' observed across the lifespan
  - Evidence from behavioural and neuroimaging research
- Familiarity - relatively spared but observe atypicalities in frontal neural response (greater activity to non-social stimuli cf. faces)
- But does not address issues relating to premature ageing in WS

Paired-associates paradigm

- Verbal task – semantically related (boot / shoe), unrelated (e.g. napkin / hill)
- Remember the word pairs
- Perform item- and associative memory tasks
- Two typically developing control groups
  – Chronologically age-matched adults (CA)
  – Older adults aged 65+ years (65s)

Verbal paired-associates stimuli

Related	**Unrelated**
Sandal / Slipper	Kettle / Dance
Boot / Shoe	Locker / Quilt
Doctor / Nurse	Team / Stone
Author / Poet	Forest / Infant
Sardine / Herring	Napkin / Hill
Mussel / Minnow	Shield / Cigar
Hand / Thumb	Nail / Farm
Puddle / Pond	Bump / Wing

Verbal item recognition

- At test – shown pair of words, only one presented at study
- Have to identify which word they saw previously

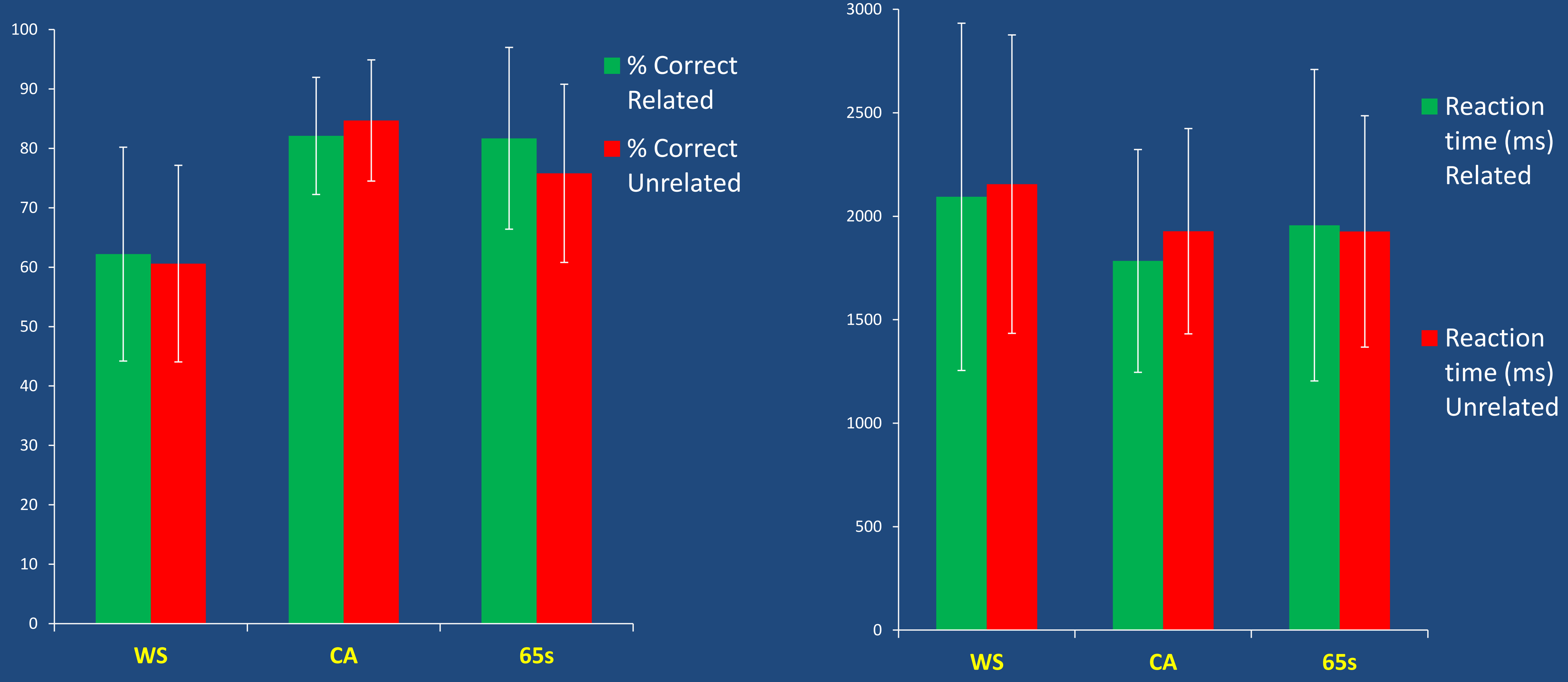
SONG / TUNE

HAND / FOOT

BUILDER / **CIGAR**

PATTERN / **FARM**

Verbal item recognition results

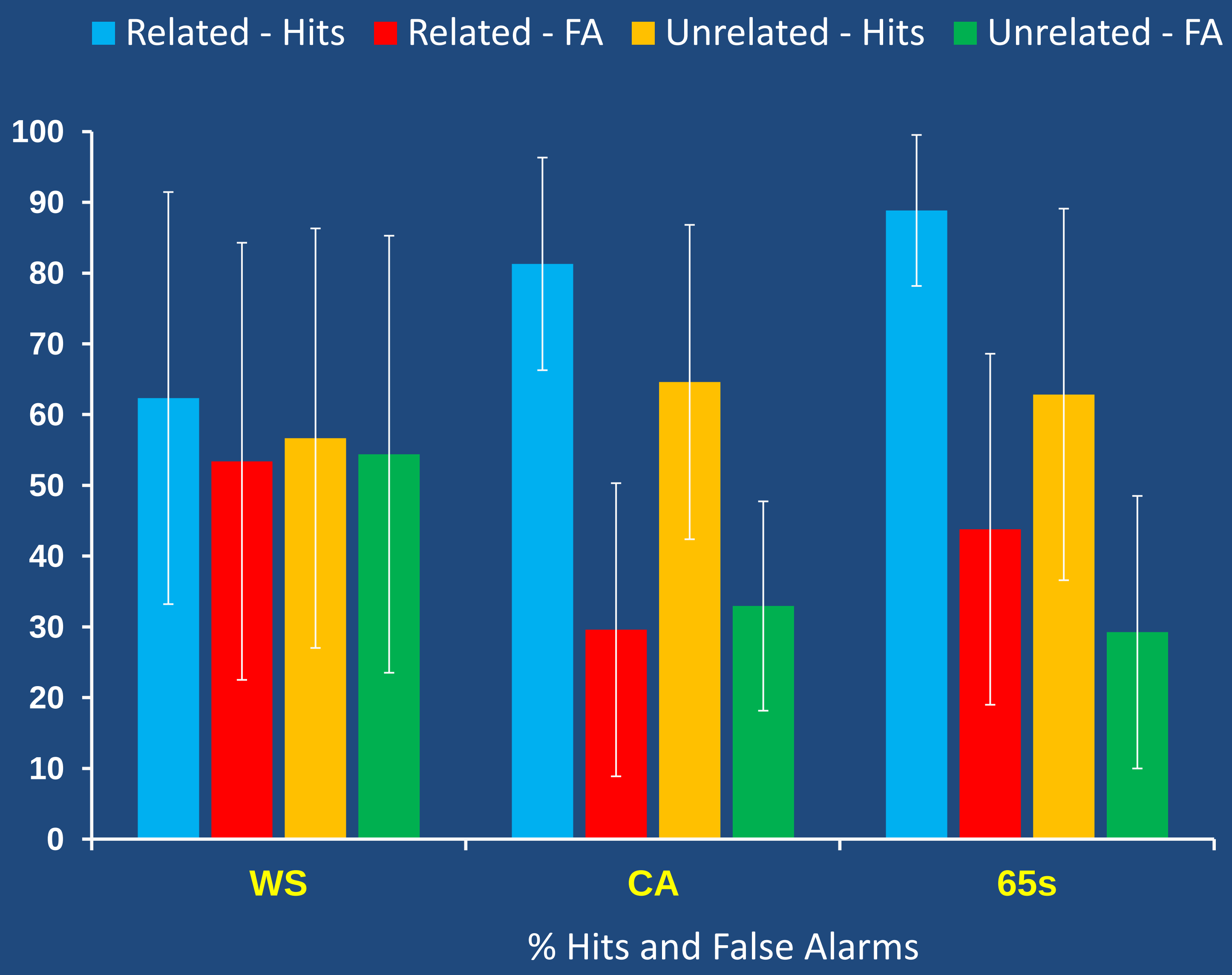


Verbal associative memory

- At test, participants shown pairs of words, either intact or recombined from study
- Have to identify whether they have seen the pair before or not

Intact	**Recombined**
Boot / Shoe	Author / Nurse
Team / Stone	Sardine / Minnow
Puddle / Pond	Kettle / Quilt
Sandal / Slipper	Doctor / Poet
Forest / Infant	Locker / Hill
Bump / Wing	Mussel / Herring

Verbal associative memory - results

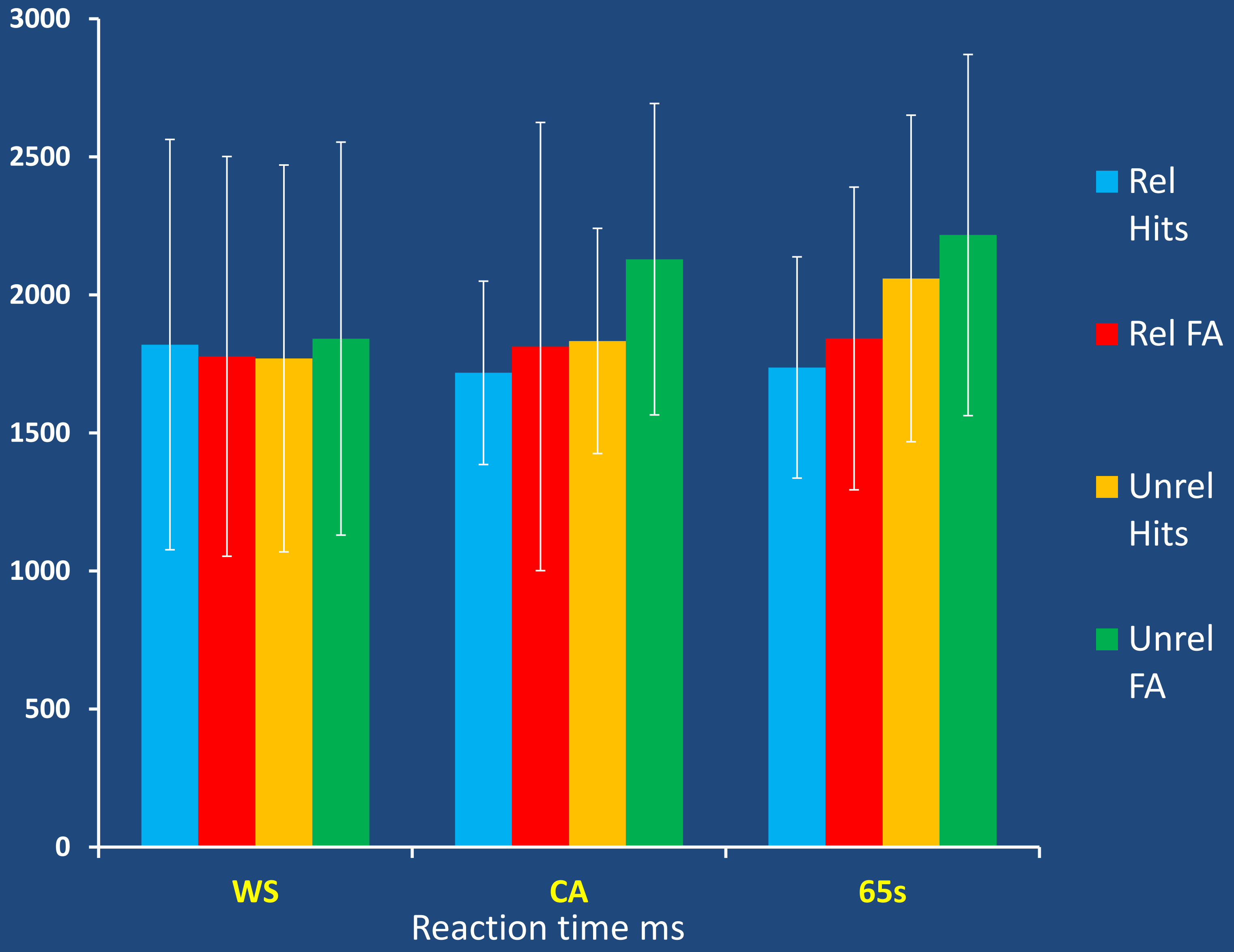


WS group found this task difficult

Performance at chance in both conditions

No comparable performance with either the CA or 65s groups

Verbal associative memory – reaction time



No overall difference in reaction time between the groups

WS group – no difference in RT across conditions

Control groups showing a trend for longer evaluation of rearranged pairs in the Unrelated condition

Visual paired associates task

- 48 picture pairs, all semantically unrelated
- Need to make spontaneous semantic encoding strategy

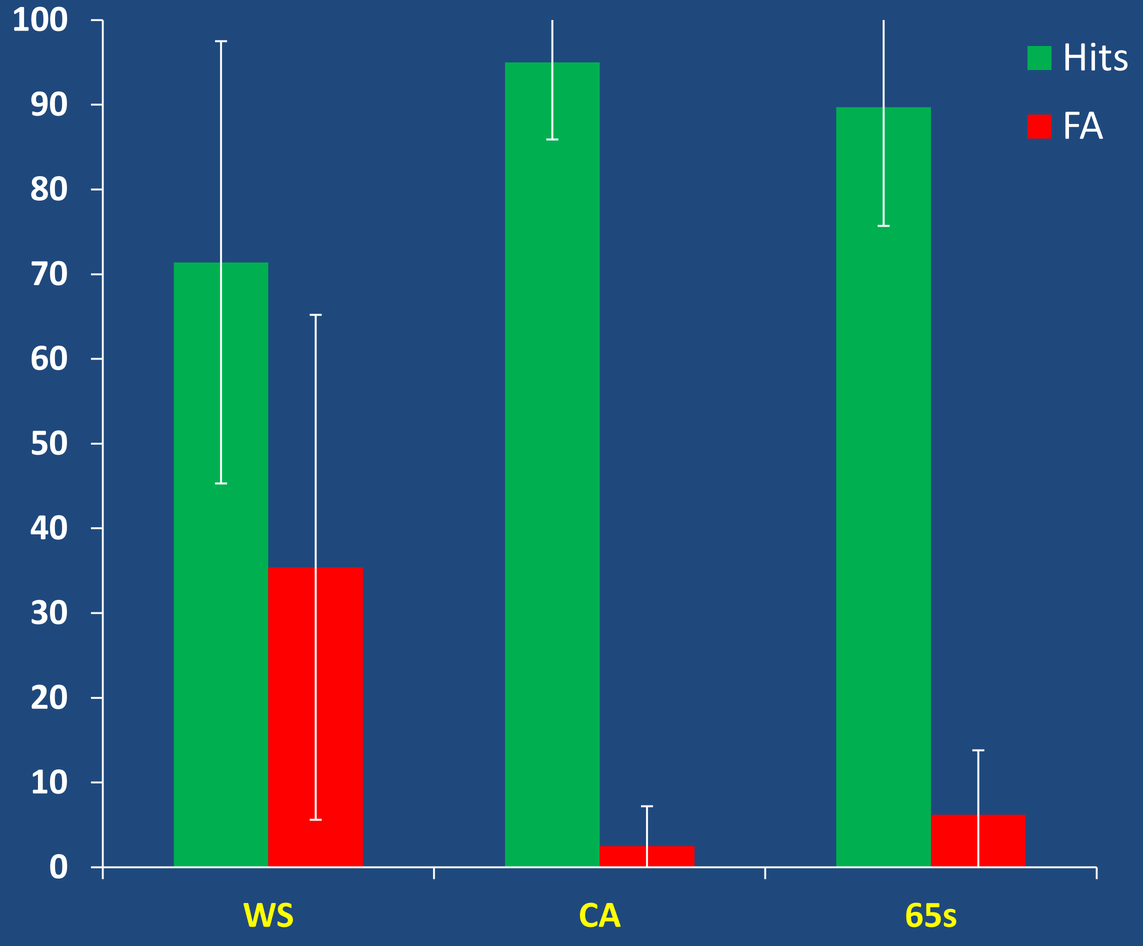
Visual item recognition

- Shown individual pictures one at a time
- Need to identify if they have seen the picture or not (familiarity)

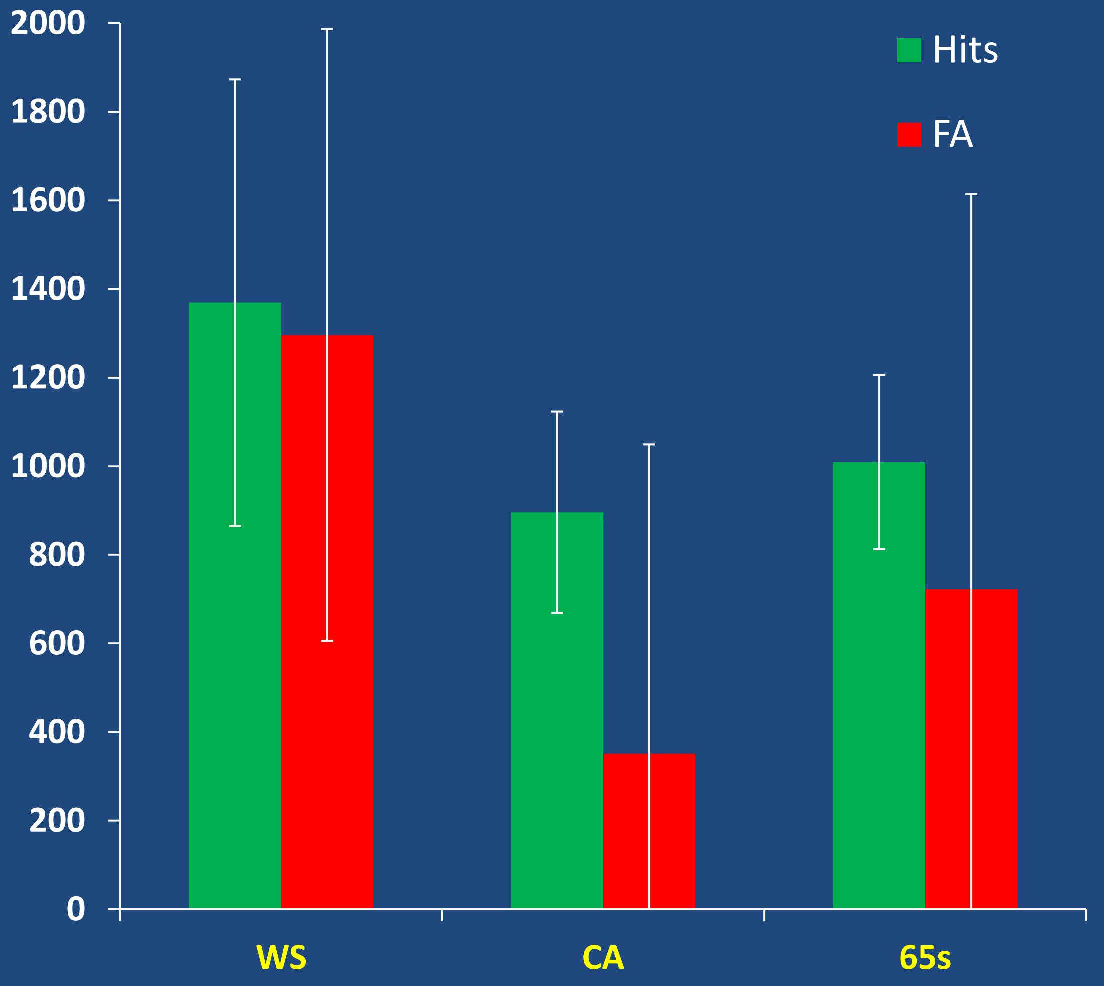
Yes **No**




Visual item recognition results



% Hits and False Alarms

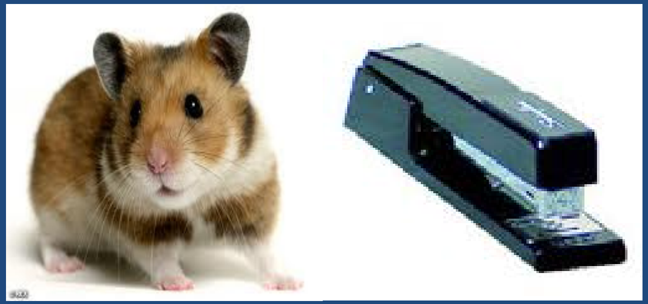


Reaction time (ms)

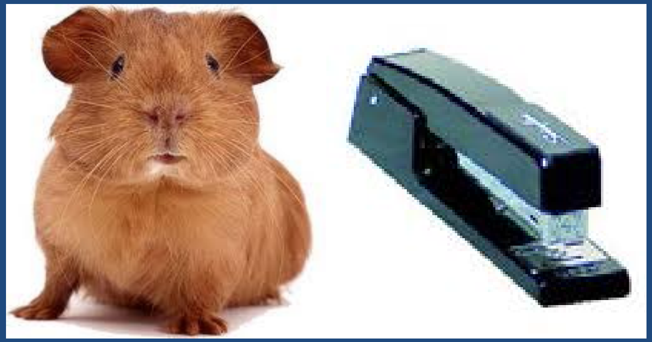
Visual associative memory

- Shown pairs of pictures – identify if seen the pair or not
- Some intact from study phase, some recombined with very similar image

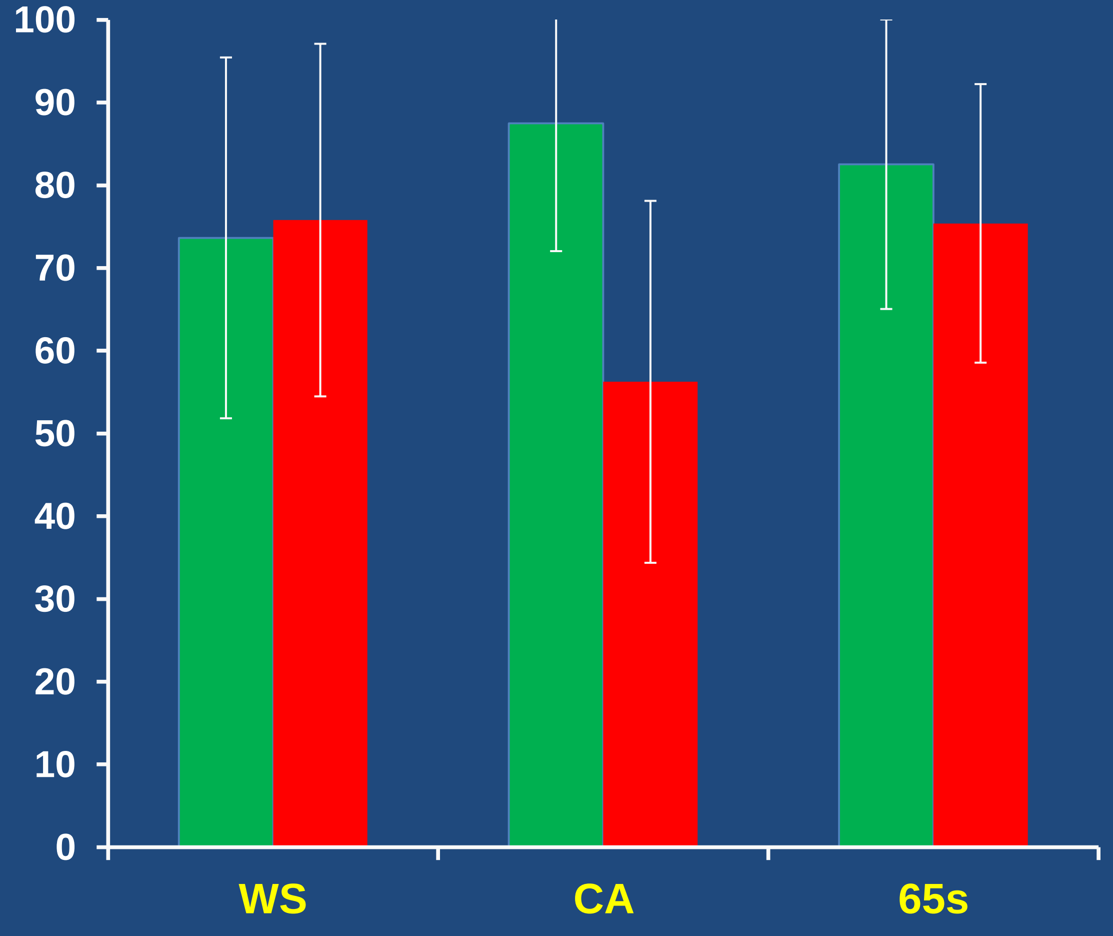
Study



Test (recombined)



Visual associative memory results



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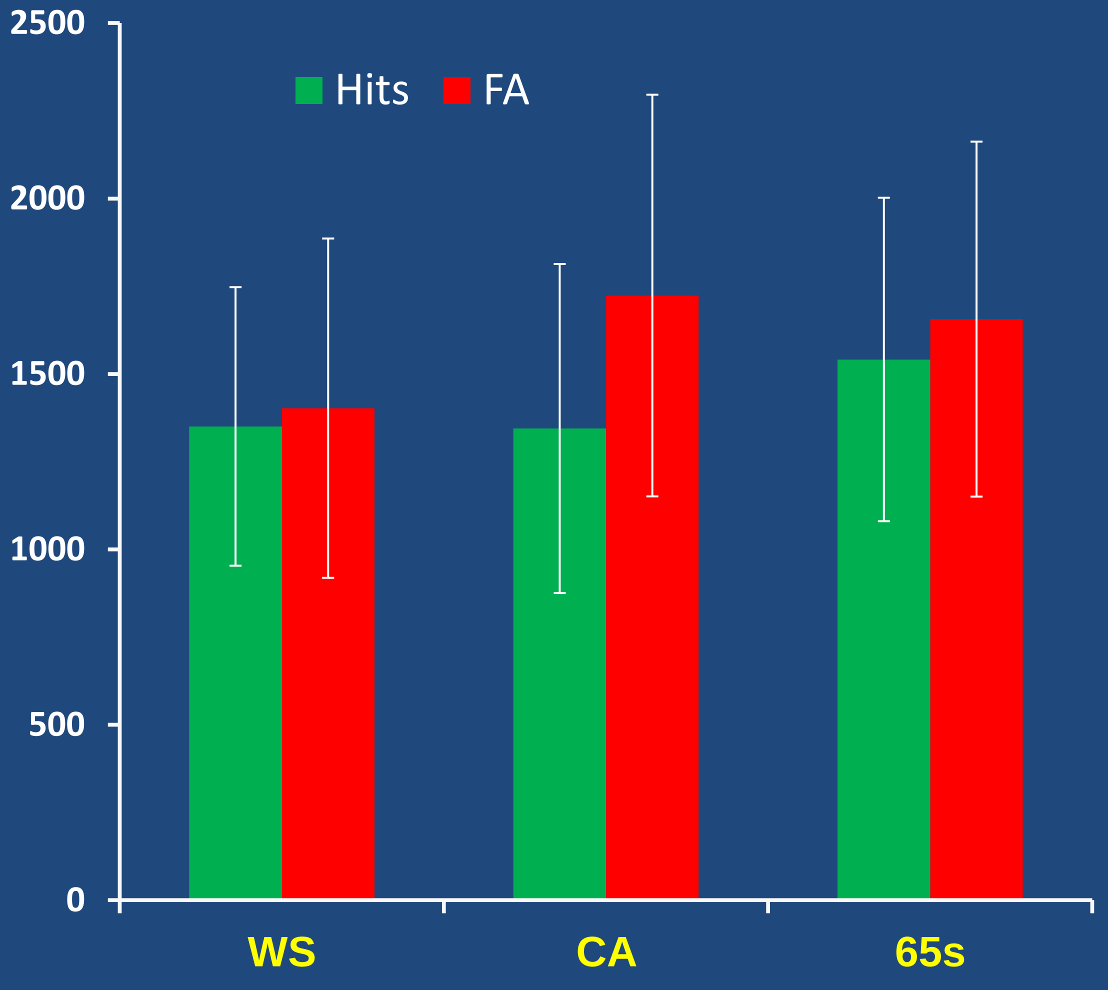


Reaction time (ms)

Summary

- Difficult tasks for WS group – require focussed attention
- Overall impairments on attention
  - verbal task, hits at chance level
- Visual item recognition
  - greater FA rate and slower RT – deficits in error monitoring
- Verbal AM task – unable to benefit from semantic memory
- Visual AM task – unable to form spontaneous semantic encoding strategies
- Would adults with WS benefit from semantic support at encoding?

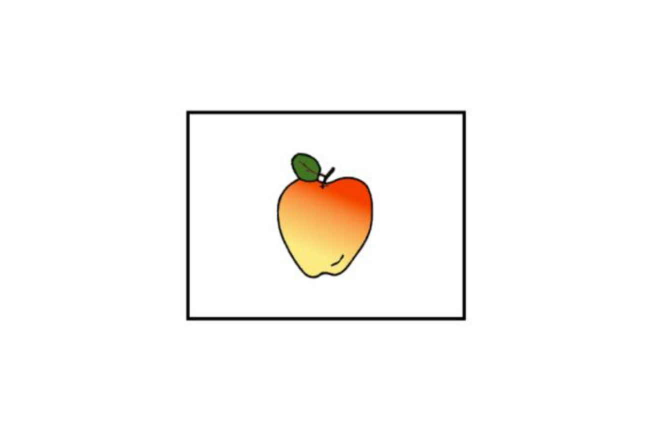
Semantic support (Levels of Processing)

- LoP – greater recall for items encoded with deeper LoP than shallow
- Deep – e.g. focus on semantic categorisation (fruit / clothing / vehicle)
- Shallow – e.g. focus on perceptual features

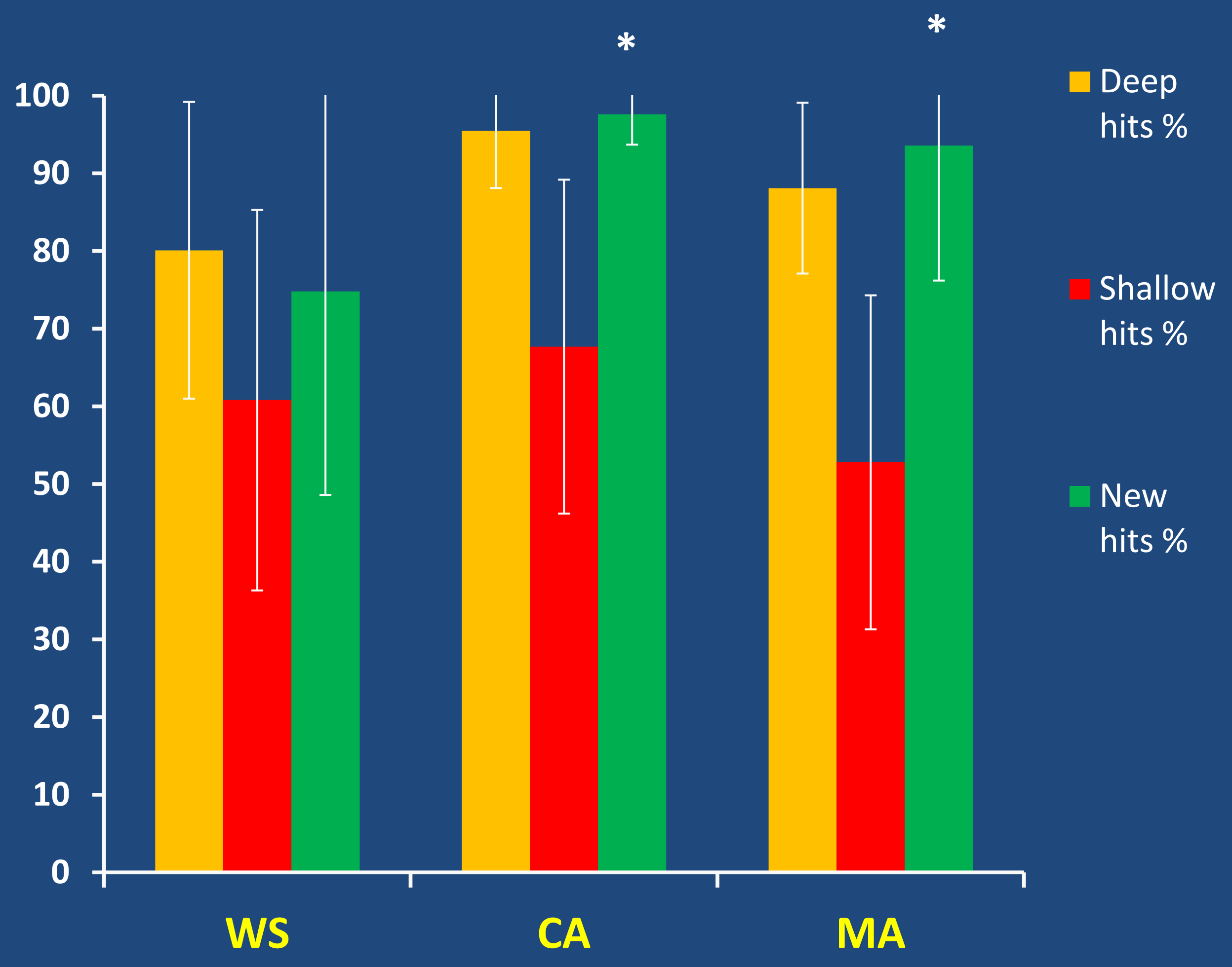
- Test whether adults with WS can benefit from LoP during encoding to facilitate recall on episodic memory task

LoP paradigm

- Individual items presented one at a time
- Preceded with either a deep or shallow encoding question
  - Is the next item a type of fruit / vehicle / toy (deep) ?
  - Is the next item in a frame (shallow)?
- Verbal '*Yes / No*' response
- At test – half seen / half new
- Button press response – '*Yes / No*'
- Controls –
  - CA (as before)
  - Children matched for verbal mental ability (MA)

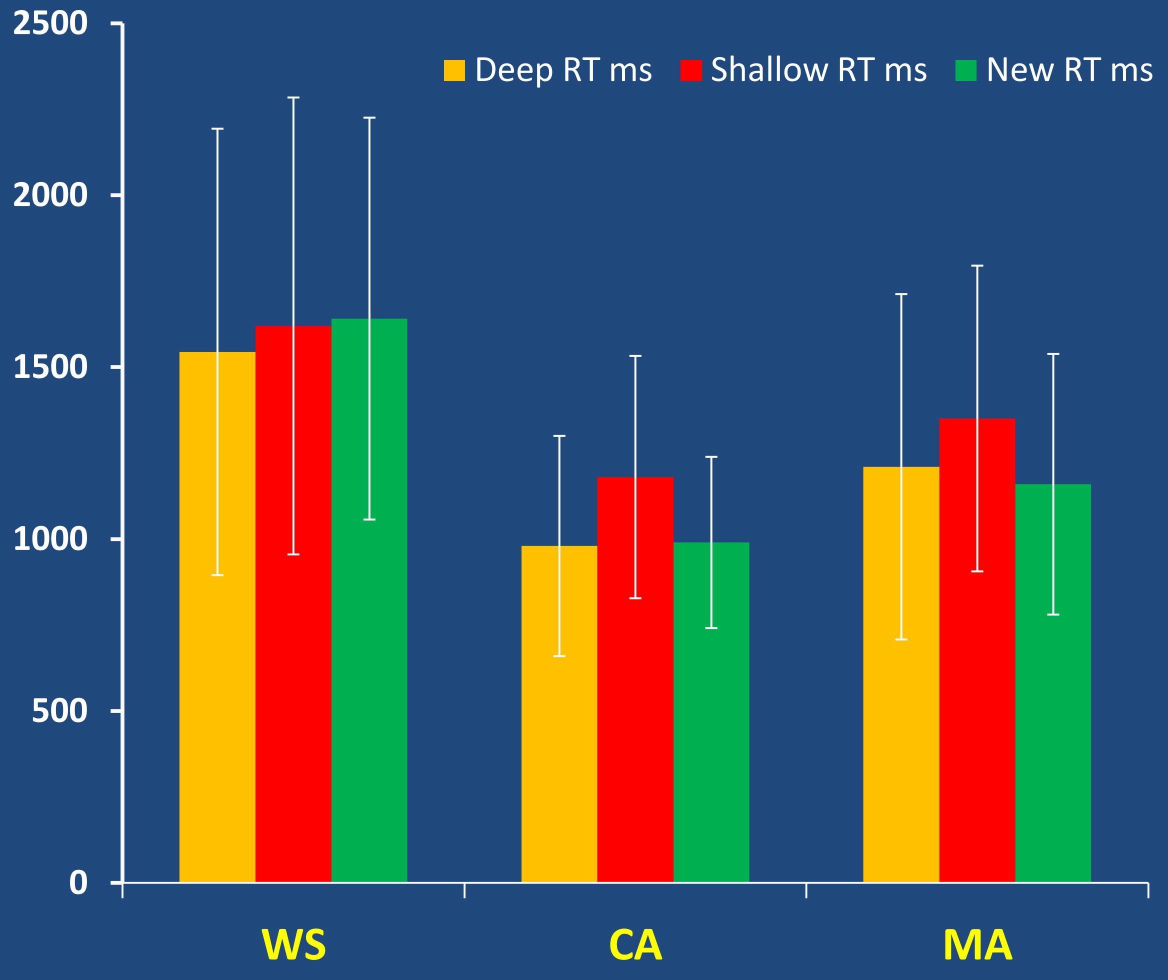


LoP results



Greer et al., 2014

% Hits and False Alarms



Reaction time (ms)

Summary

- WS can benefit from deep level of processing during encoding
- Hits same as MA group –are they performing same as mental age?
- Suggests performance due to learning difficulties – but need to be cautious with interpretation when not statistically significant
- Error monitoring –
  - difficulty rejecting new items, despite longer RT

What have these two studies told us?

- No evidence for premature cognitive ageing in this group of adults with WS
- More evidence for atypicalities in ‘binding’ – however paradigm may have been too challenging for WS
- WS <u>benefit</u> from semantic support during encoding
- Lower hit rates and increased RT to false alarms further evidence for deficits in processes (attention / inhibition) controlled by frontal brain regions

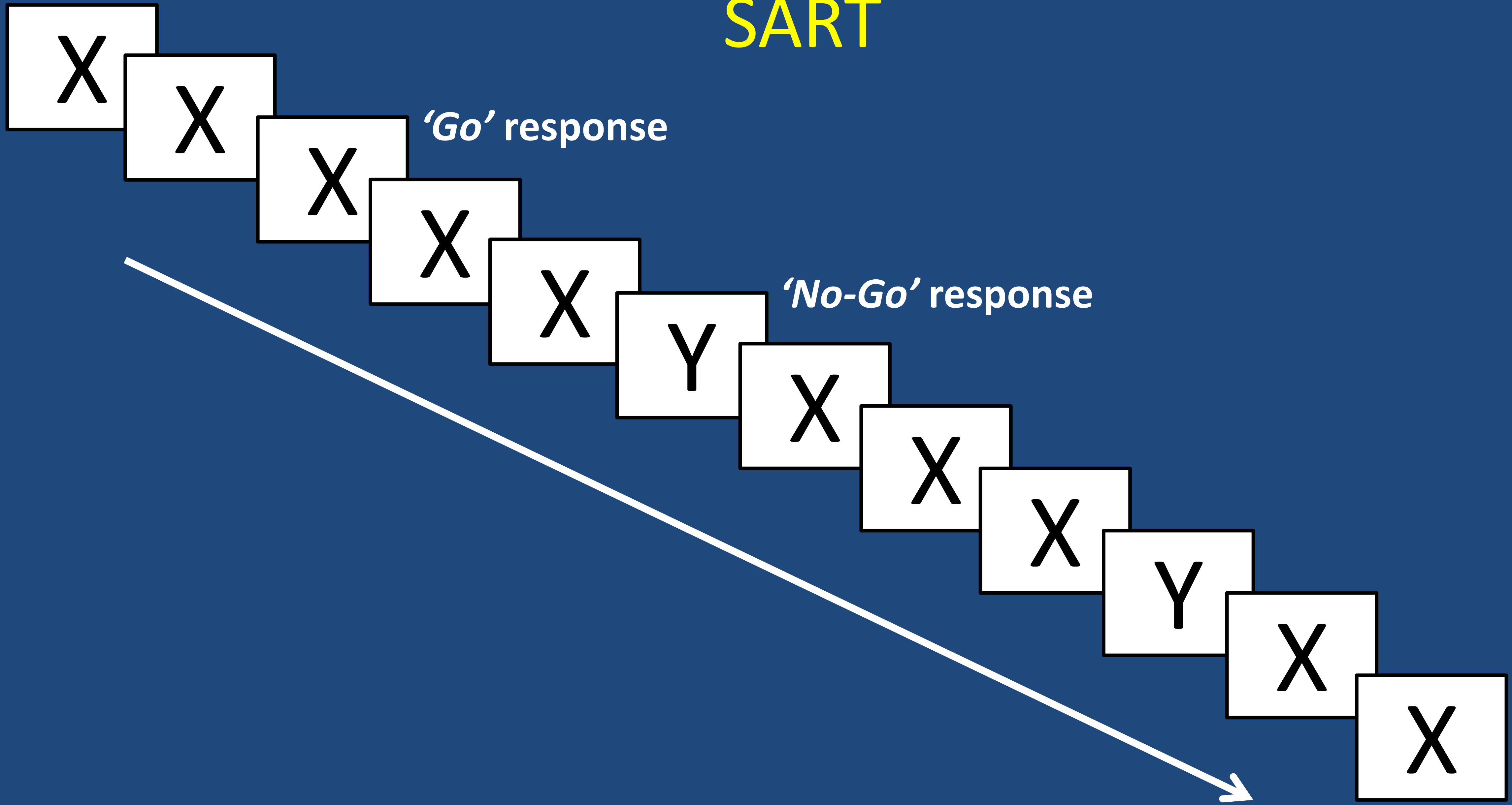
Frontal lobe atypicalities

- Neuroimaging research evidence for differences in frontal brain regions in WS
- fMRI research (using brain scanner to) – deficits in frontal network responsible for response inhibition
- EEG (measuring cortical electrical signal on surface of the brain) - unusual profile also linked to response inhibition
- Deficits in inhibitory control can be linked to behavioural, social and cognitive profile associated with WS

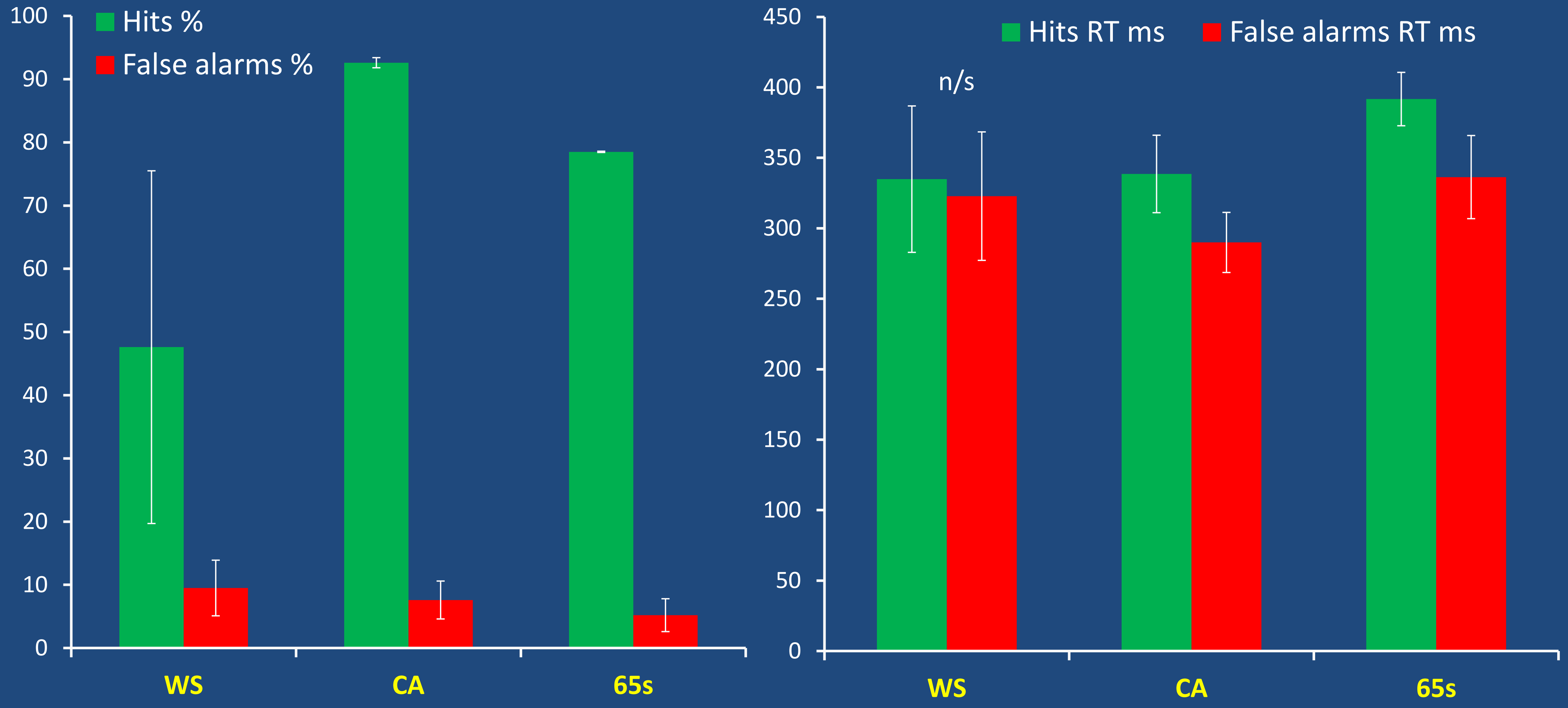
Sustained Attention to Response Task

- SART - *Go / No Go* task
- Respond to a frequent non-target stimulus (X)
- Withhold response to infrequent target (Y)
- Fast-paced
- Automaticity of responding
  - requires engagement of sustained attention and
  - activation of inhibitory control in order to avoid response to the target
  - Controls – chronologically age matched (CA), older adults 65+ (65s)

SART



SART behavioural results



Greer et al., 2013

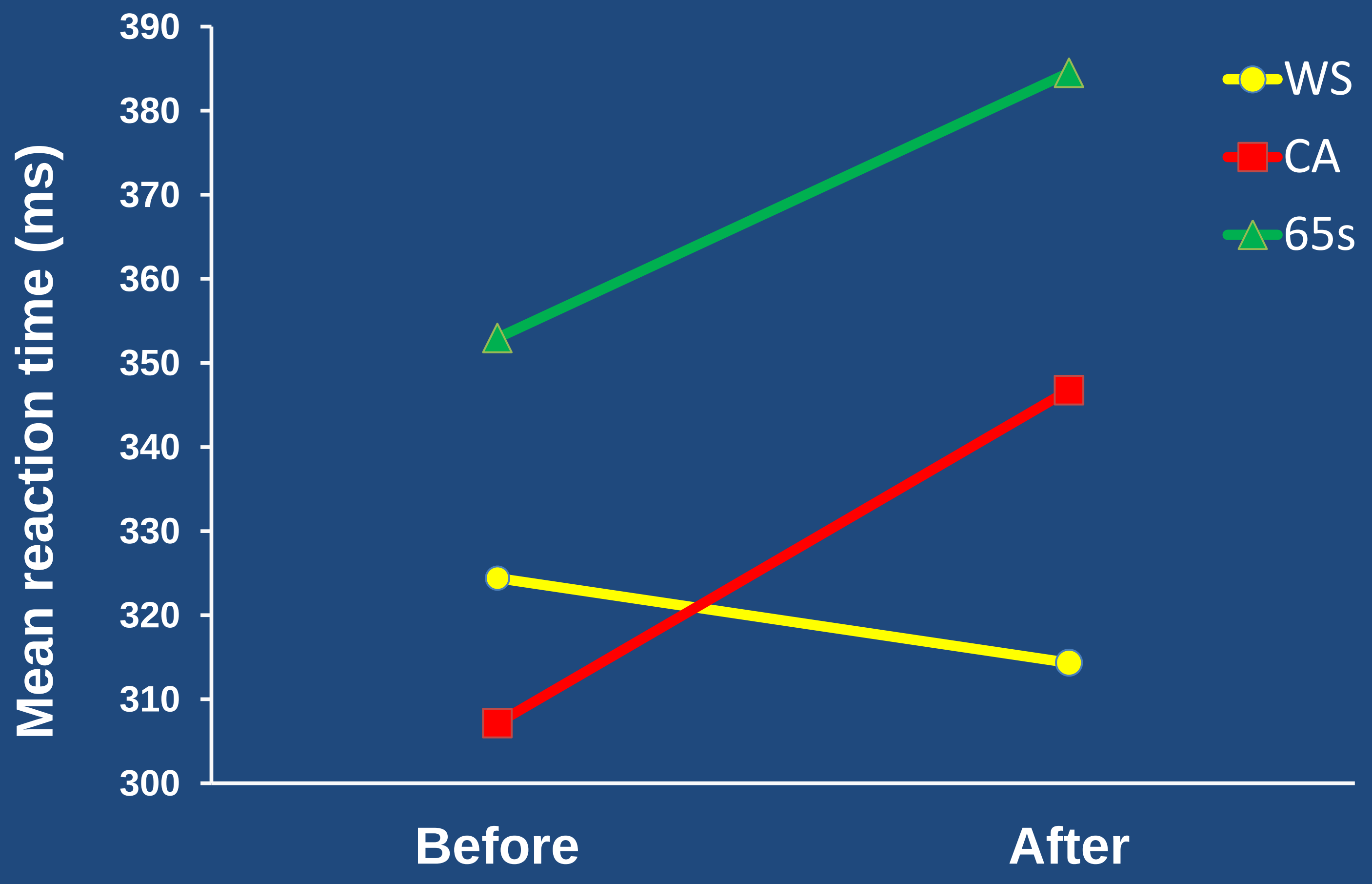
Initial summary of SART results

- WS demonstrate impaired sustained attention (hits at chance level)
- Very high levels of variability cf. controls
- Greater FA rate than controls (sig cf. 65s)
- No difference in RT between hits and FAs
- WS making more mistakes despite longer evaluation of the stimulus
- Whereas controls' FA rate reflective of momentary and occasional lapse in attention (quicker RT)
- 65s lower FA rate due to speed-accuracy trade-off (slower RT)

Evaluation of reaction time before and after a FA

- Fast-paced task, evidence for lack of drop in sustained attention observed in the reaction time (RT) when making a FA (error of commission)
- Reduction in sustained attention = RT speeds up = make a FA
- Attention re-directed back to the task
- Re-allocation of sustained attention then evidence by a slowing in RT post-error

SART before after results



Both control groups' RT increases post error – as expected

WS group – <u>no</u> difference in RT post FA

Lack of error monitoring, no reallocation of attentional control

Same profile observed in traumatic brain injured (TBI) individuals, not older TD adults

Greer et al., 2013

Recap

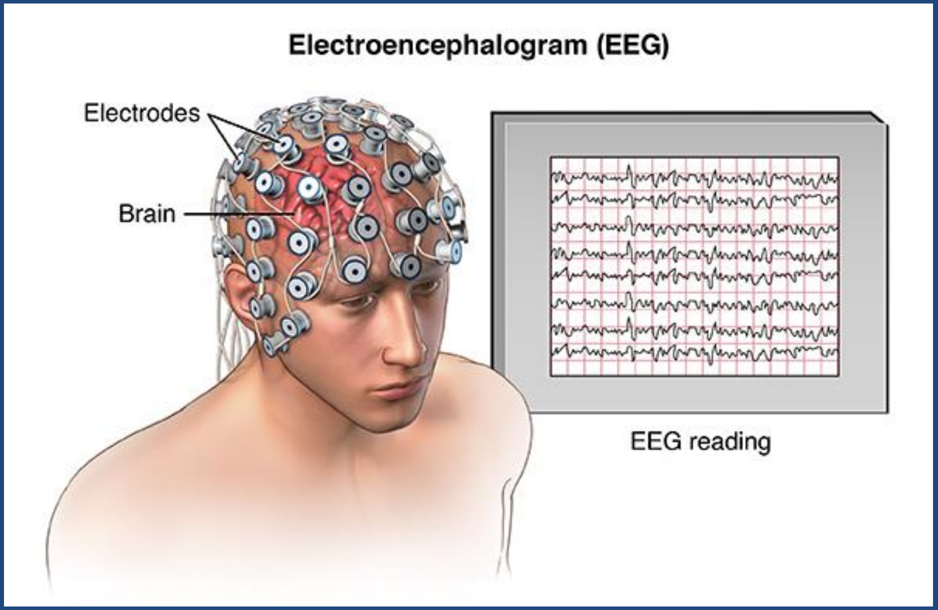
- Evidence for atypicalites in frontally controlled EF processes
  - Impaired sustained attention
  - Deficits in inhibitory control

- Parallels between WS and individuals who have suffered frontal traumatic brain injury
  - but we need to be careful comparing atypical development with brain injured typical development

Benefit of neuroimaging techniques

- Can discriminate how behavioural differences / similarities between TD & atypical development present at the neural level

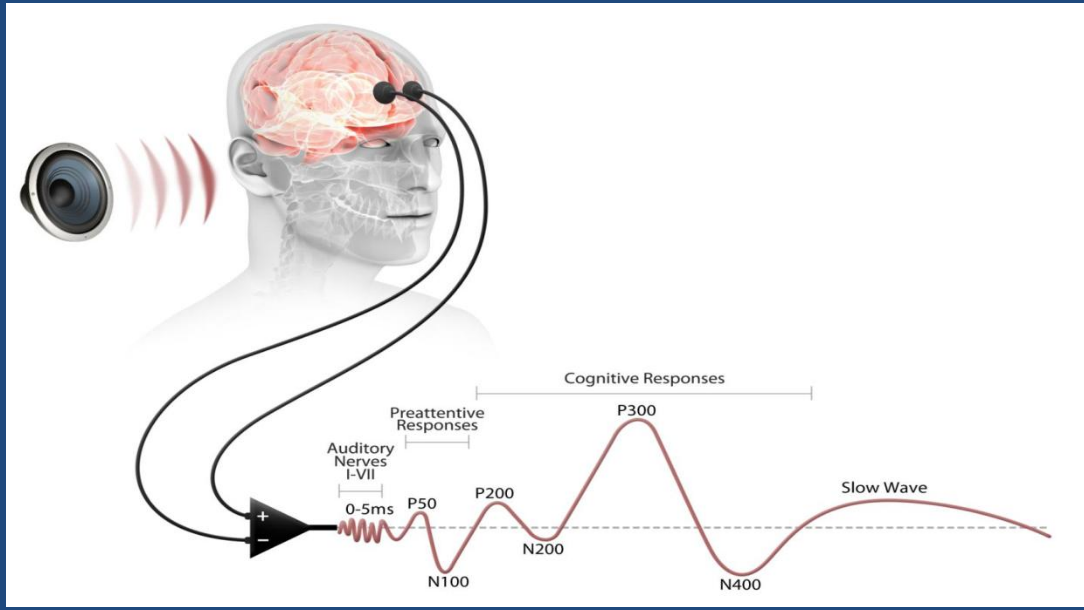
- Cortical electrical activity measured via electrodes connected to the scalp



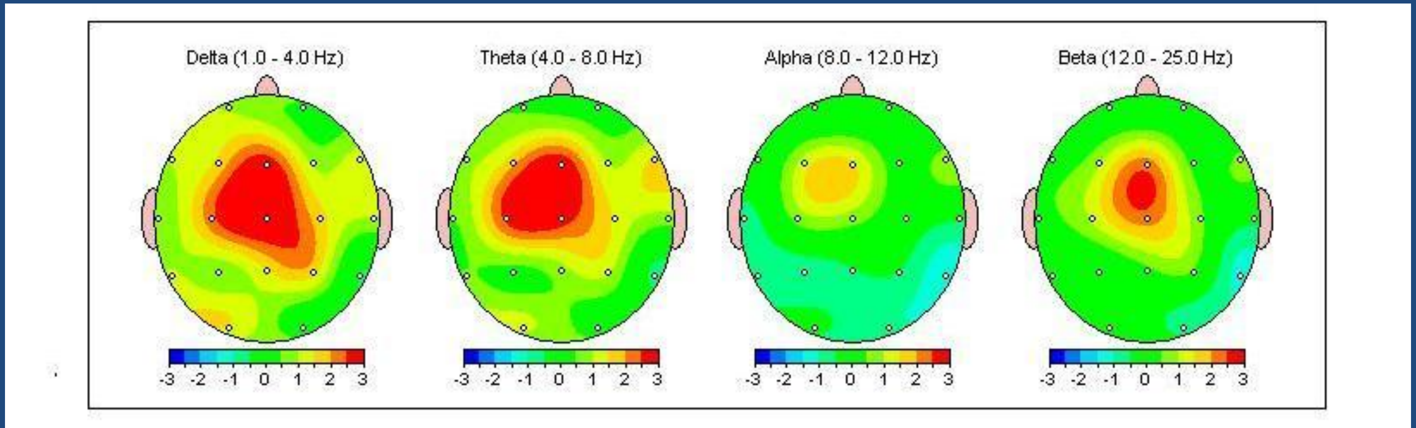
- Ideally suited for WS – non-invasive, quiet (unlike fMRI – need to consider sensory issues e.g. noise / confinement)

Types of brain activity measurement

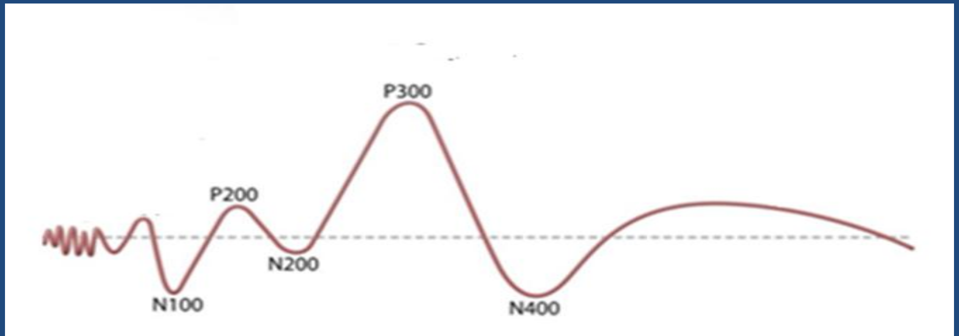
- Event related potentials (ERPs) – can measure neural response (amplitude and latency) to a stimulus with millisecond precision



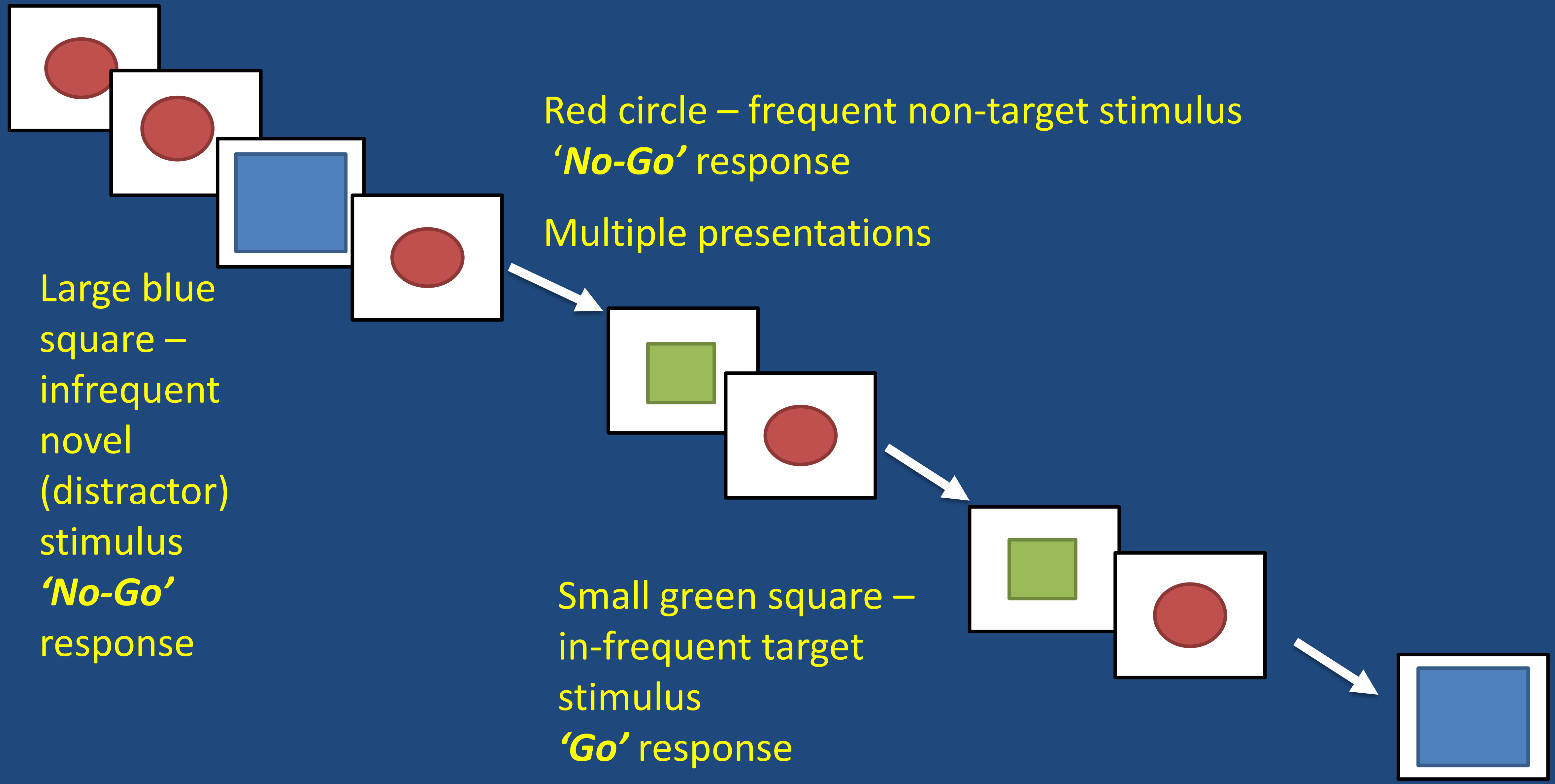
- Electroencephalography (EEG) – topographical distribution of cortical electrical activity (frequency bands)



Three-stimulus oddball task

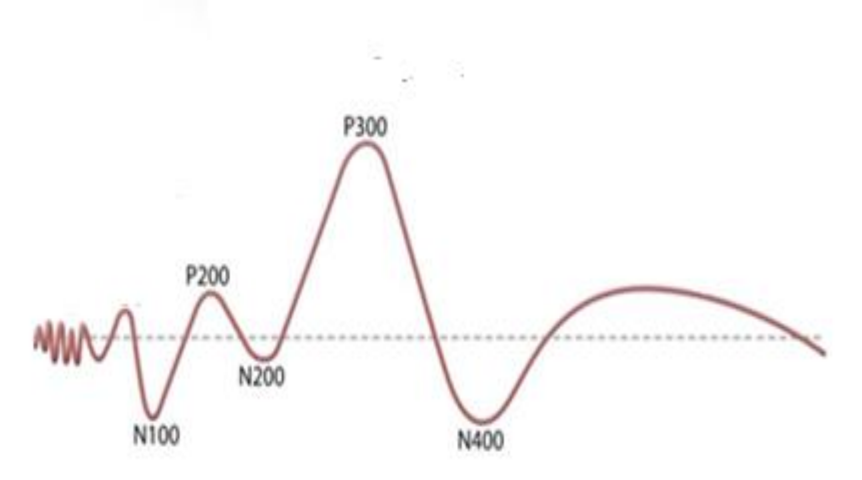


- Measures ERPs (waveforms)
- Highly sensitive to neural responses during voluntary and involuntary attentional processes
  1. Infrequent target (green square)
  2. Infrequent novel (distractor) (LARGE blue square)
  3. Frequent non-target (red circle)
- Participants withhold their response to the novel & non-target stimuli, respond only to the infrequent target
- Unlike the SART – does not require high levels of sustained attention


Red circle – frequent non-target stimulus
'No-Go' response
Multiple presentations
Large blue square – infrequent novel (distractor) stimulus *'No-Go'* response
Small green square – in-frequent target stimulus
'Go' response

ERP profile – N2

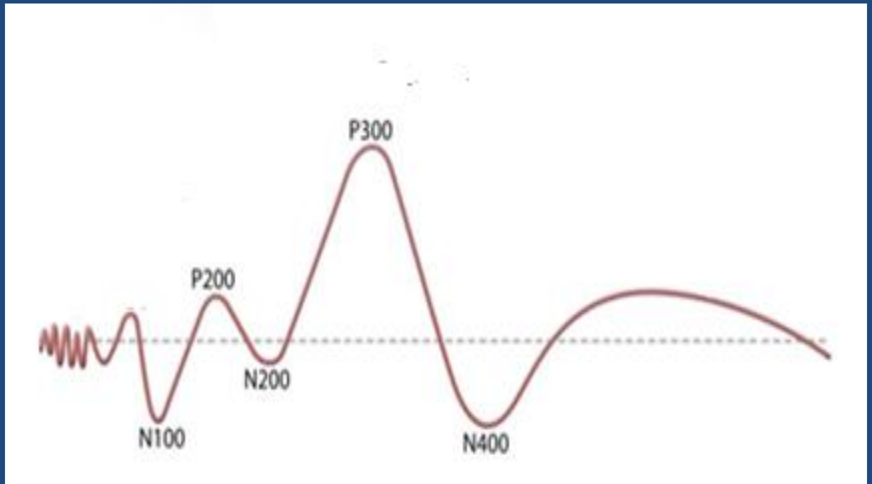
- N2 – 2^{nd} negative waveform
- Discriminates between novelty detection (e.g. big blue square – non-target) and cognitive control (e.g. small green square – target)



- N2 (*No-Go* response) - reflective of response inhibition, typically observed fronto-centrally
- N2 (*Go* response) - the degree of attention that is needed for processing stimuli context, typically observed centro-parietally

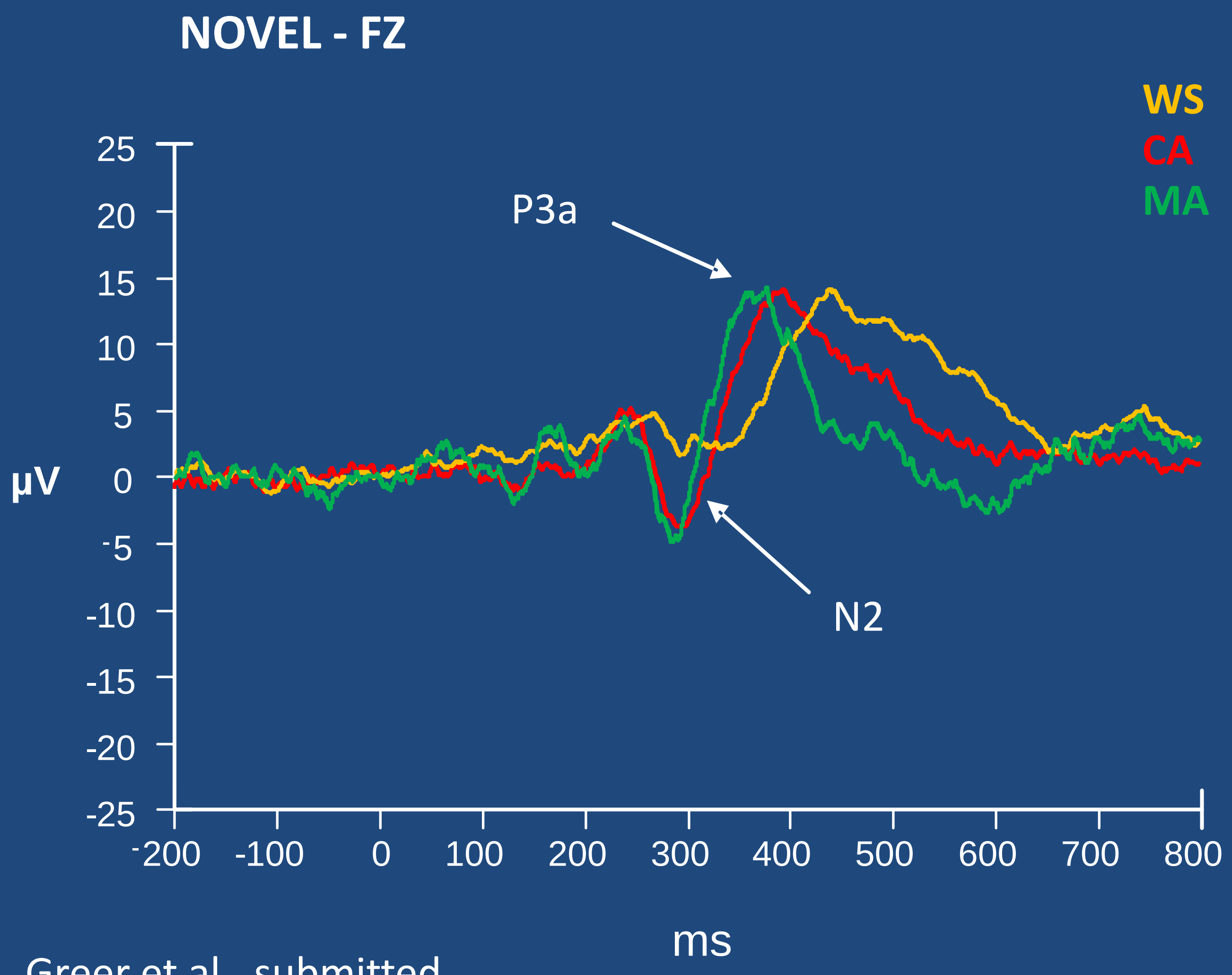
ERP profile – P3

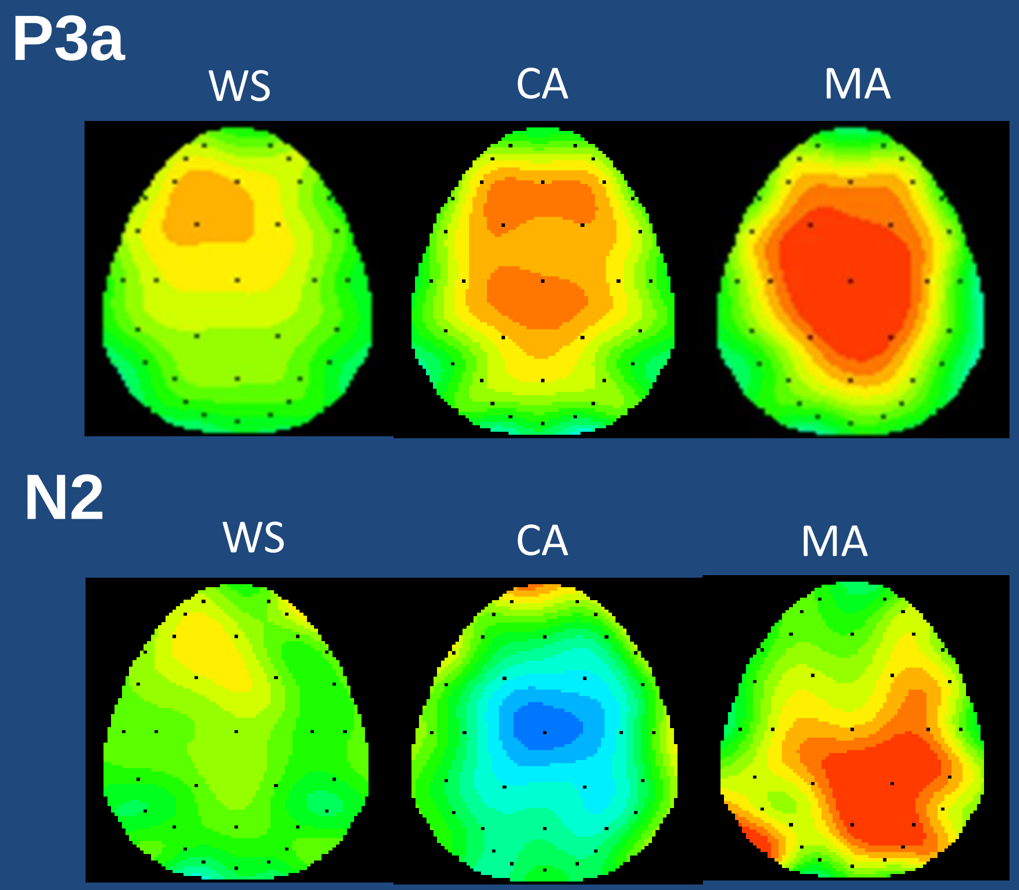
- P3 – 3rd positive going waveform
- Subcomponents of the P3
  – represent different functions in brain activity



- P3a (*No-Go* response) – automatic responses during attention, inhibition, & orienting to the environment (big blue square, distractor, don't respond)
  – fronto-central distribution
- P3b (*Go* response) - controlled processes required during stimulus evaluation (i.e. the target so need to respond / greater attentional resources required)
  – centro-parietal distribution

Results - novel



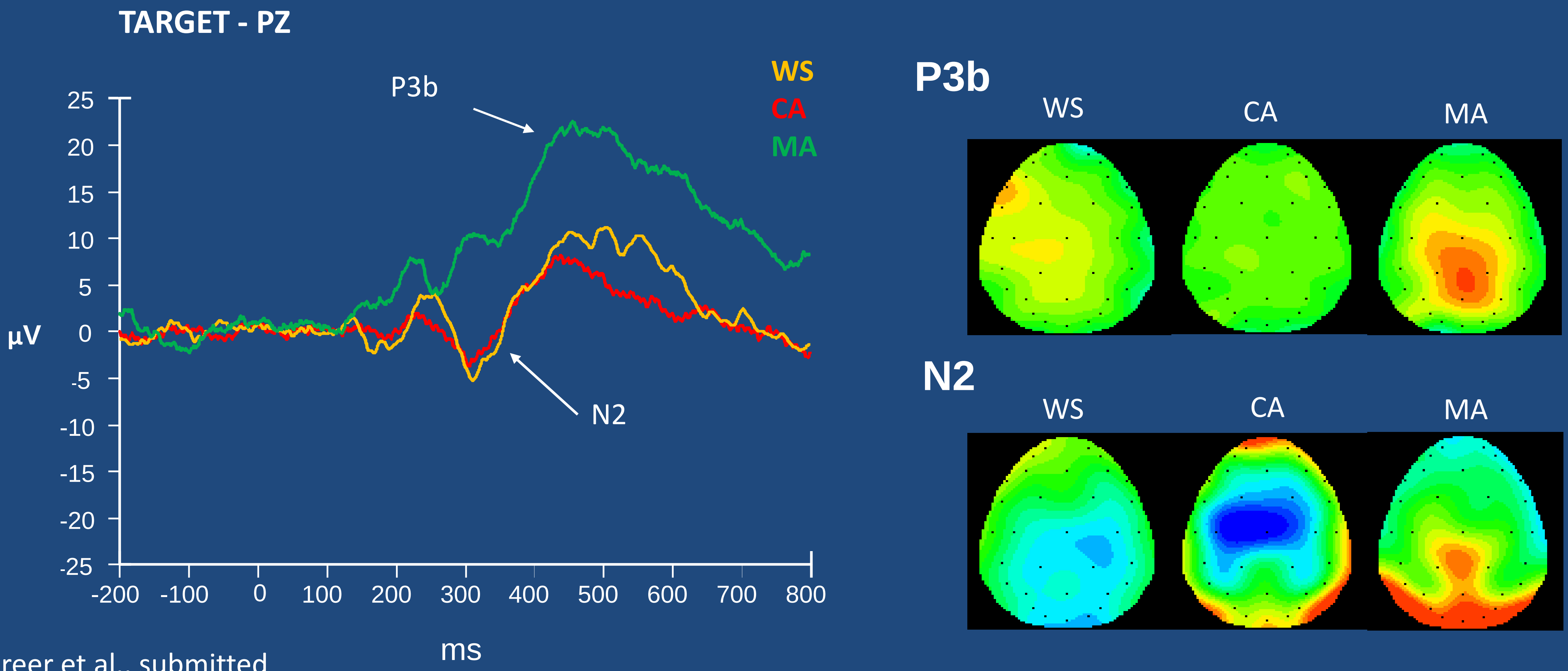


Greer et al., submitted

Results (Novel)

- No difference in P3a amplitude in WS group cf. controls
  - suggests comparable automatic / involuntary shift in attention to unexpected event
- Longer P3a latency
  - indicative of delay in this orienting response, i.e. re-directing attention from task to unexpected event
  - previously reported in WS and FXS
- N2 – amplitude significantly smaller fronto-centrally cf. CA group

Results - target



Greer et al., submitted

Results (Target)

- P3b – no difference in amplitude or latency between WS and CA groups
  - Suggests this task did not place heavy demands on attentional processes in WS group

- N2 amplitude in WS significantly smaller centrally cf. CA group

- (MA profile most likely reflective of their stage in the typically developing maturational processes)

Oddball summary

- Behavioural results – 100% hit rate in all 3 groups (WS slower RT)
- WS - smaller N2 amplitude to both novel and target
- Smaller N2 thought to reflect propensity to respond, whereas greater N2 amplitude indicative of readiness to withhold a response
- TD – greater N2 amplitude linked with fewer False Alarms
- Can’t make direct comparisons here, but the data suggests that WS have an underlying propensity to respond (lack of inhibition)
- Cautious suggestion, need to link this to social profile experimentally

Resting states - EEG

- Previous studies – can see how task difficulty affects task performance in WS (obviously!)
- BUT – N2 amplitude data also tentatively suggest underlying neural profiles that can be linked to the WS behavioural profile, even when task performance <u>the same</u> as controls
- Using different neural mechanisms to achieve the same behavioural result
- Resting states – measure EEG, avoid confounds of atypicalites / differences in cognitive processes during task performance

Alpha / beta frequency bands

- EEG measured across different frequency bands
- Alpha
- Linked to attentional and inhibitory control processes
- Inverse profile –alpha band levels <u>HIGH</u>, means <u>less</u> cortical activity
- At rest – high alpha evidence of inhibitory control, preventing cognitive activity
- During brain activity – decrease in alpha power
  - release from inhibitory control, cortical activity required for task demands

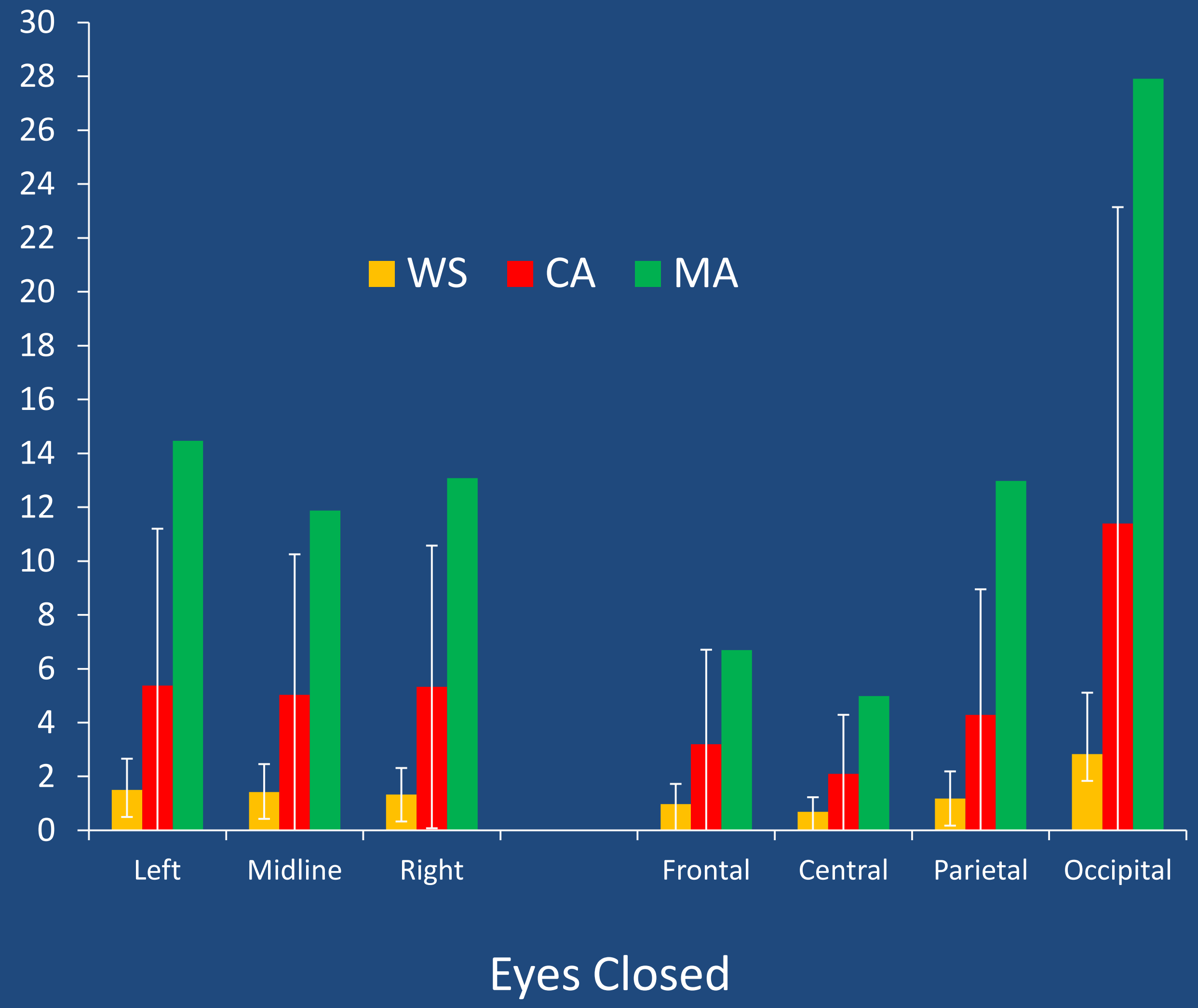
Alpha / beta frequency bands cont.

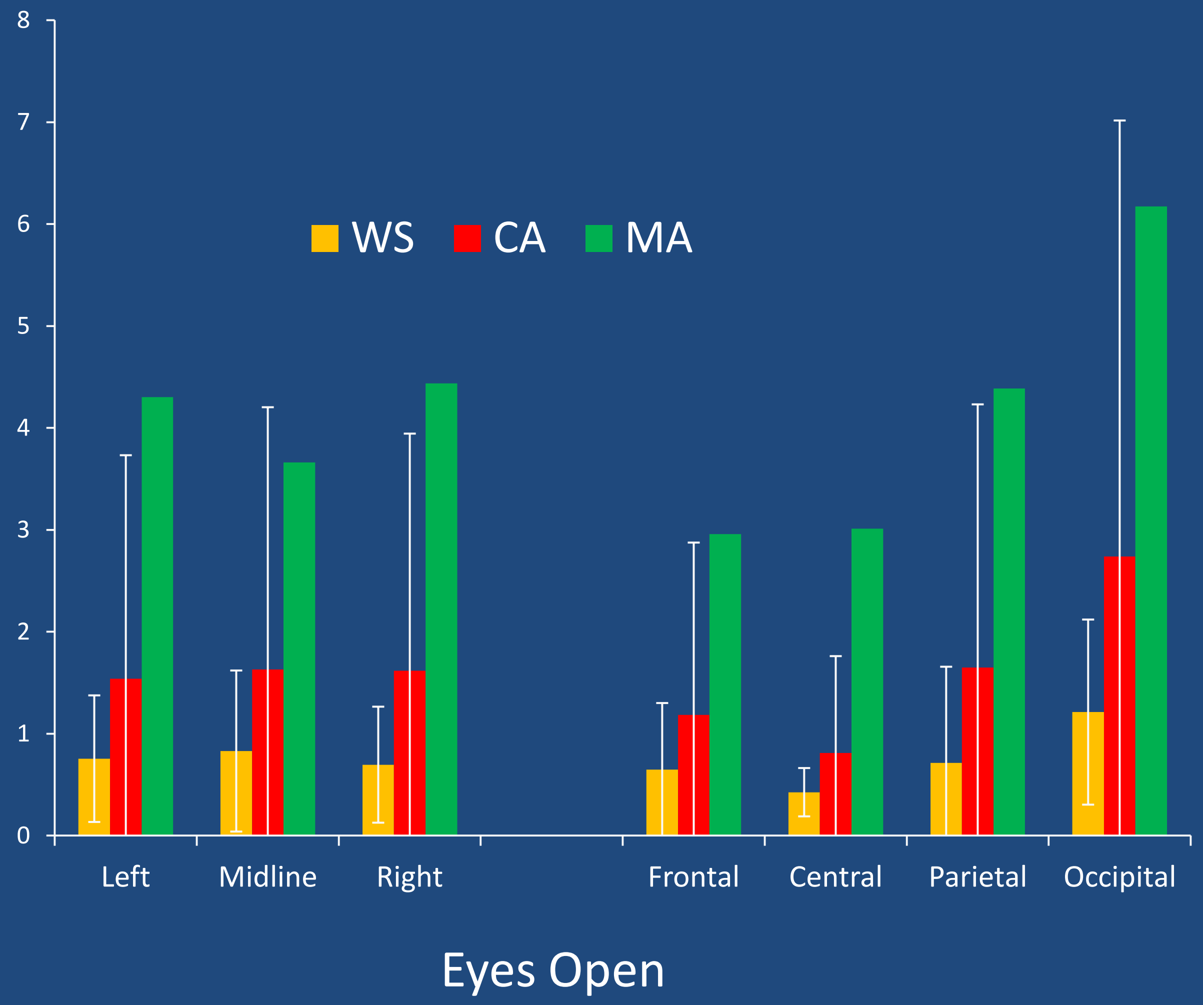
- Beta
- Linked with visuo-attentional processing
- Higher levels of beta power associated with better performance on tasks which recruit attentional processes
- Increases and decreases in beta power are also associated with the execution and inhibition of voluntary movements

Eyes Closed / Eyes Open paradigm

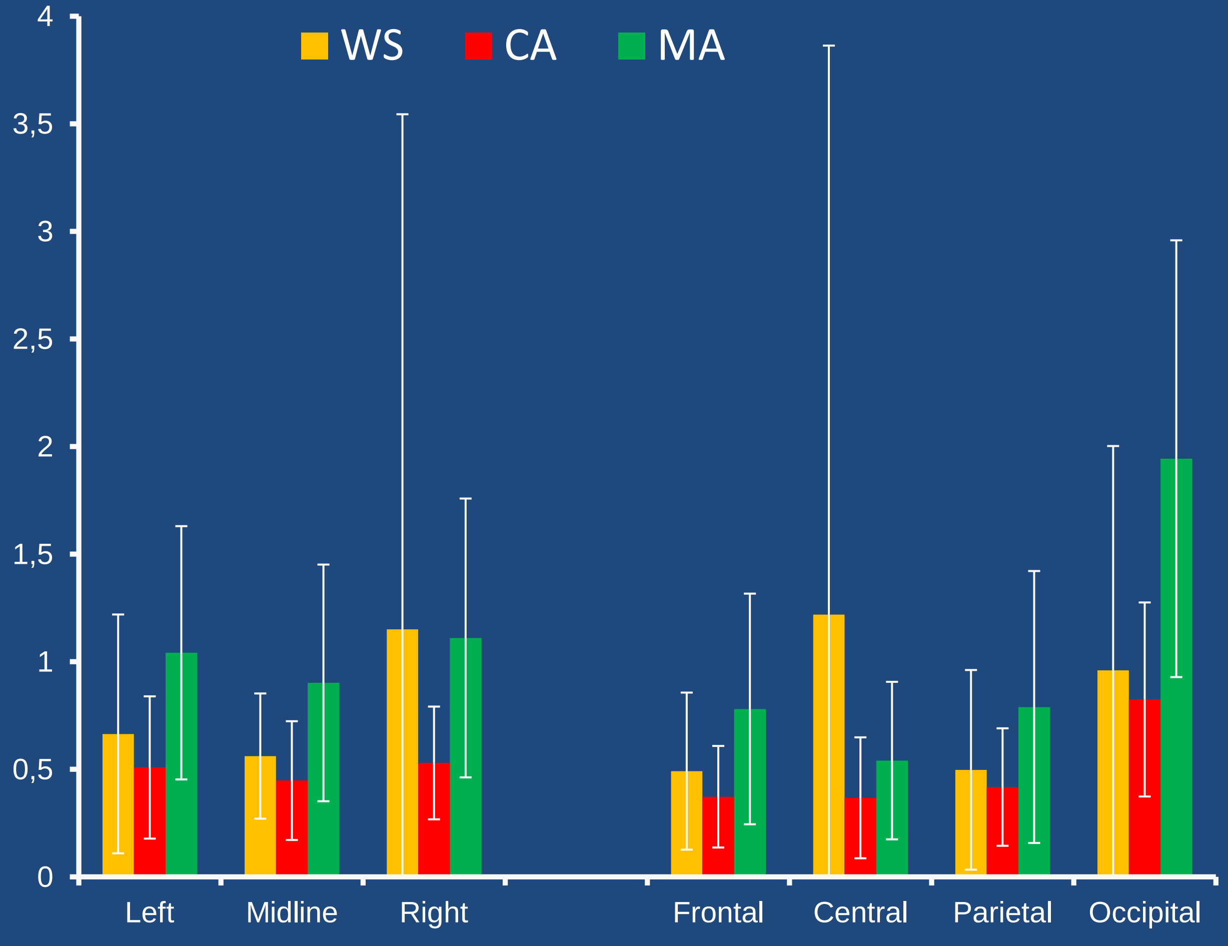
- Participants rest for e.g. 2 minutes in each condition
  - EC – baseline cortical arousal
  - EO - baseline cortical activity in preparation for cognitive processing
- EC – expect to see high alpha and beta power
- EO – decrease in power value but topographical shift
  - Alpha – greater occipto-parietal decreases
  - Beta – less posterior decrease, but increases fronto-centrally
  - Recruitment of frontally controlled EF processes

Results - Alpha

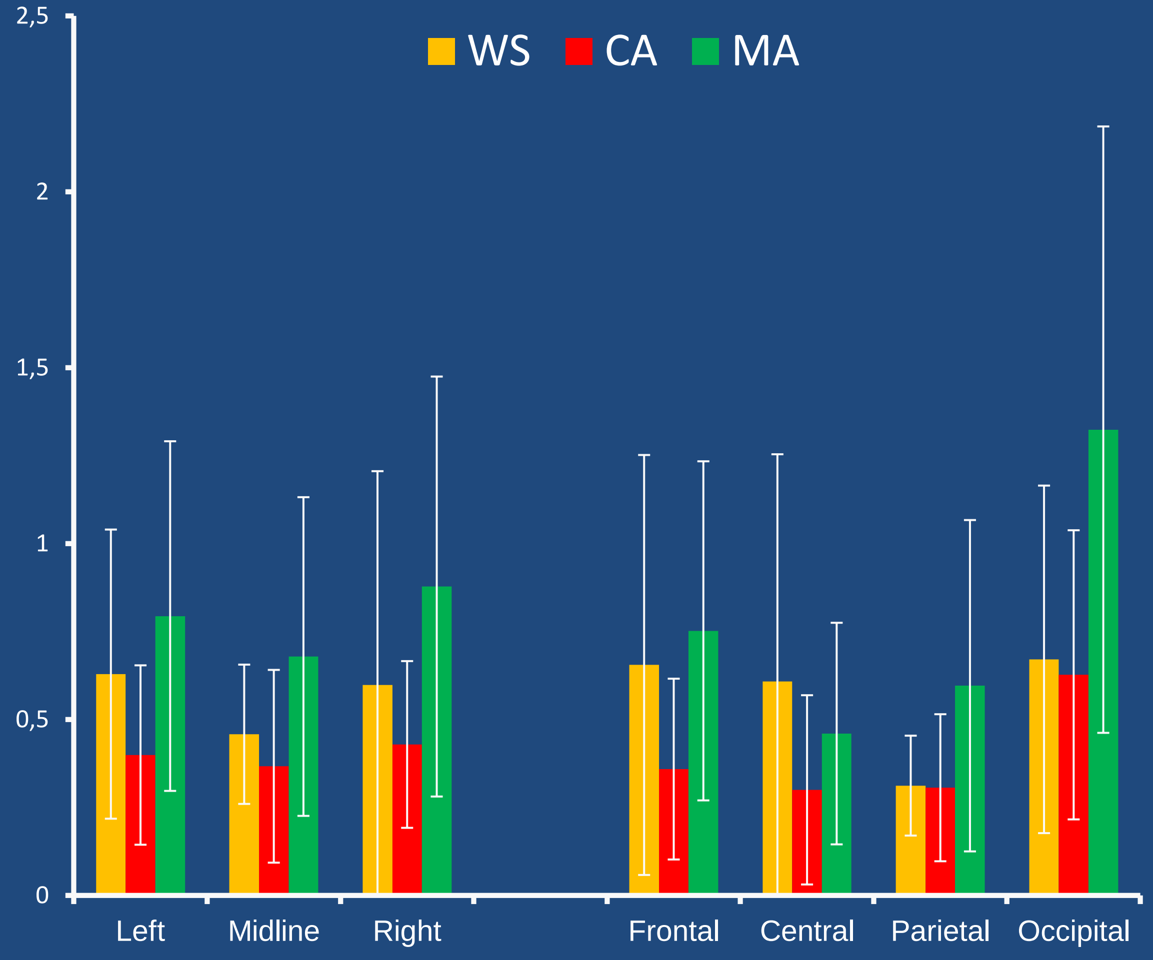




Results - Beta



Eyes Closed



Eyes Open

EC / EO summary

- WS – low alpha power values during EC and EO cf. CA adults
- No difference in beta cf. controls – suggests at rest WS have EEG profile for successful attentional processing / control
- Alpha - at rest, EEG profile in WS suggests a state of hyper-cortical activity
- No inhibitory control during resting states – so how can this activate when cognitive processes require inhibitory control?
- Low variability – WS typically associated with high variability
- In ADHD low alpha variability associated with poorer behavioural performance
- Very early suggestions – we need much more research

Overall summary

- Associative memory – further evidence of atypicalites in ‘binding’ but no evidence for premature cognitive ageing
- WS can benefit from semantic support at encoding
- Behavioural deficits grounded in frontal deficits – attention / inhibition
- Error monitoring
- ERP – early inhibitory deficits (N2), delayed orienting response (P3a), but comparable attentional response during less demanding task (P3b)
- EEG – low alpha at rest, suggests lack of inhibitory control in absence of cognitive activity
- Need to consider role of EEG variability in behavioural performance

With deepest thanks to…

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- My PhD supervisors
  - Dr Leigh Riby
  - Dr Debbie Riby
  - Dr Colin Hamilton
- **Members of the WSF UK for their invaluable participation!**