Sensory-Motor processing in People with Parkinson's Disease with and without Freezing of Gait

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Talk Overview

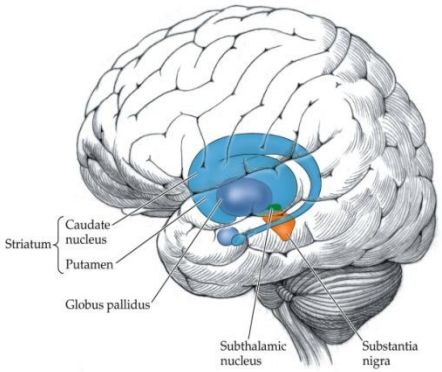
- Unisensory Responses
- Multisensory Responses
- Motor and Decision making Processing
- Dual task Motor and Decision Making

Parkinson's Disease

- Movement Disorder
- Characterised Tremor
- Sensory Deficits
- Freezing of Gait
- Dementia

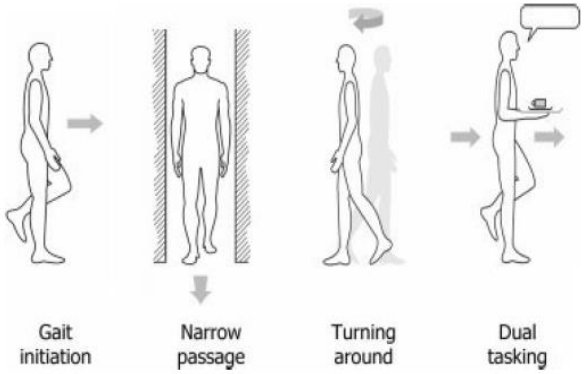
Parkinson's Disease

- Parkinson's disease (PD): neurodegenerative disorder characterised by loss of dopaminergic signalling in the basal ganglia
- Motor symptoms
  - Tremor
  - Bradykinesia
  - Rigidity
  - Postural disturbance
  - Freezing of gait
- Non-motor features: constipation, depression, anxiety, cognitive impairment, autonomic instability, hallucinations and impulse control disorders.
- Treatment: dopamine replacement or deep brain stimulation



Freezing of Gait

- Intermittent gait disturbance - feet glued to floor
  - Most apparent in late-stage Parkinson's disease
- Affects up to 60% patients with Parkinson's disease

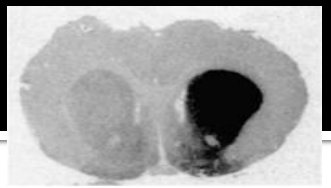


- Causes falls

- Poorly understood
  - No effective treatments
  - Difficult to study
  - Heterogeneous

From Parkinsonism and Related Disorders Springer Video Atlas

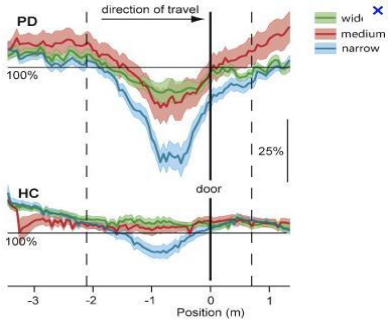
Proposed pathophysiology - Phenomena



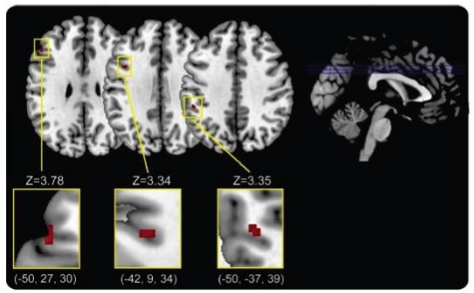
1. Dopamine depletion:
   - More freezing when "off"
   - But…"on-freezing"

2. Loss of internal rhythmicity / pattern generation
   - Reliance on cues or conscious cortical control

3. Sensorimotor integration:
   - Certain sensory inputs (e.g. narrow doorways) can precipitate FOG whereas others alleviate it

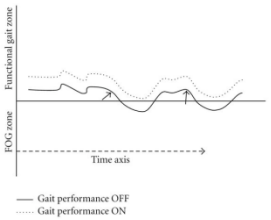


4. Cognitive dysfunction
   - FOG have significantly more executive dysfunction than non-FOG
   - <u>Dual tasking causes freezing</u>

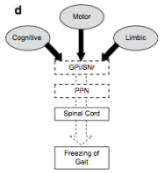


Proposed pathophysiology - Models

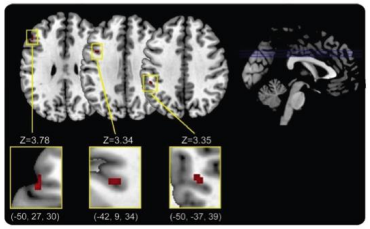
1. Threshold Model:
   - Deterioration of multiple gait features -> falls below threshold of movement breakdown



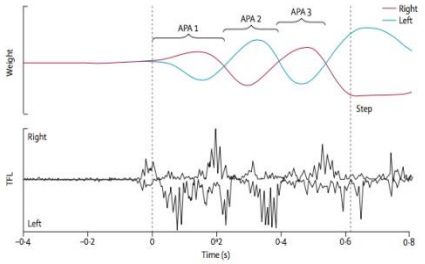
2. Interference Model:
   - Competing motor/cognitive/limbic inputs in basal ganglia



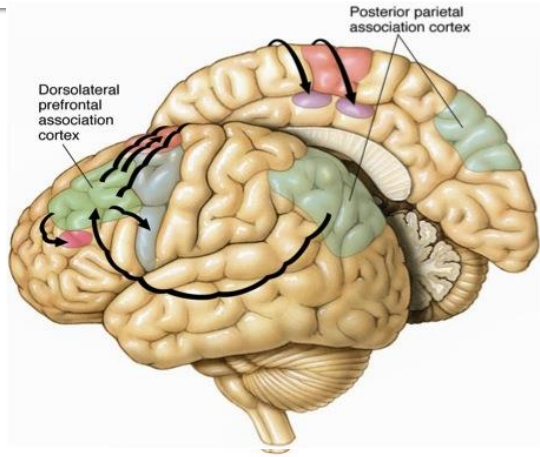
3. Cognitive Model:
   - Behavioural indecision to conflicting responses



4. Decoupling Model:
   - Failure in automatic generation of a movement pattern when it mismatches a prepared (automatic) motor program



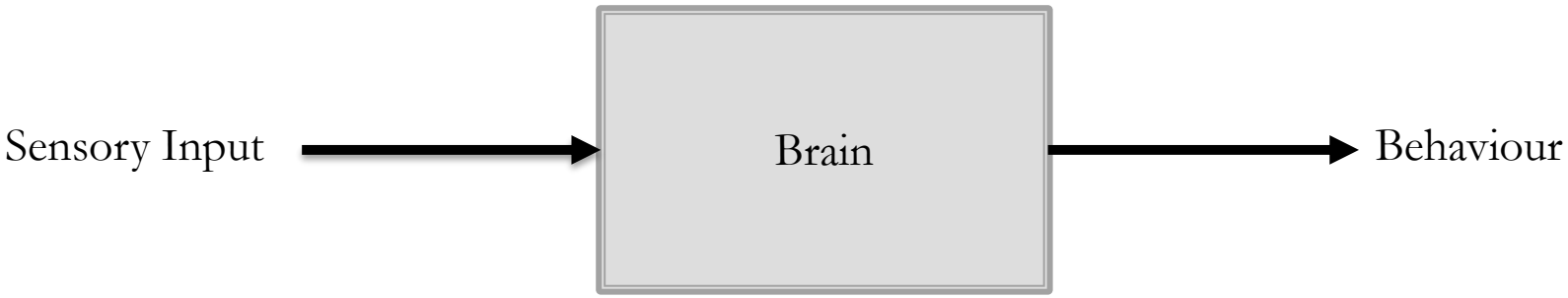
Proposed pathophysiology – Localisation



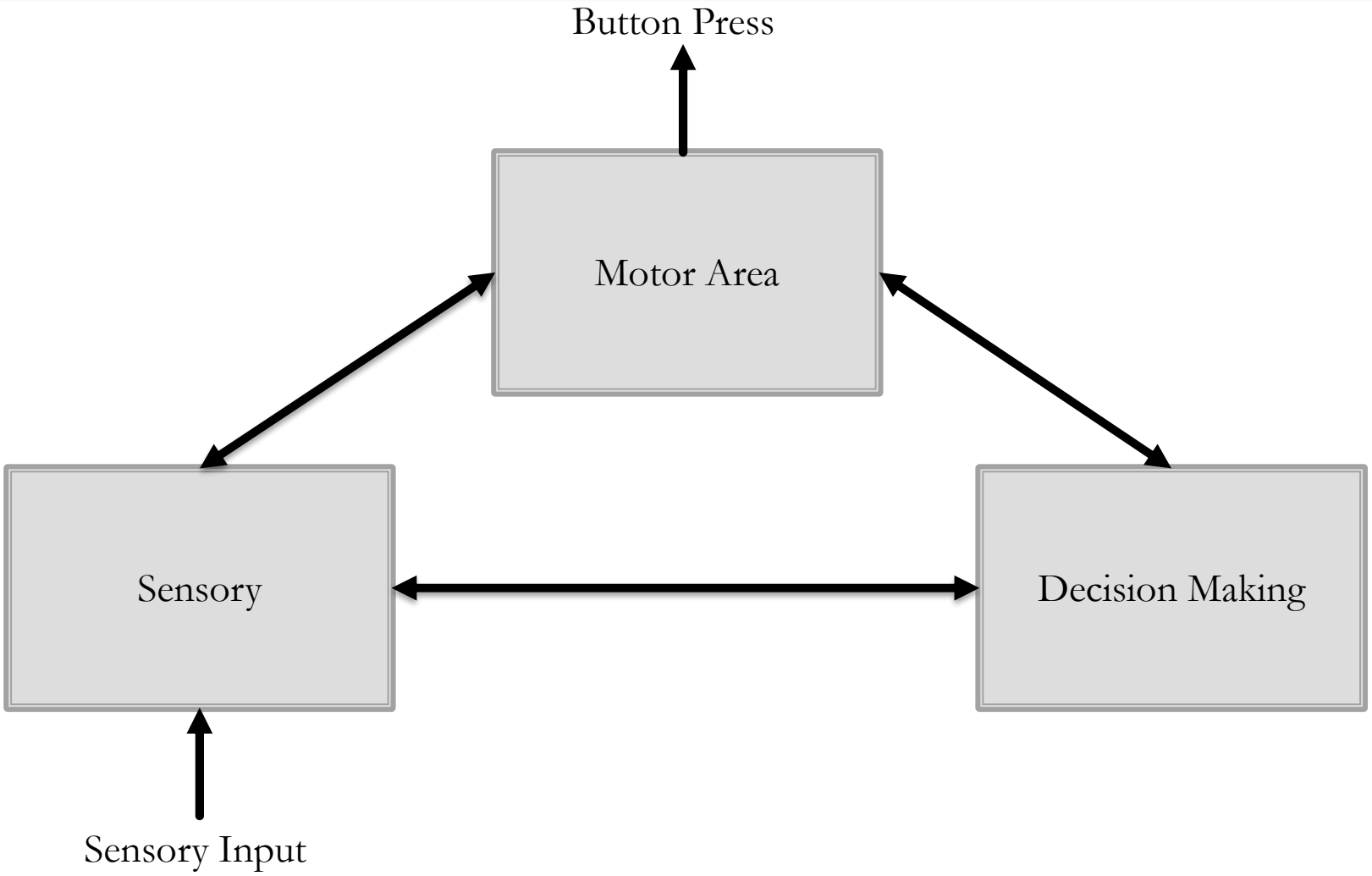
- Dorsolateral PFC:
  - Executive function, motor planning
- Inferior frontal gyrus:
  - Resolving dual-task interference
- Posterior parietal cortex:
  - Shifting attention during simultaneous multisensory stimulation
- Supplementary motor area:
  - Initiation of internally generated movement
- Basal ganglia (ventral striatum):
  - Decision-making and reward physiology
- Insula
  - Motor learning (among many others)

Cognitive Control Network

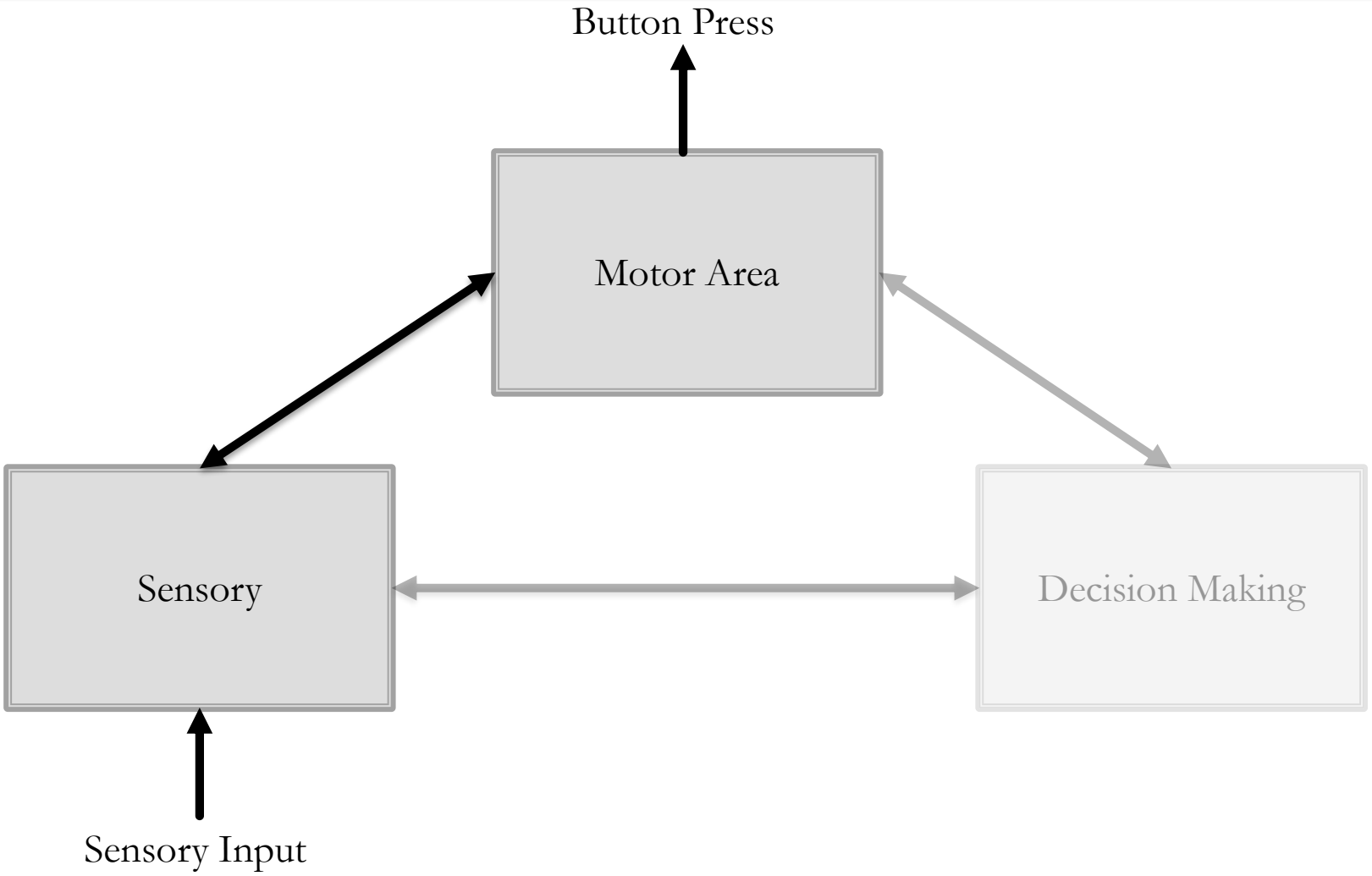
The Brain as a Box



Sensory Motor Decision Making



Reaction Time task



A Simple Audio Visual Paradigm

Conditions:

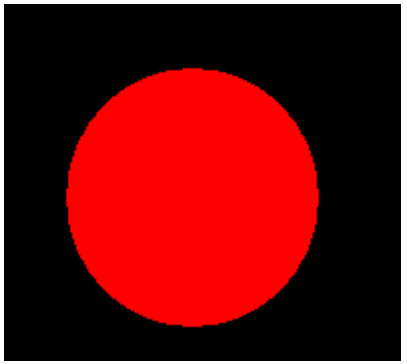
Auditory Alone (A): 1000 hz tone, 60 ms

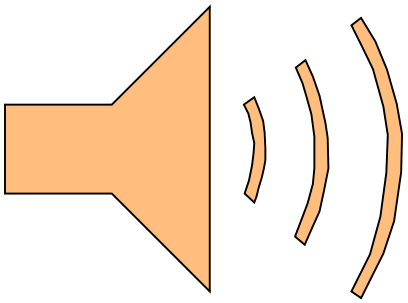
Visual Alone (V): a red circle, 3.2 cm, 60 ms

Audiovisual (AV): simultaneous presentation of the auditory and visual alone conditions

Task:

Participants are instructed to press a button as quickly as possible when they see the circle, hear the tone, or see the circle and hear the tone

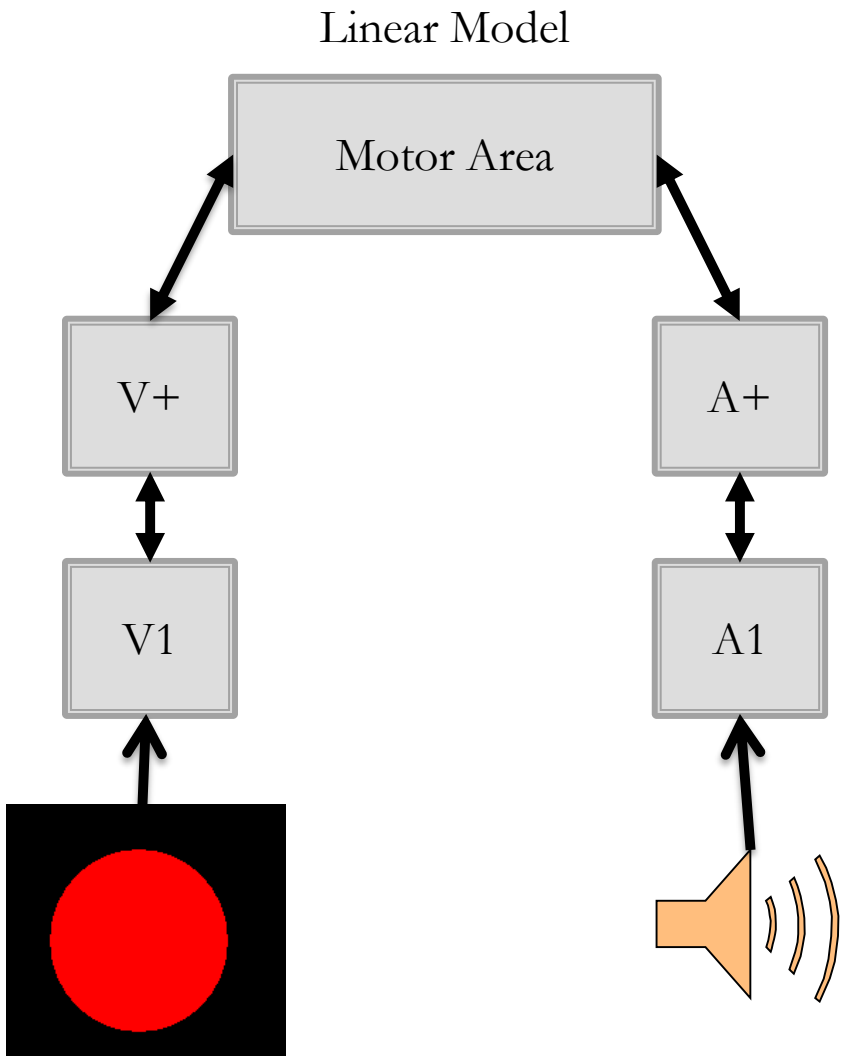




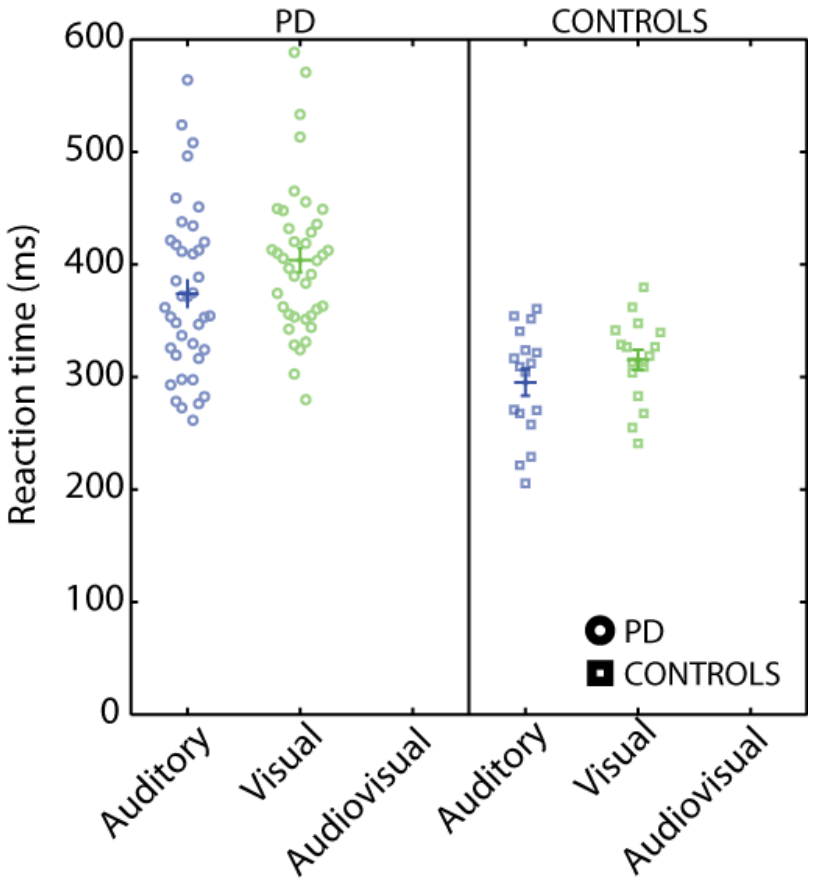
Participants

	Controls	All PD	Freezers	Non-Freezers
N	17	39	23	16
Age	66 (9.7)	67.4 (9.8)	68.7 (9.7)	66.7 (10.05)
Gender (M:F)	10:7	23:16	15:8	8:8
H&Y stage		2.6 (0.7)	2.9 (0.6)	2.3 (0.3)
Disease Duration (years)*		10.1 (9.4)	14.0 (10.5)	5.2 (4.6)
UPDRS		34.1 (14)	38 (13)	30 (14)
MOCA		24.7 (4.8)	24.4 (3.3)	26.3 (3.6)
FAB		15.7 (3.3)	15.4 (2.8)	17.1 (1.5)

Visual or Auditory Reaction Time

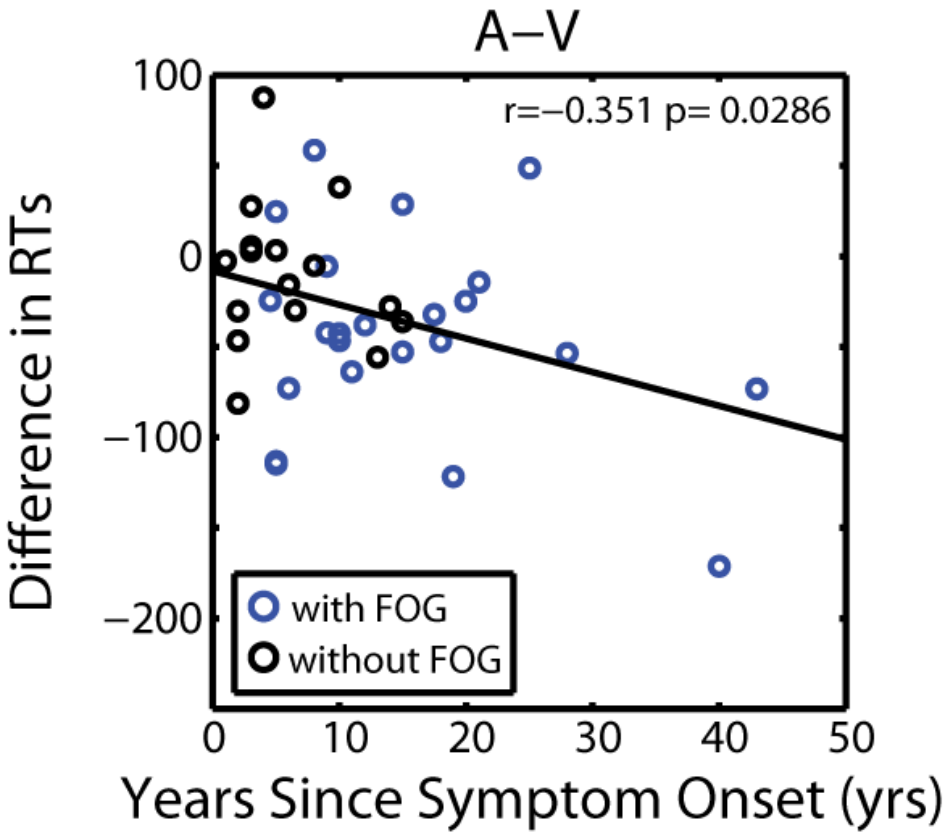


Unisensory Response



Significant slower Auditory and Visual reaction times for people with PD

Years Since Symptom Onset

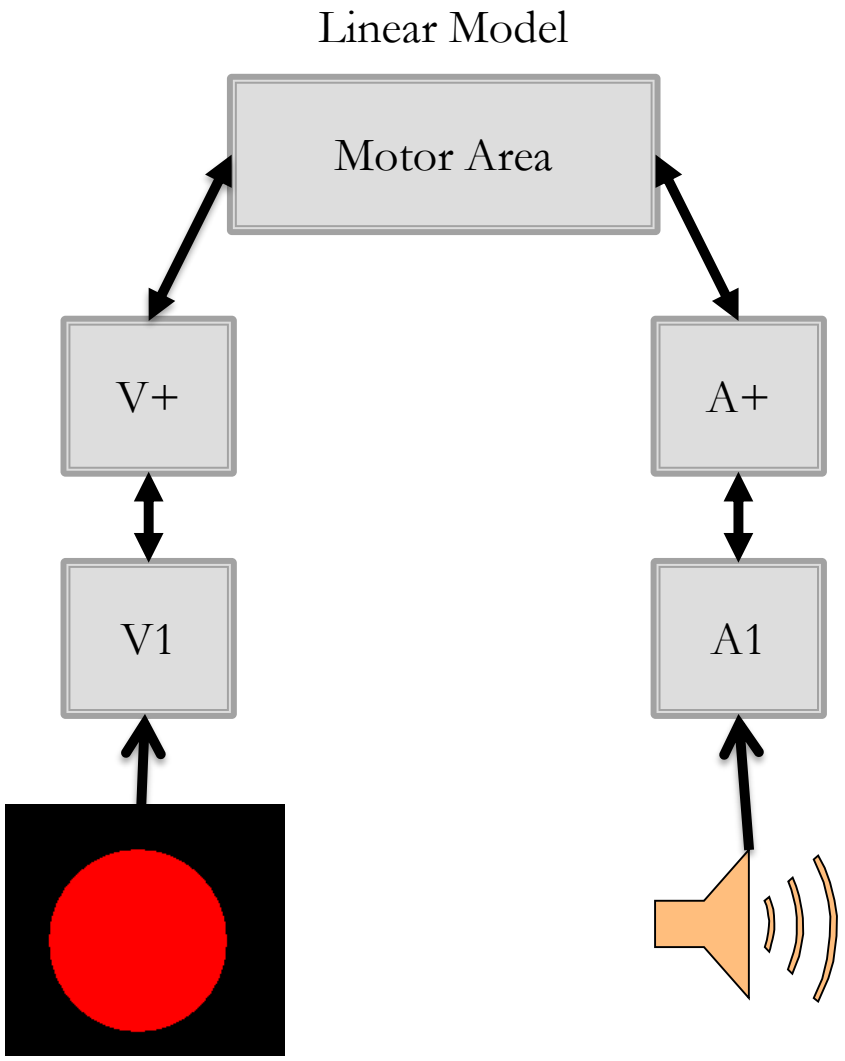


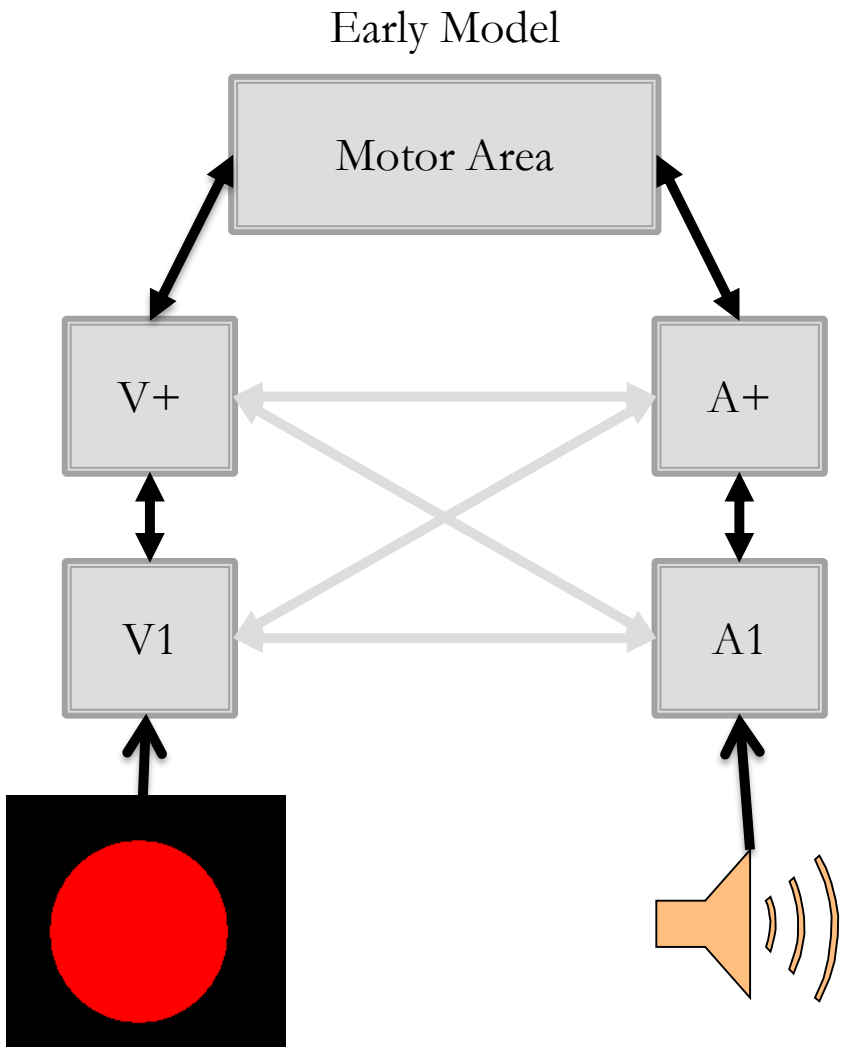
Relative unisensory difference correlated with years with symptoms onset

Multisensory information

- Talking
  - Audio, Visual
- Typing
  - Audio, Visual, Somatosensory
- Eating
  - Audio, Visual, Olfactory
- Walking
  - Visual, Vestibular, Somatosensory, Proprioception

How does the Brain combine signals?





Enhanced multisensory integration in older adults

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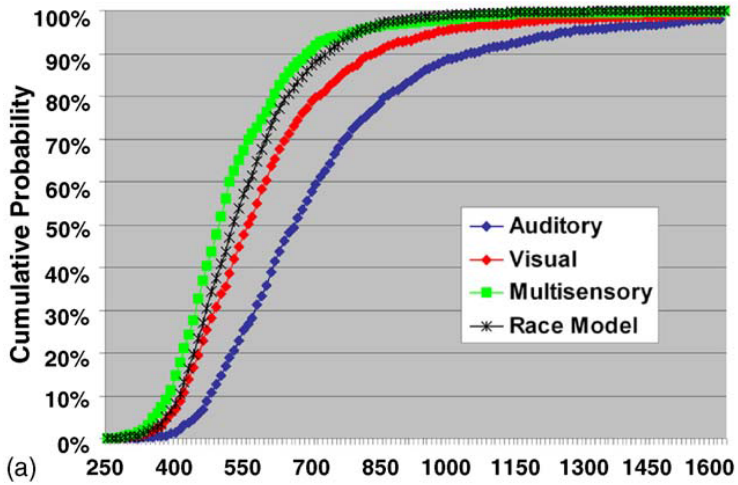
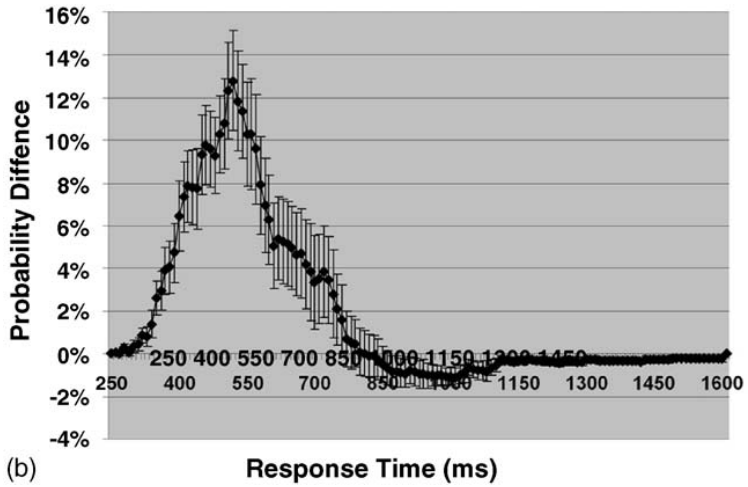
Mean response time (ms) and mean accuracy (%) with standard deviations for multisensory and visual redundant target discrimination tasks

	Auditory	Visual	Multisensory
Multisensory			
Elderly			
RT	714 (127)	614 (111)	527 (89)
Accuracy	99.4 (1.2)	95 (4.2)	97.7 (4.0)
Young			
RT	623 (128)	538 (117)	485 (93)
Accuracy	99.0 (1.4)	97.4 (3.0)	98.4 (2.9)

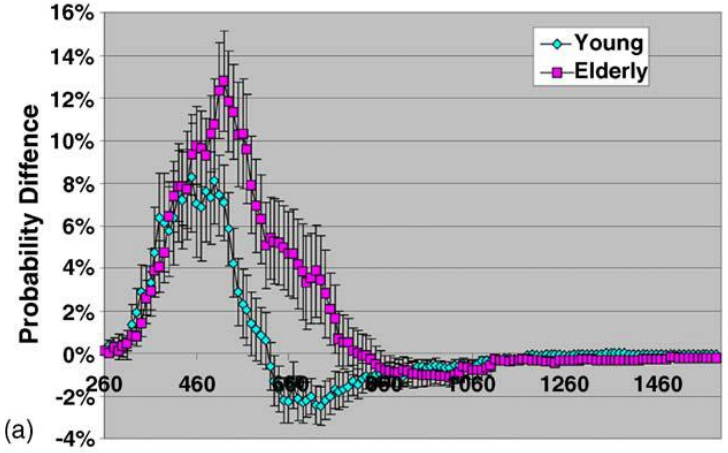
Results



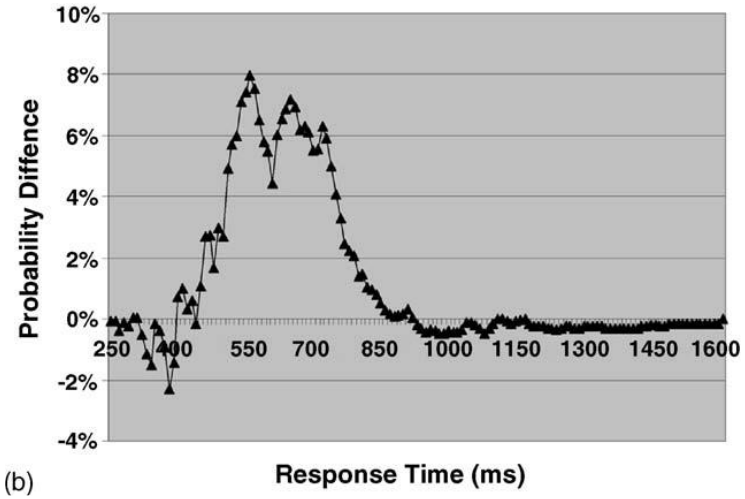
(a)



(b)

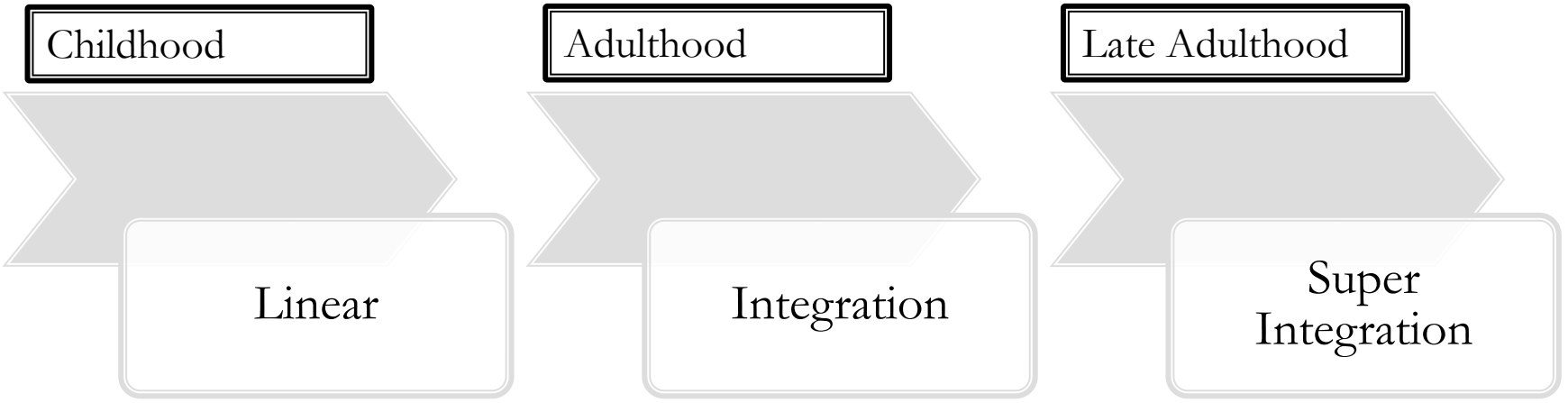


(a)

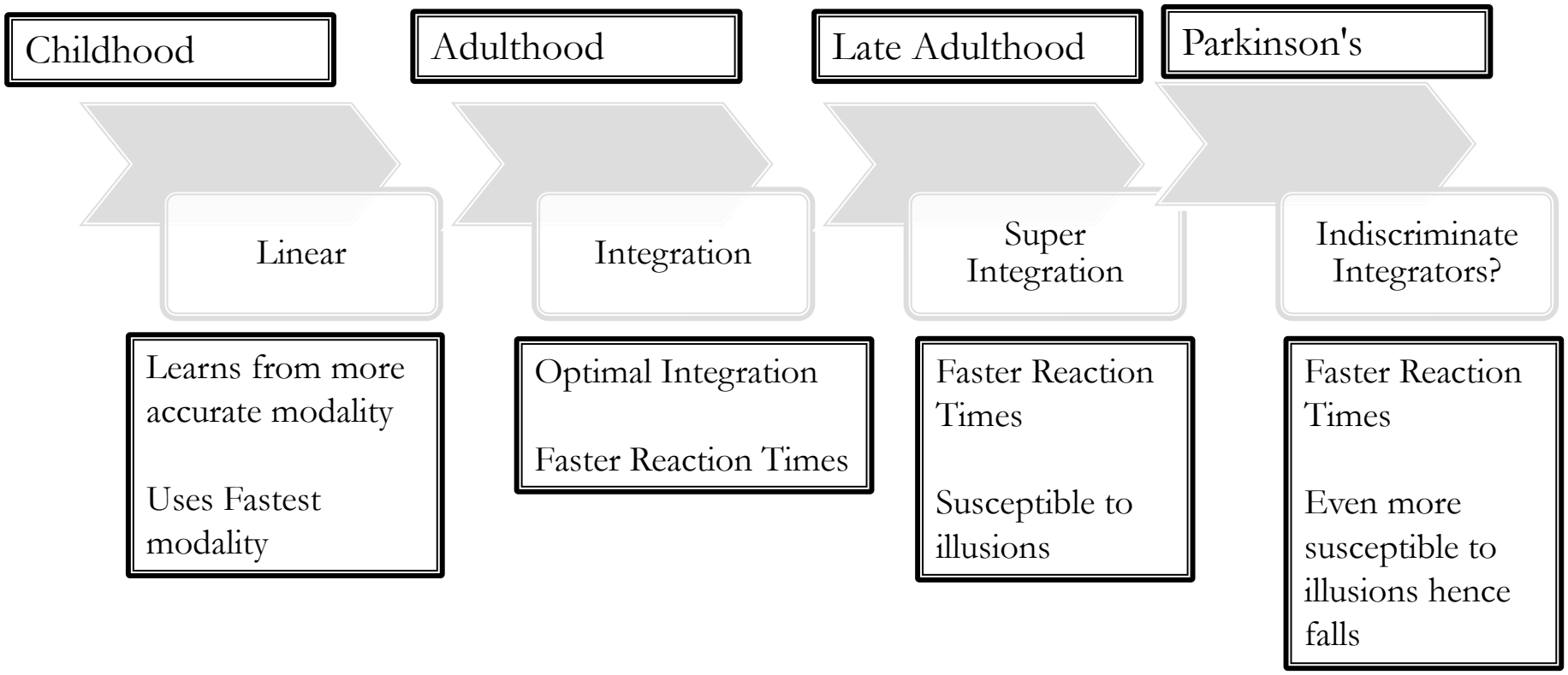


(b)

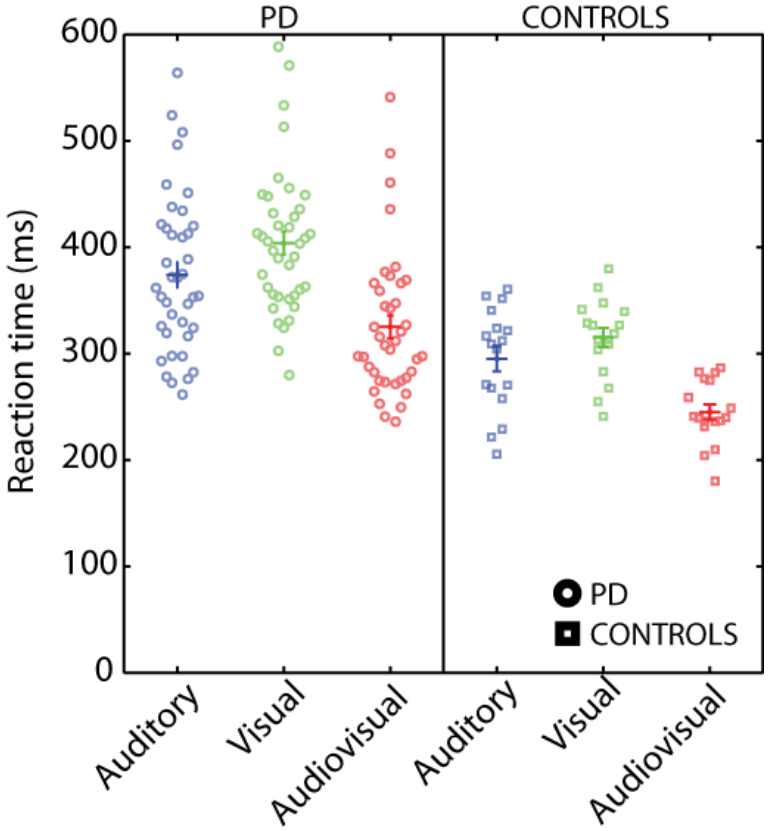
The Development Trajectory of Multisensory Integration



The Development Trajectory of Multisensory Integration

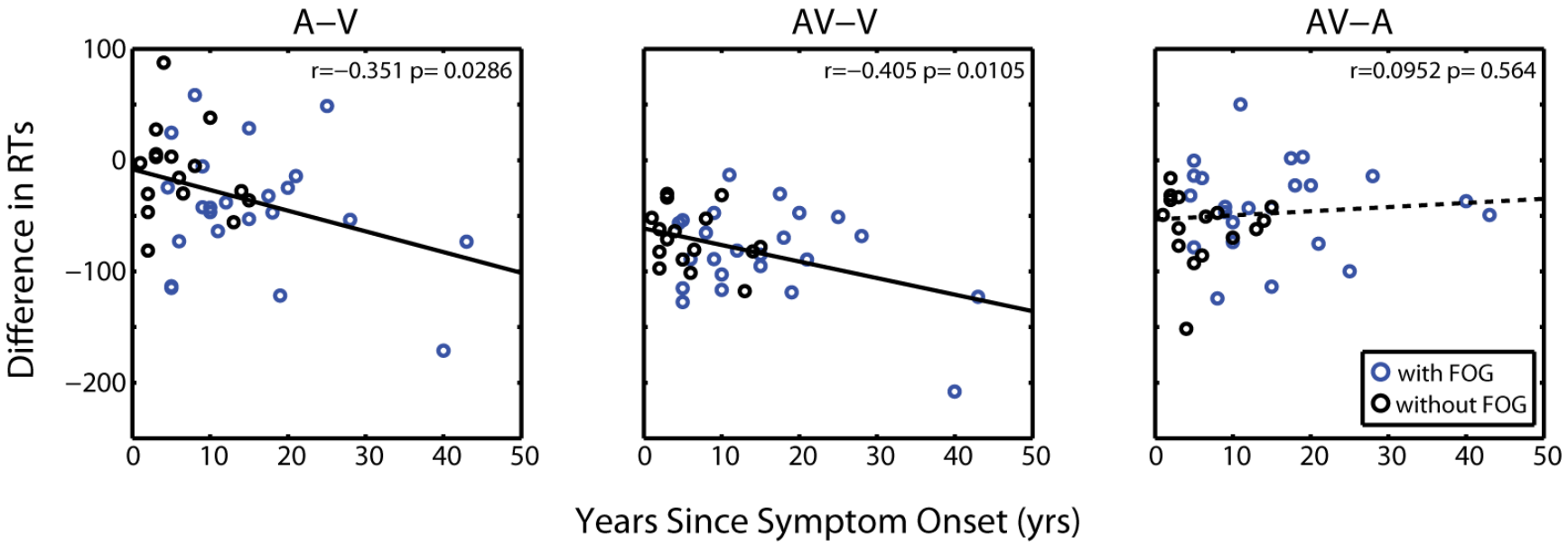


Multisensory Task



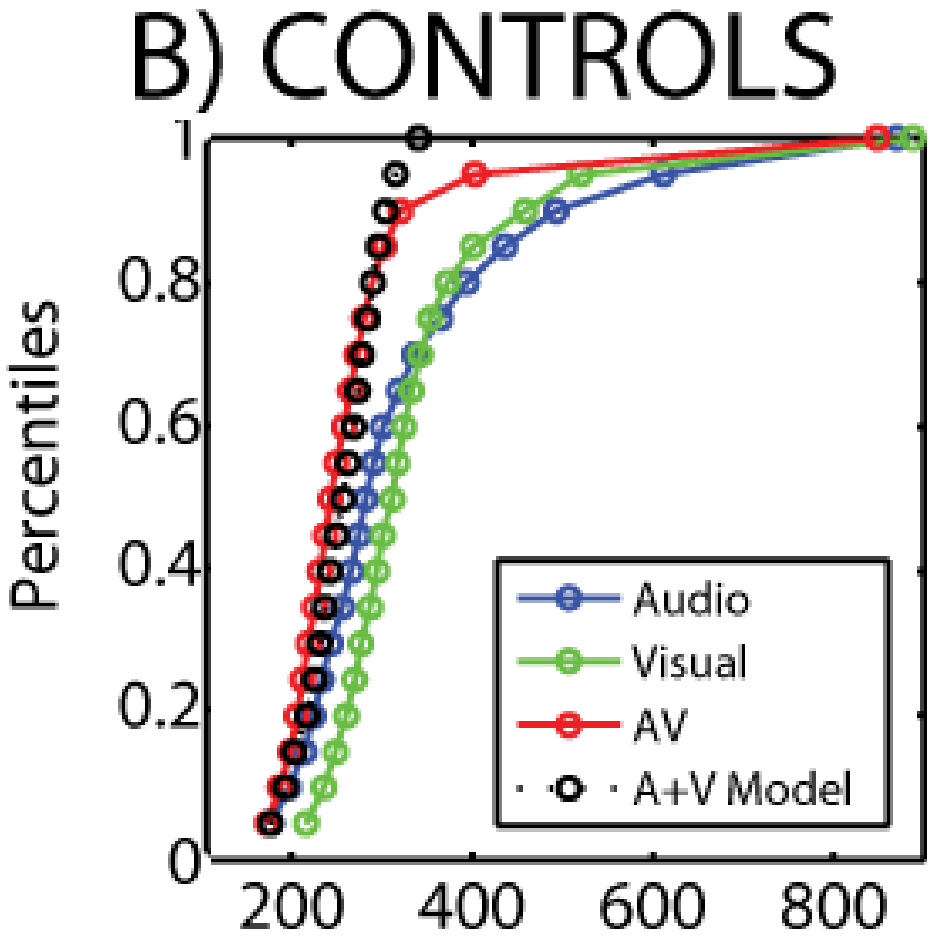
Faster reaction times for the Audiovisual trials for PD and controls

Years Since Symptom Onset

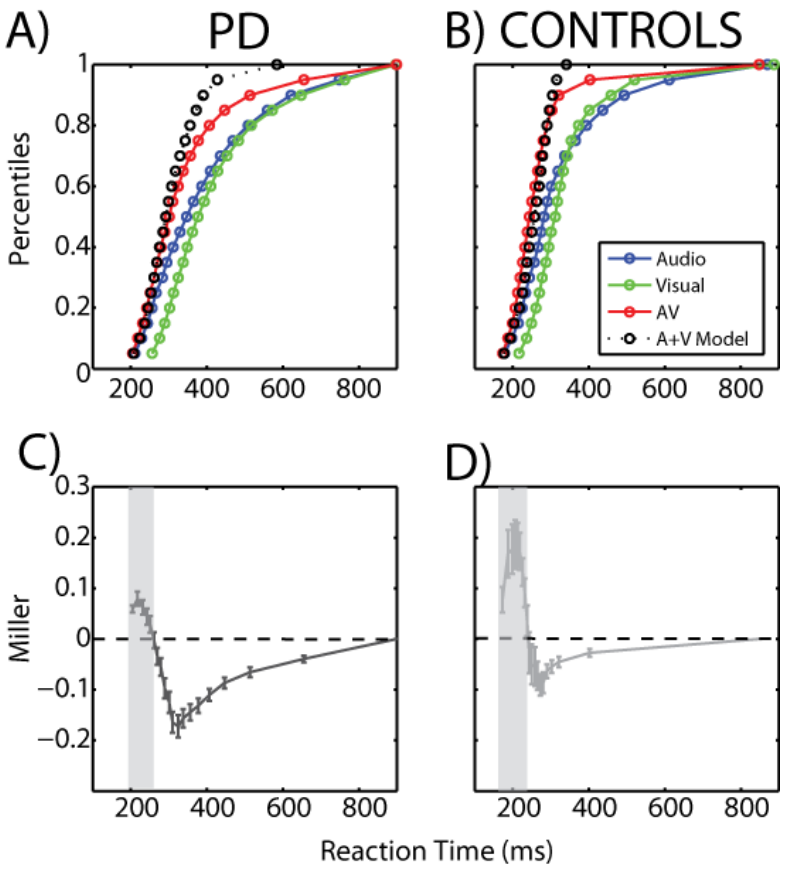


Relative visual difference correlated with years with symptoms onset

Race Model

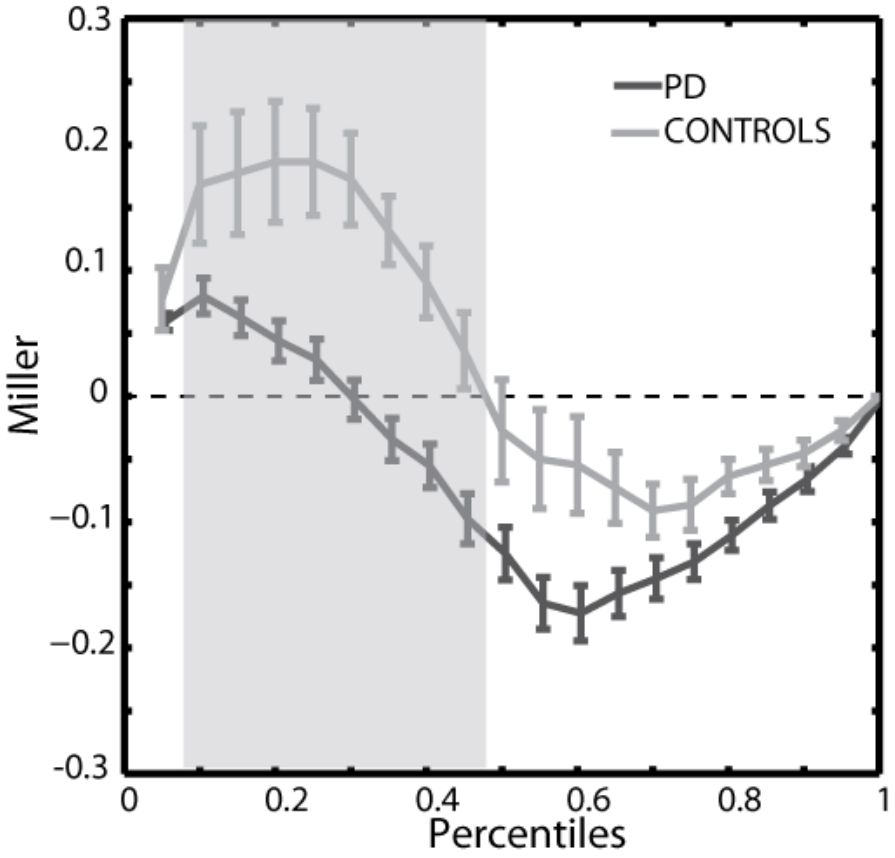

B) CONTROLS
Percentiles
1
0.8
0.6
0.4
0.2
0
200
400
600
800
Audio
Visual
AV
A+V Model

Race Model



Race Model violation (non-linear) sensory integration for both groups

Race Model

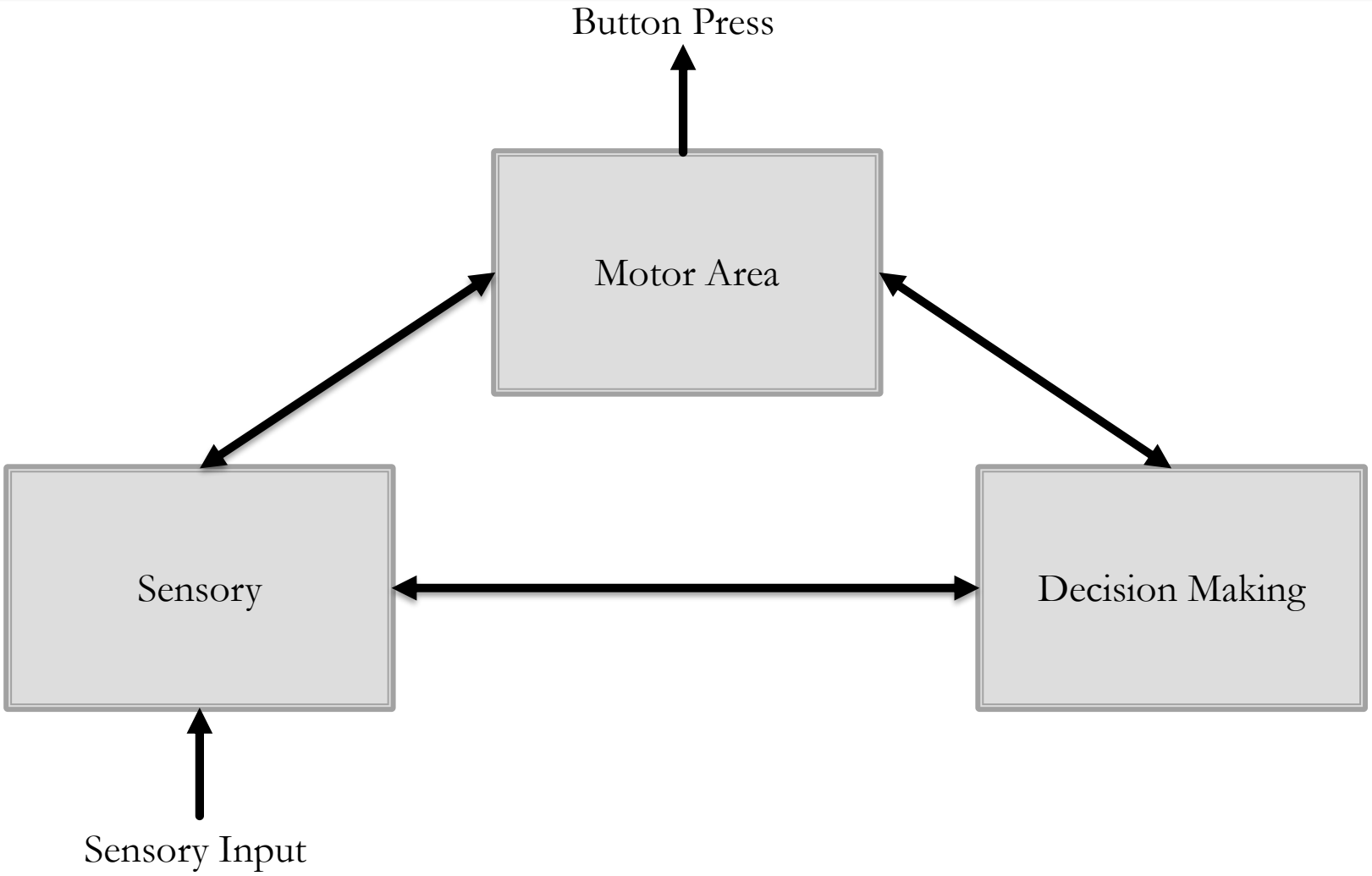


Reduced race model violation for PD group

Summary I

- Both unisensory and multisensory delayed reaction times exist in people with PD, in line with previous findings.
- Relative differences in auditory and visual processing occur in people with PD and correlate with FOG and longer disease duration.
- Multisensory integration of auditory and visual stimuli is significantly less enhanced compared with age-matched healthy controls, adding to the literature supporting both simple and higher order sensory processing abnormalities in PD

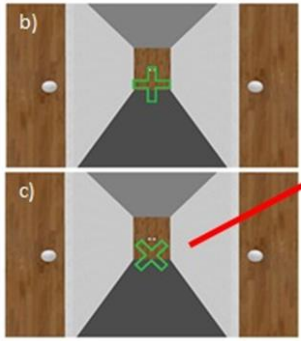
Sensory Motor Decision Making

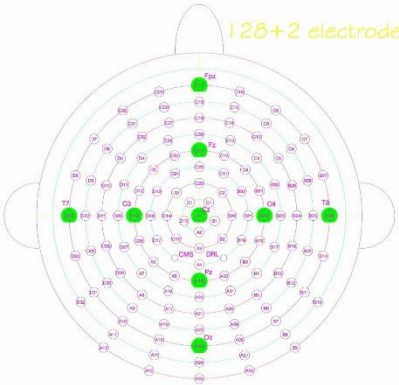


Oddball task

	FOG-	FOG+
N	10	10
Age (years)	62.5 (7.9)	65.3 (7.6)
Gender (M:F)*	4:6	8:2
H&Y stage (median)	2.3 (0.35)	2.6 (0.37)
Disease Duration (years)*	7.0 (3.6)	13.5 (9.1)
UPDRS	29.1 (14)	28.3 (9.7)
MOCA	26.1 (2.9)	24.3 (2.9)
FAB*	17.3 (1.3)	15.2 (2.6)

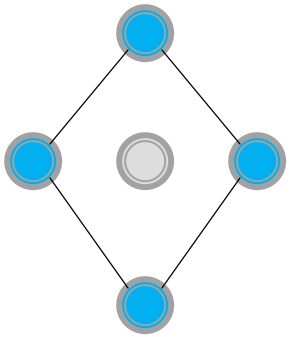
- Standard (80%)
- Target (20%)
- Button Response
- 1000ms epochs
- 128 channels

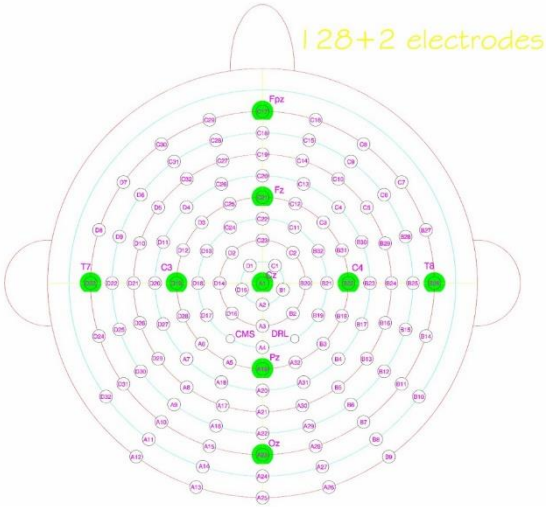




Current Source Density

- CSD
- Second Spatial Derivative
- Local Reference
- Laplacian



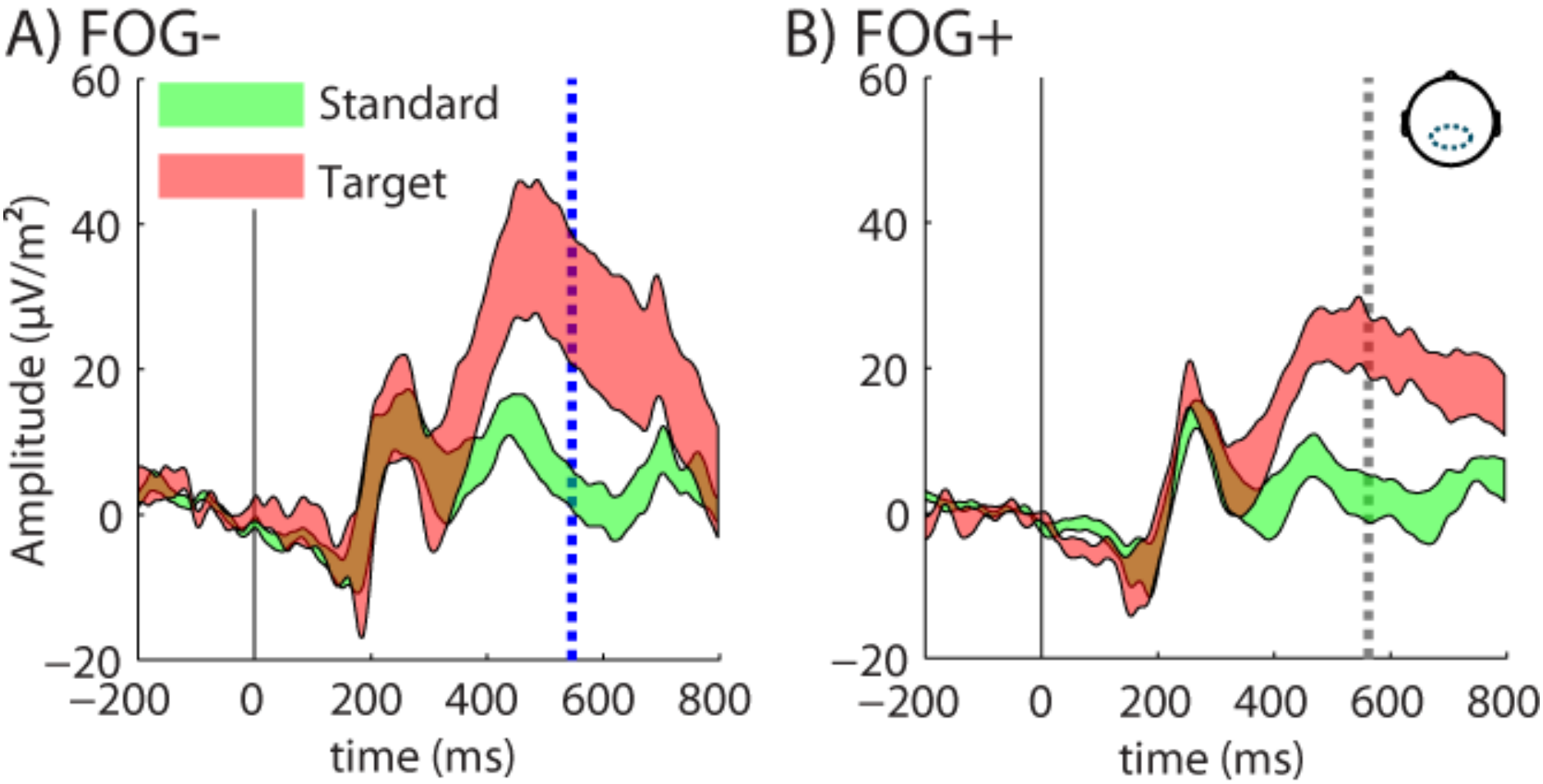


Behavioural Response

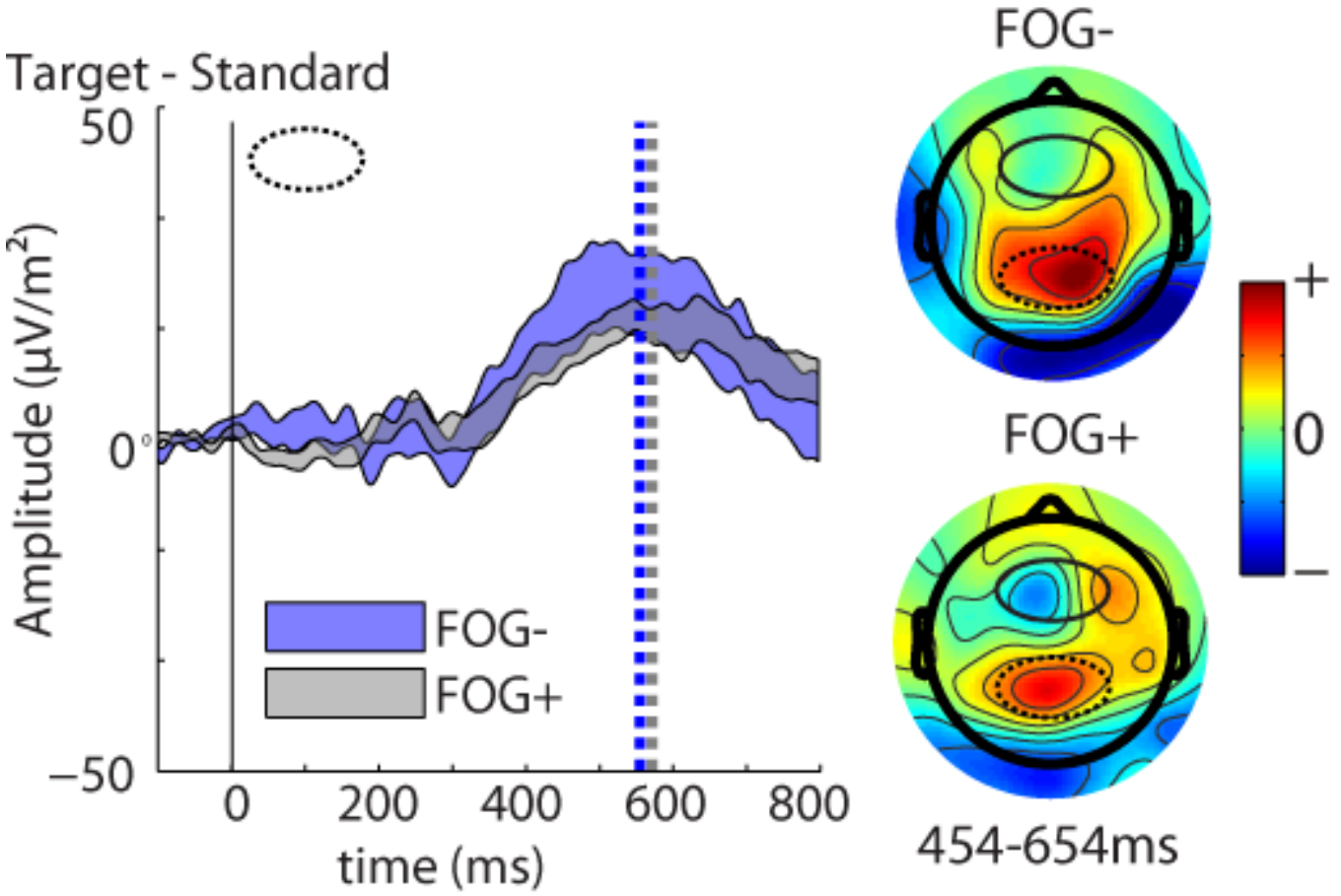
- There was **no significant difference** in mean response times between the ten PwP without FOG (FOG-: blue) (M= 546.0, SD=72.95) and the ten with FOG (FOG+: grey) (M= 562.2, SD=57.02) conditions; (t(18)=-0.5527, p = 0.58760, JZS Bayes Factor =2.25).

- Similarly, there was **no significant difference** in the standard deviation of reaction times for FOG- (M=84.1, SD=28.6) and FOG+ (M=86.4, SD=24.53) conditions; (t(18)=-0.1967, p = 0.84, JZS Bayes Factor =2.482).

Standard vs Target

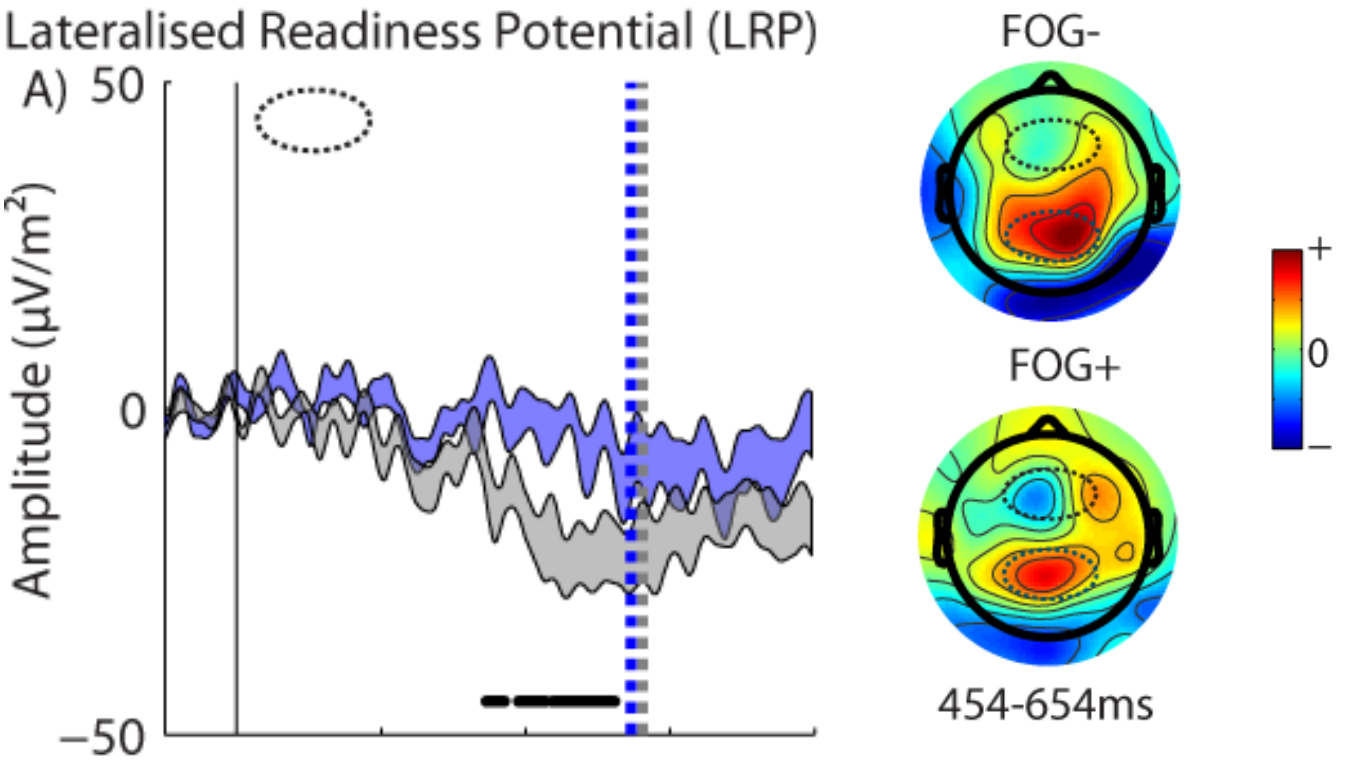


Subtraction Waveform (CPP)



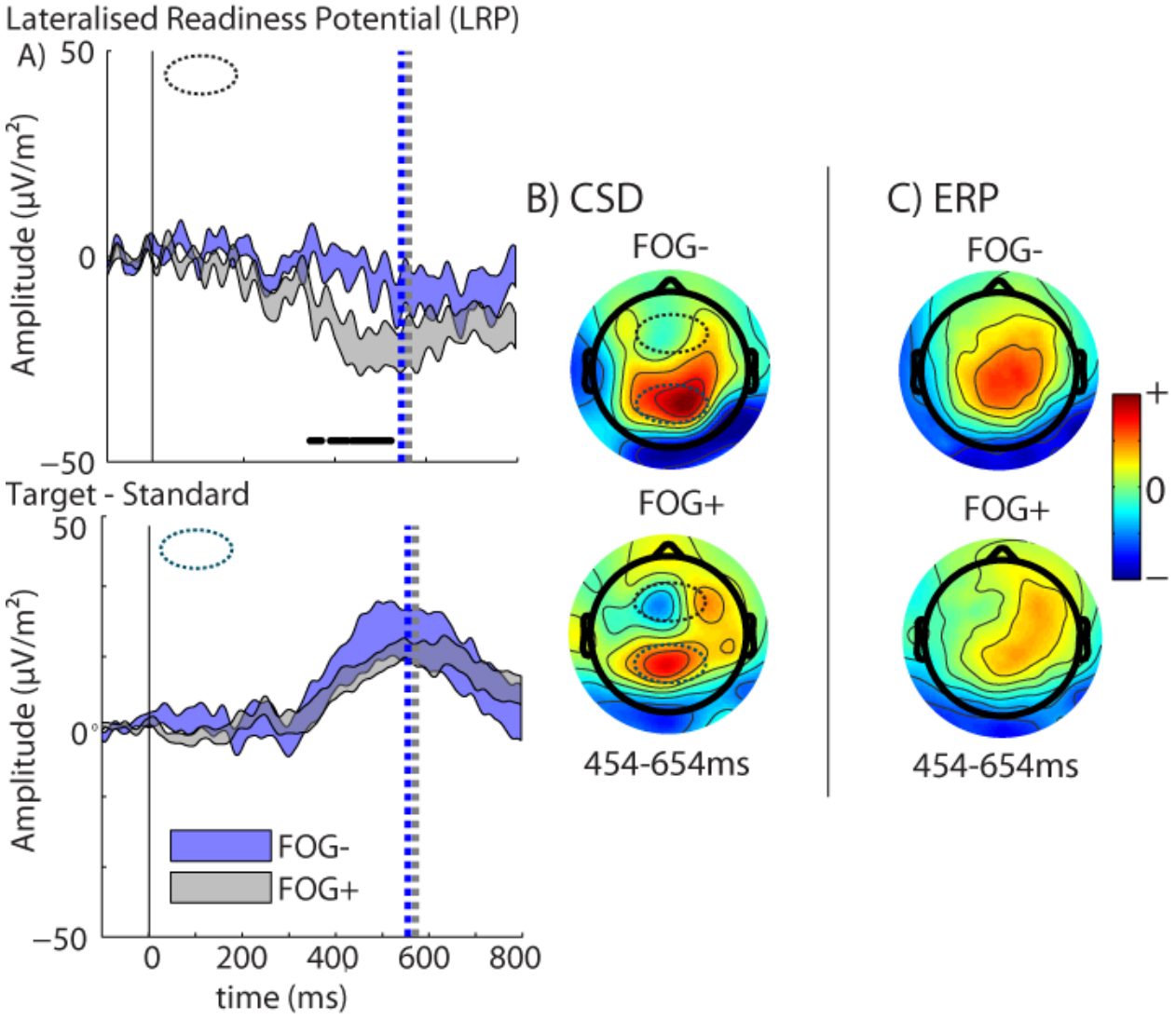
No significant difference in CPP/P3 between groups $F(1,18)=0.357$, $MSE=131.91$, $p=0.55$, JZS Bayes Factor $=2.217$.

Readiness Potential

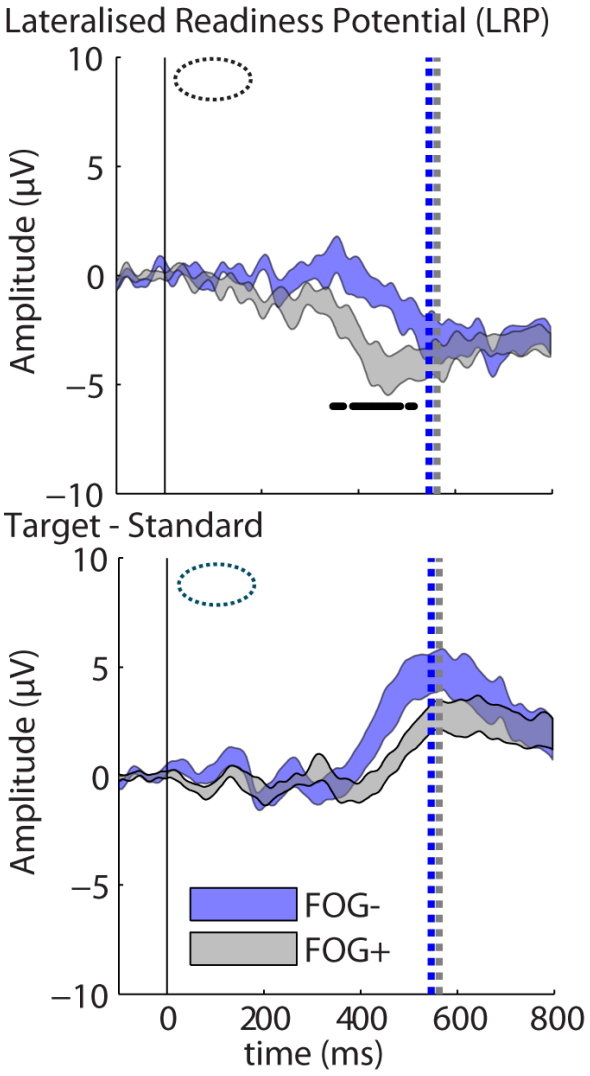


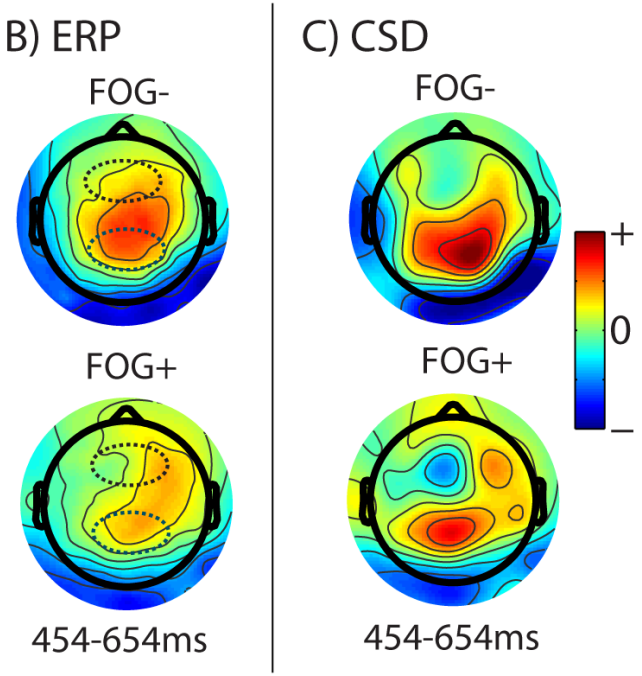
Significant difference in Lateralized Readiness Potential between groups $t(18)=2.388$, $p<0.05$, JZS Bayes Factor $=0.39988$.

Readiness Potential



ERP side story

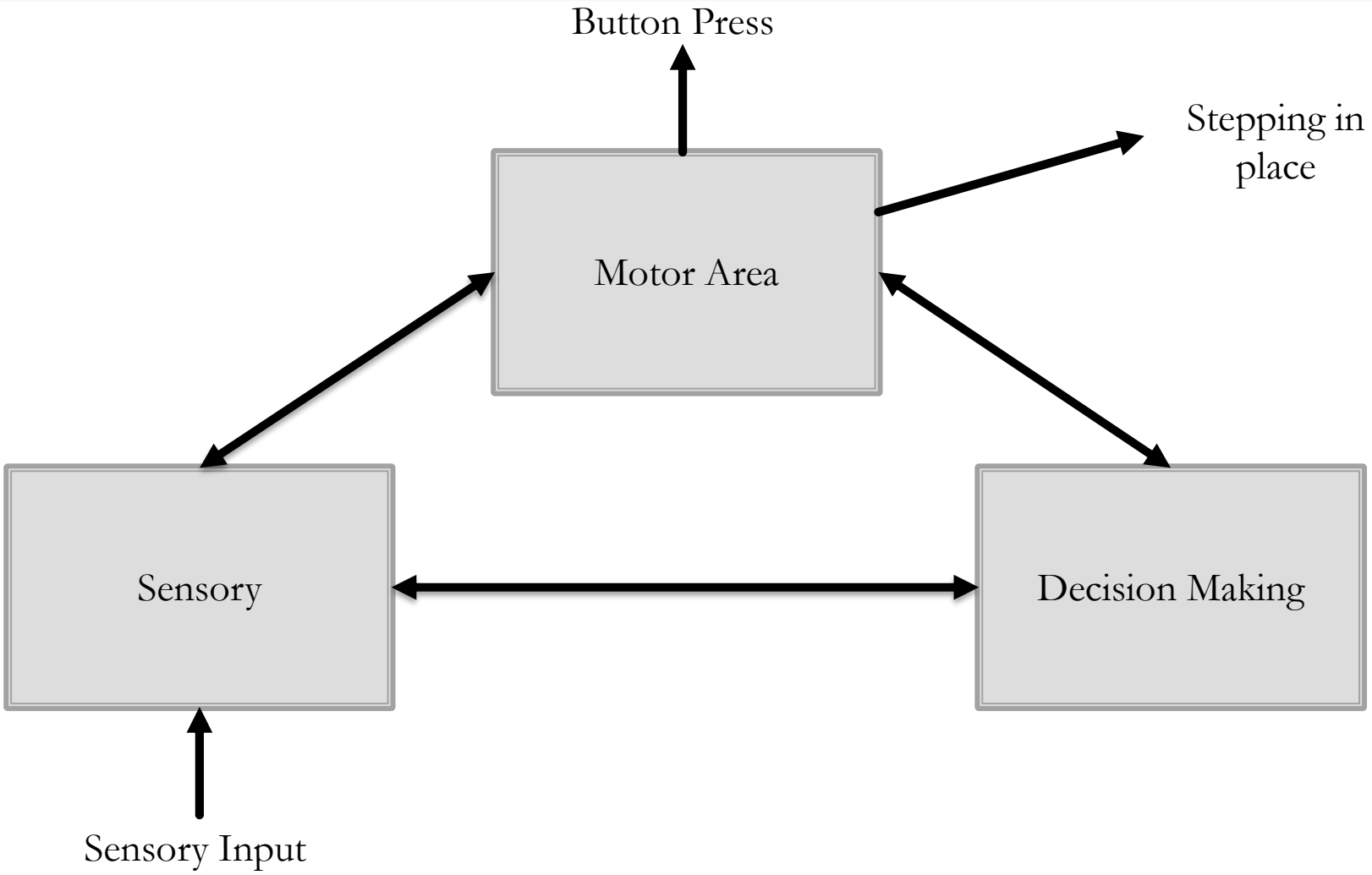




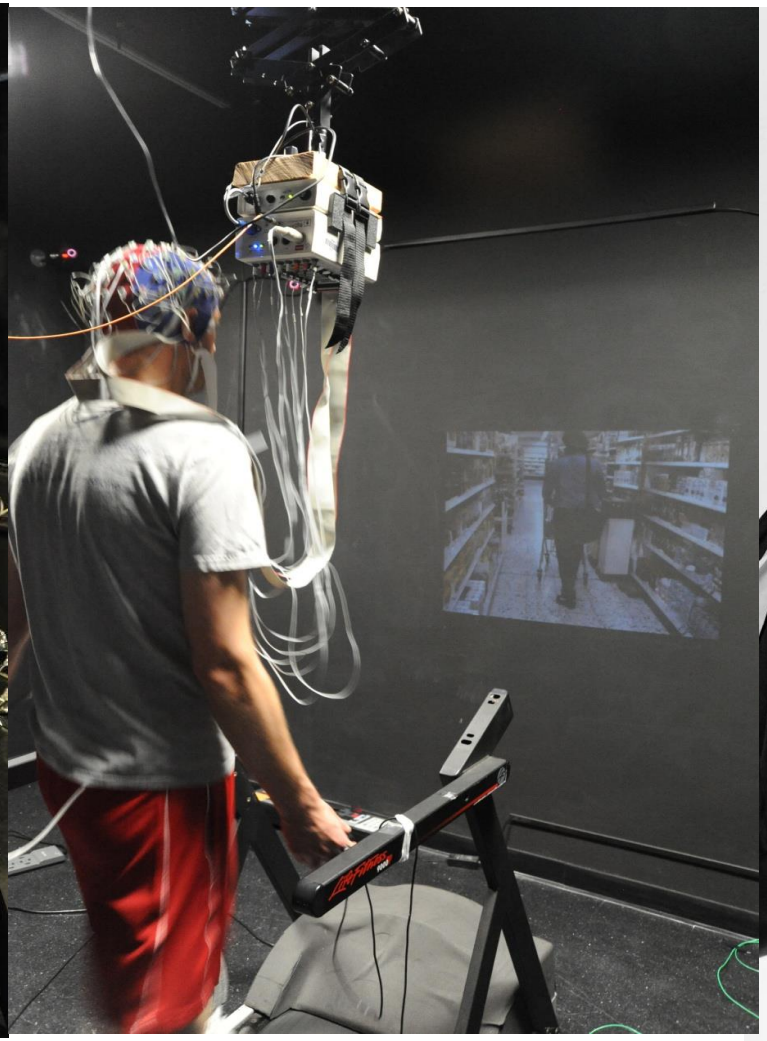
Summary II

- Decision making and reaction time in response to sensory information is equivalent in for FOG+ and FOG-.
- However, motor preparation occurs earlier and requires greater recruitment in FOG+ suggesting that this may be the primary deficit in FOG.
- FAB scores correlates with the amplitude of the lateralized readiness potential, highlighting the important interaction of executive dysfunction and motor preparation in the evolution of FOG.

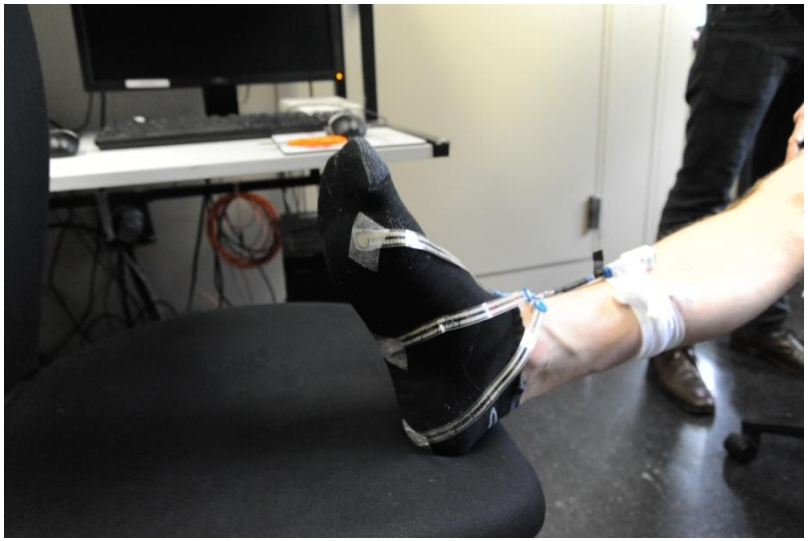
Sensory Motor Decision Making



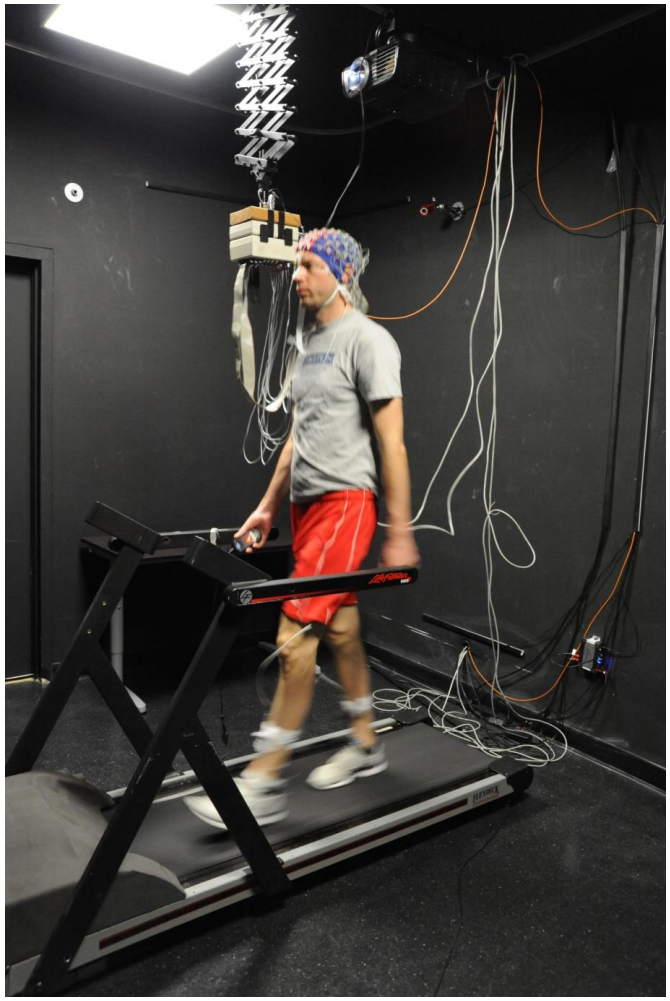
EEG while Walking



EEG while Walking

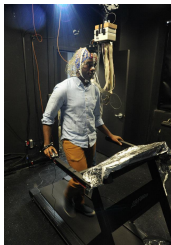


EEG while Walking



Response Inhibition Task

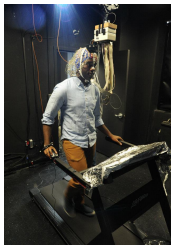
- Task
  - Go/Nogo Response Inhibition Task
  - NoGo: repetition of the same picture
  - Stimulus presentation rate 1/per sec
  - Go/Nogo = 80/20%
- Conditions
  - Sitting
  - Walking Slow (2.4 km/h)
  - Walking Fast (5 km/h)



Response Inhibition Task

- Hit:
  - correct response in a *go* trial
- Correct Rejection:
  - successful withholding of a response in a *nogo* trial
- False Alarm:
  - Executing a response in a *nogo* trial

1. Feasible to acquire usable EEG data while walking
2. Interaction of walking and response inhibition

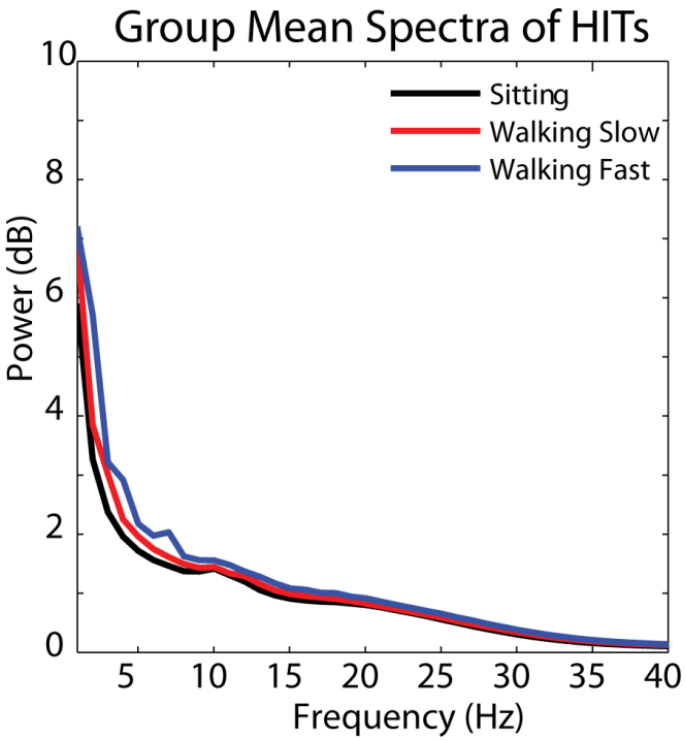


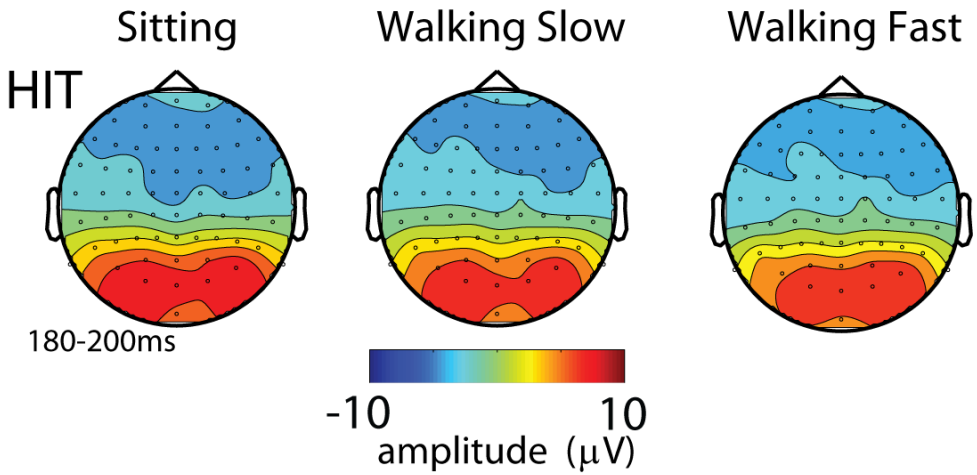
Behavioral and SNR Results

	Sitting	Walking Slow	Walking Fast	p-value
RT in msec	399.1	408.2	401.2	0.53
Hit in %	96.4	98.3	98.5	0.49
CR in %	68.6	70.4	69.4	0.6

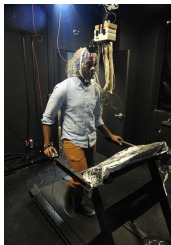
	Sitting	Walking Slow	Walking Fast
SNR Hit (dB)	54.8±2.3	53.6±1.6	49.9±2.2
SNR CR (dB)	35.3±2.0	34.0±2.5	32.6±2.2

Results



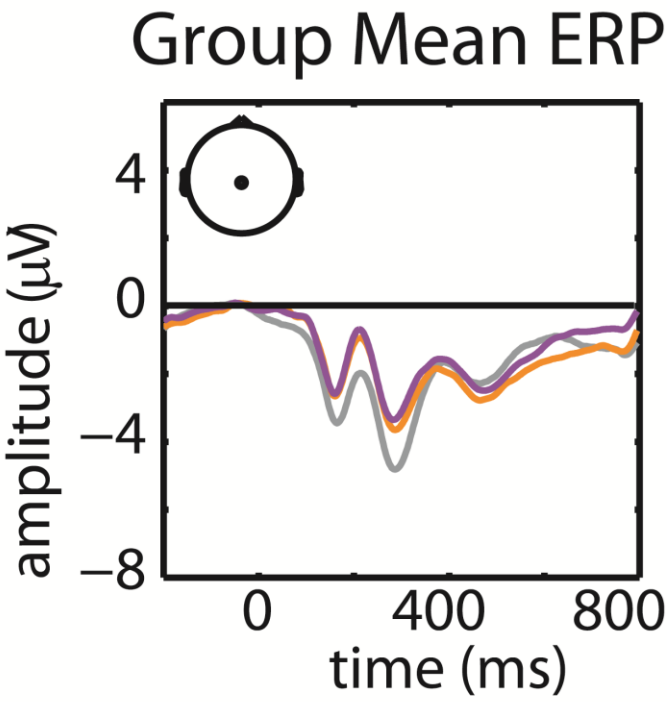


Highly similar early evoked response and power spectrum point to the feasibility of acquiring EEG while walking



Results

HIT
Sitting
Walking Slow
Walking Fast

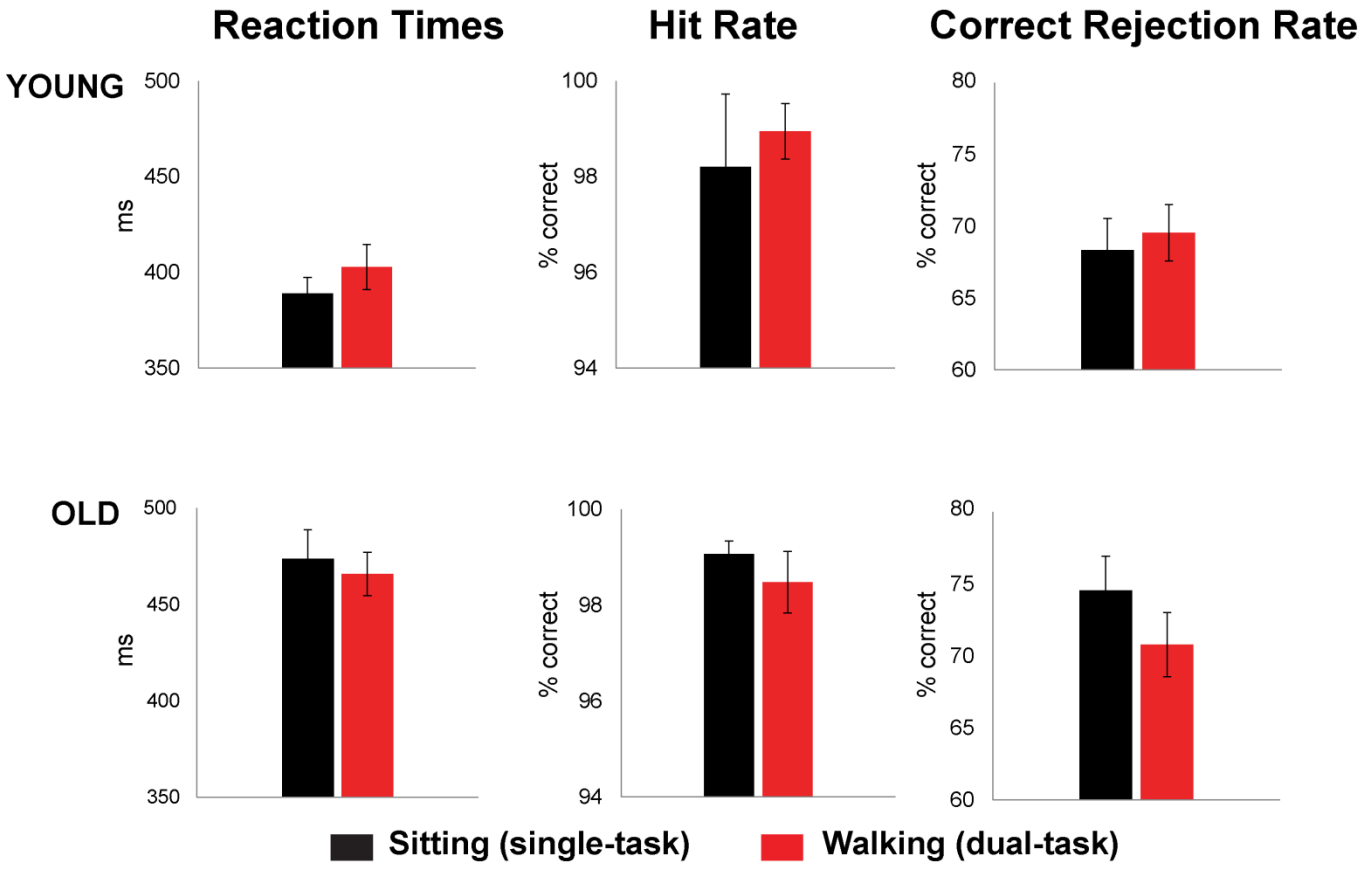


Pierfilippo De Sanctis, John S. Butler, Jason M. Green, Adam C. Snyder, and John J. Foxe

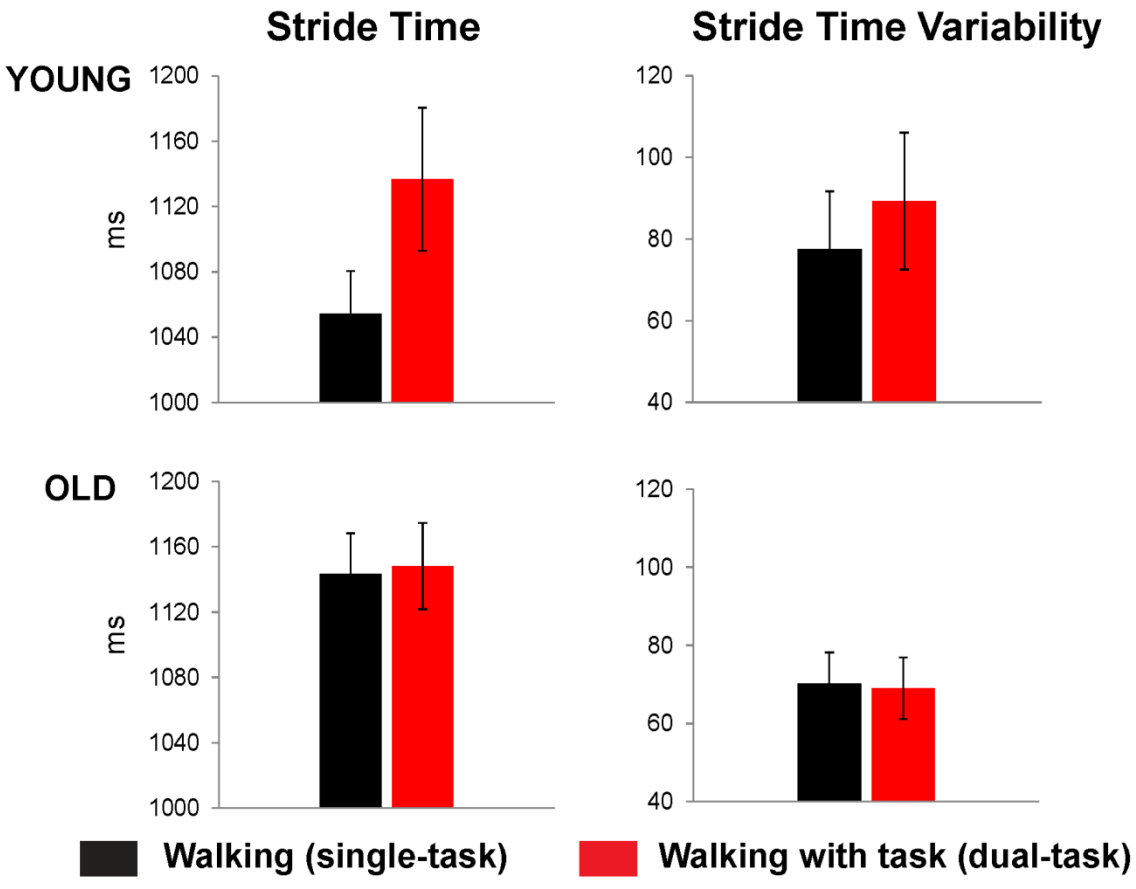
The aging brain shows less flexible reallocation of cognitive resources during dual-task walking: a mobile brain/body imaging (MoBI) study

Age	Young	Old
Range	21.8-36.1	57.7-71.0
Mean	27.2	63.9
SD	4.6	4.0
	N=18	N=18

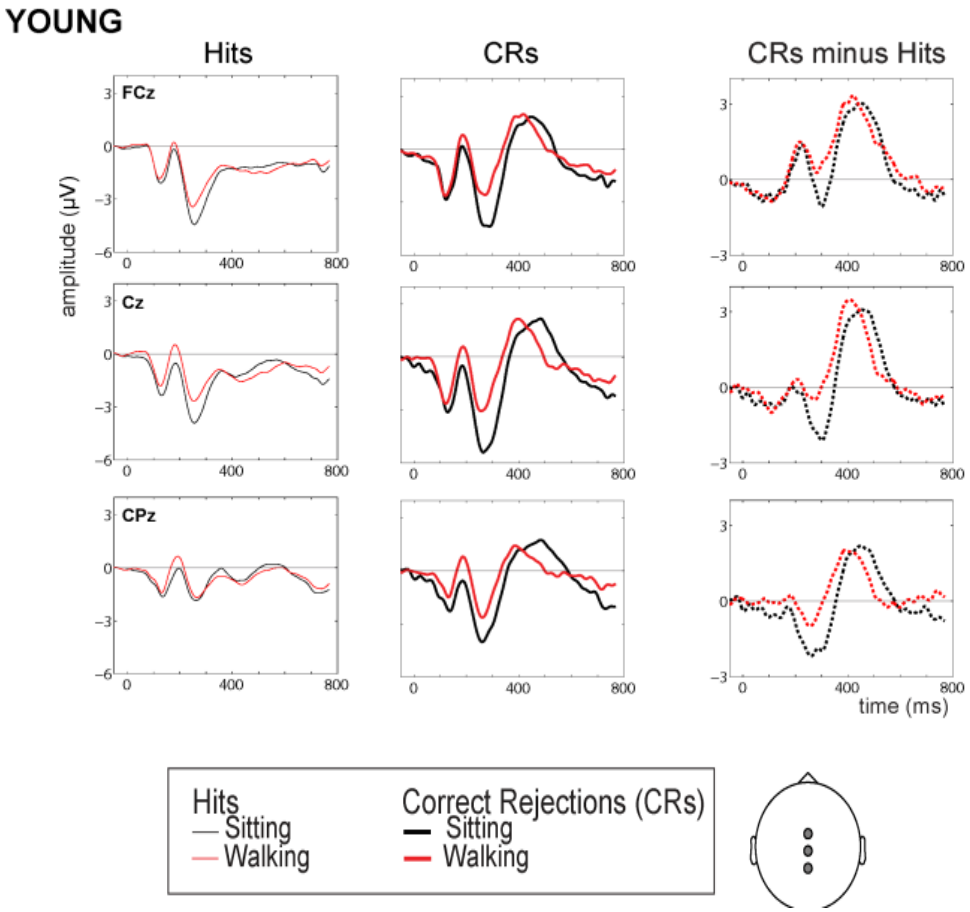
Behavioural



Gait Parameters



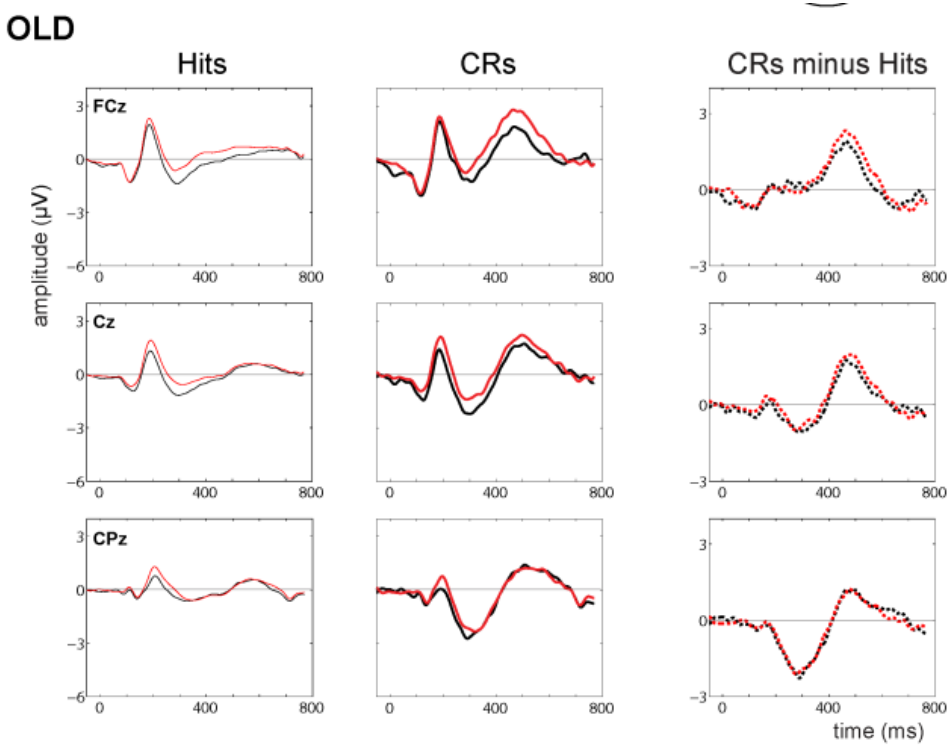
ERP - Young



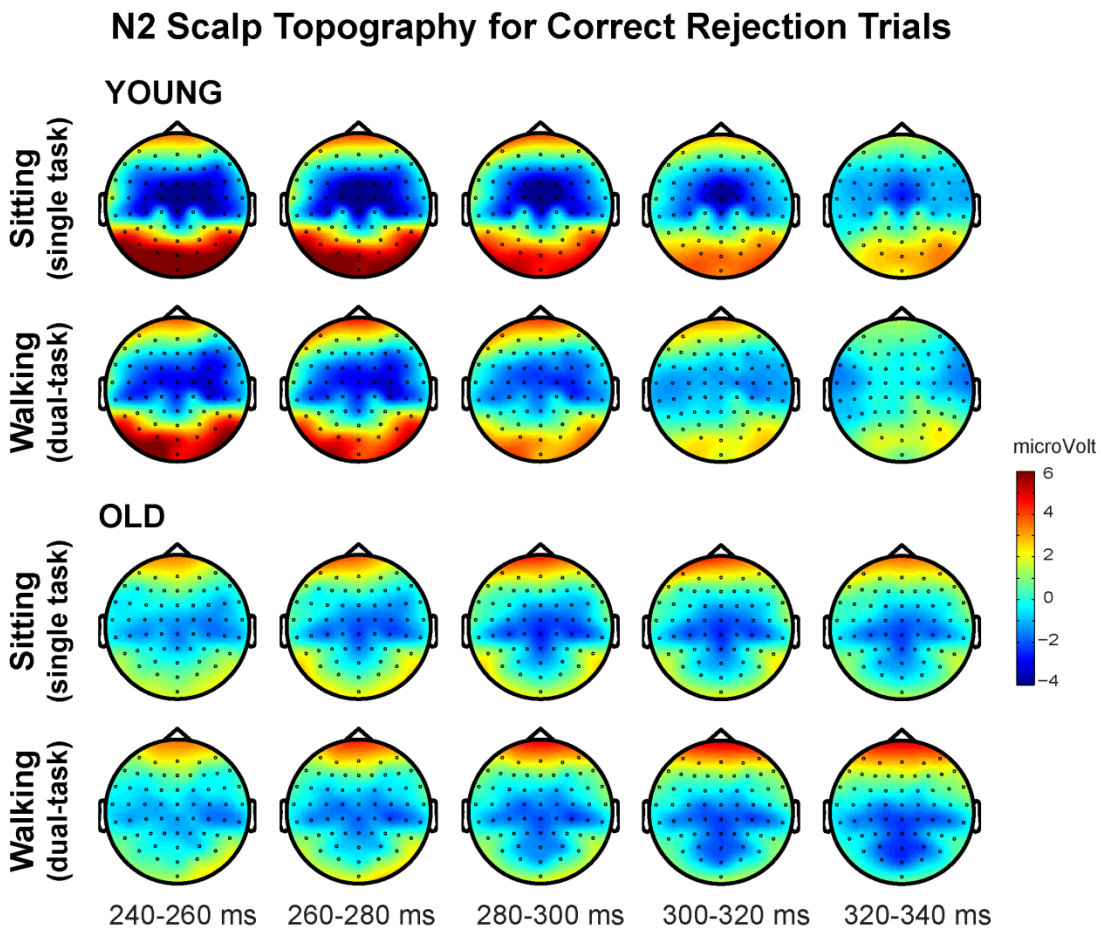
Neuroimage 2014

De Sanctis, **Butler**, Malcolm, Foxe`

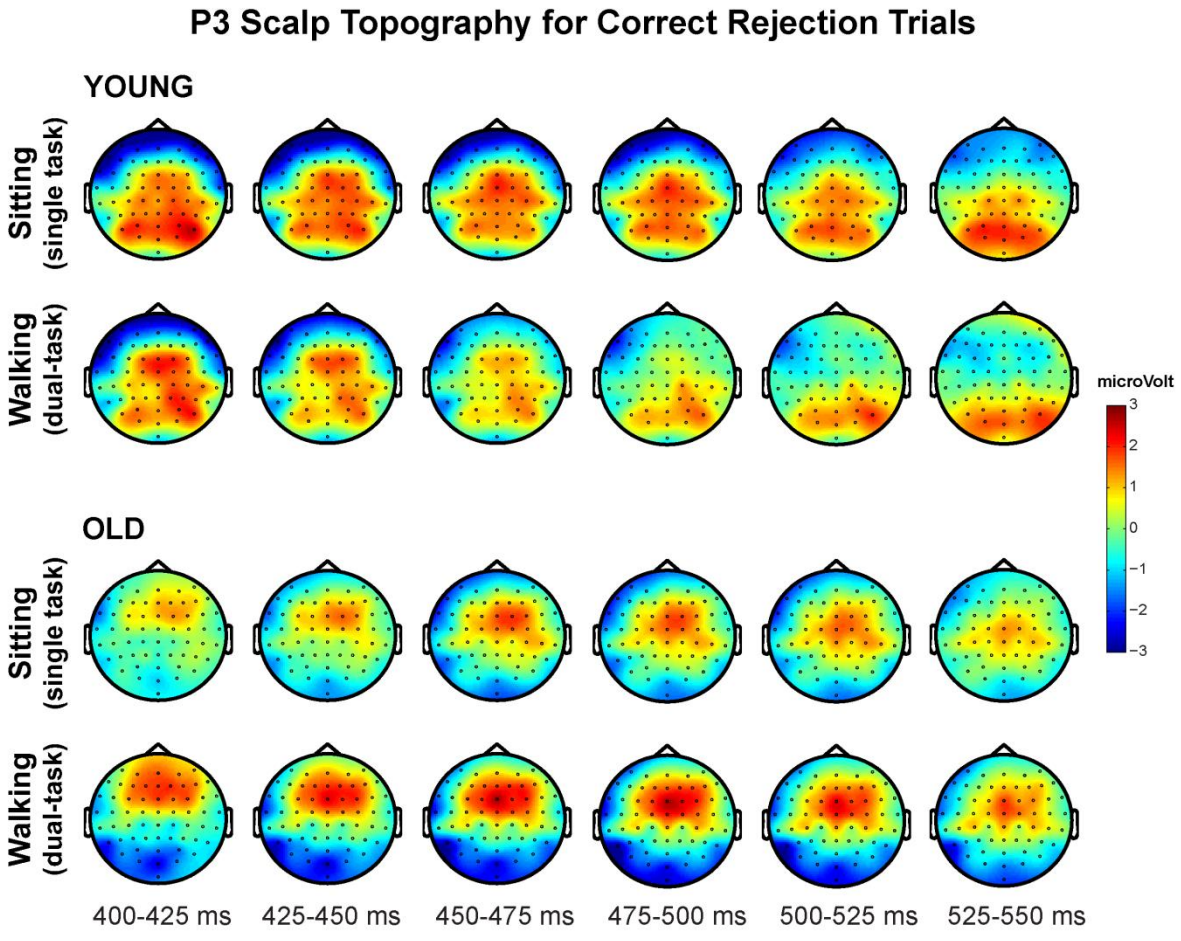
ERP - Old


OLD
Hits
CRs
CRs minus Hits
FCz
Cz
CPz
amplitude (μV)
time (ms)
Hits
Sitting
Walking
Correct Rejections (CRs)
Sitting
Walking

N2 topographical distribution



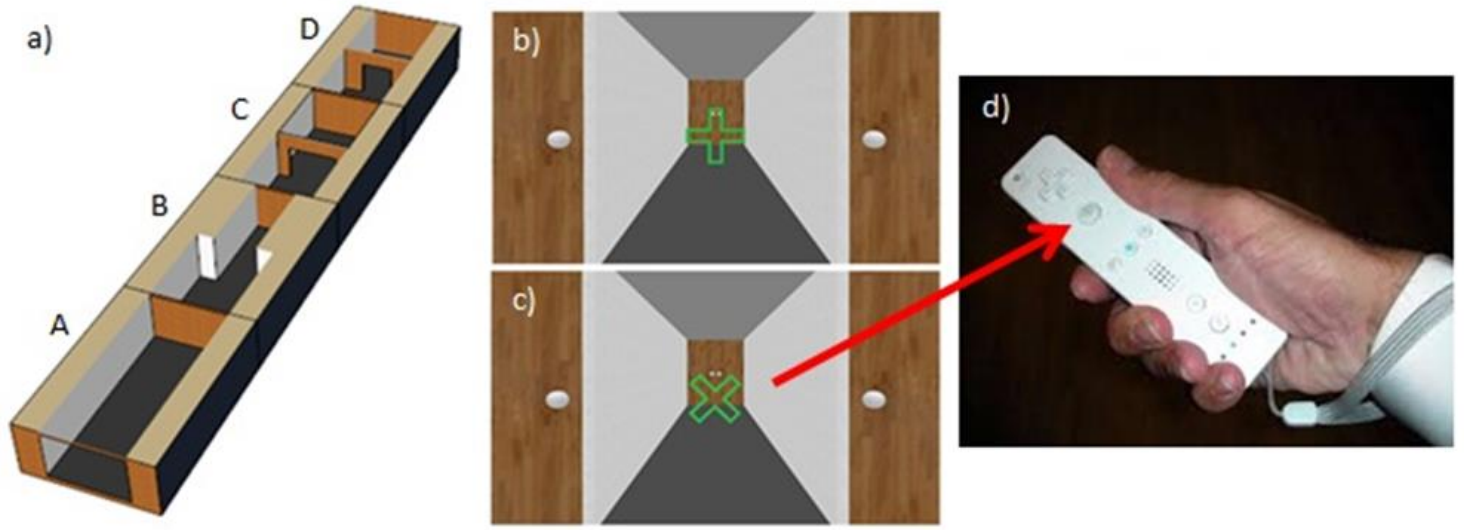
P3 topographical distribution



Summary III

- Younger adults adjust gait and cognitive control when presented with a dual task situation
- Healthy older adults show a lack of flexibility, both in terms of adjusting physical behavior and in reconfiguring cognitive control mechanisms at the neural level.

Dual Task

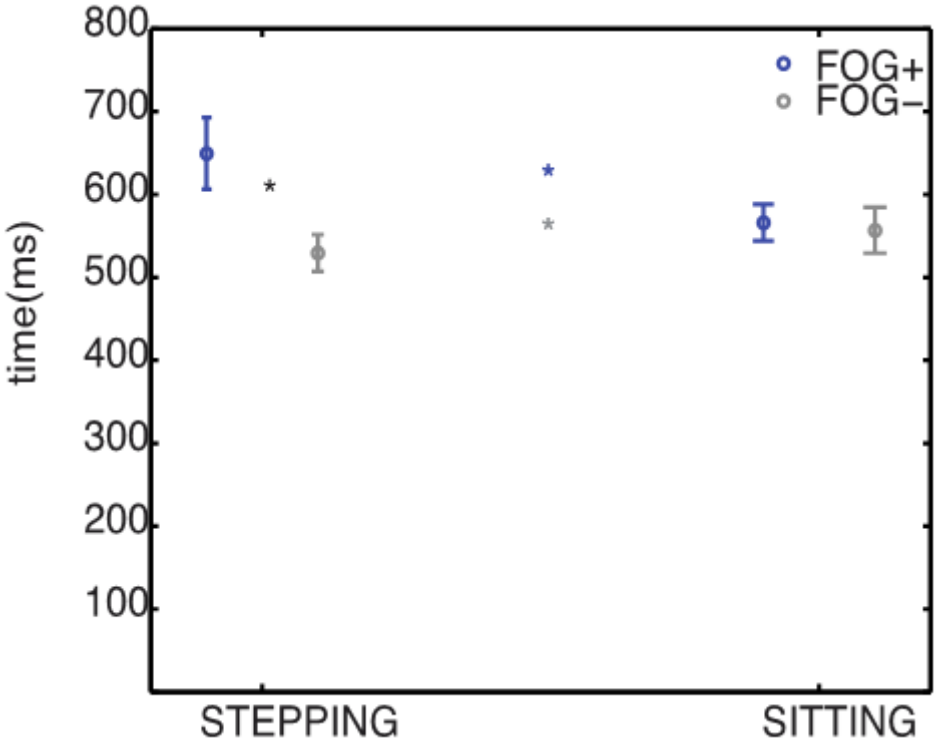


Oddball task while Stepping in Place

	FOG-	FOG+
N	10	10
Age (years)	62.5 (7.9)	65.3 (7.6)
Gender (M:F)*	4:6	8:2
H&Y stage (median)	2.3 (0.35)	2.6 (0.37)
Disease Duration (years)*	7.0 (3.6)	13.5 (9.1)
UPDRS	29.1 (14)	28.3 (9.7)
MOCA	26.1 (2.9)	24.3 (2.9)
FAB*	17.3 (1.3)	15.2 (2.6)

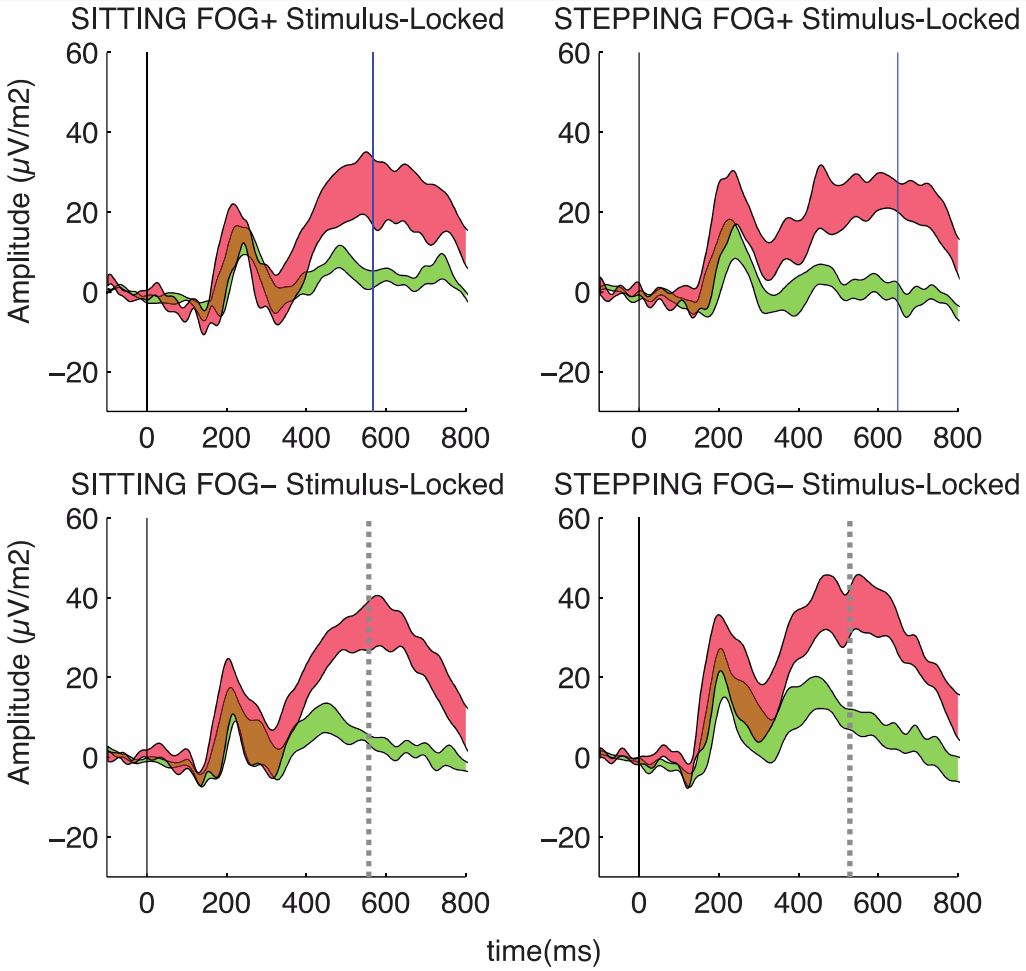
- Standard (80%)
- Target (20%)
- Button Response
- 1000ms epochs
- 128 channels

Behavioural



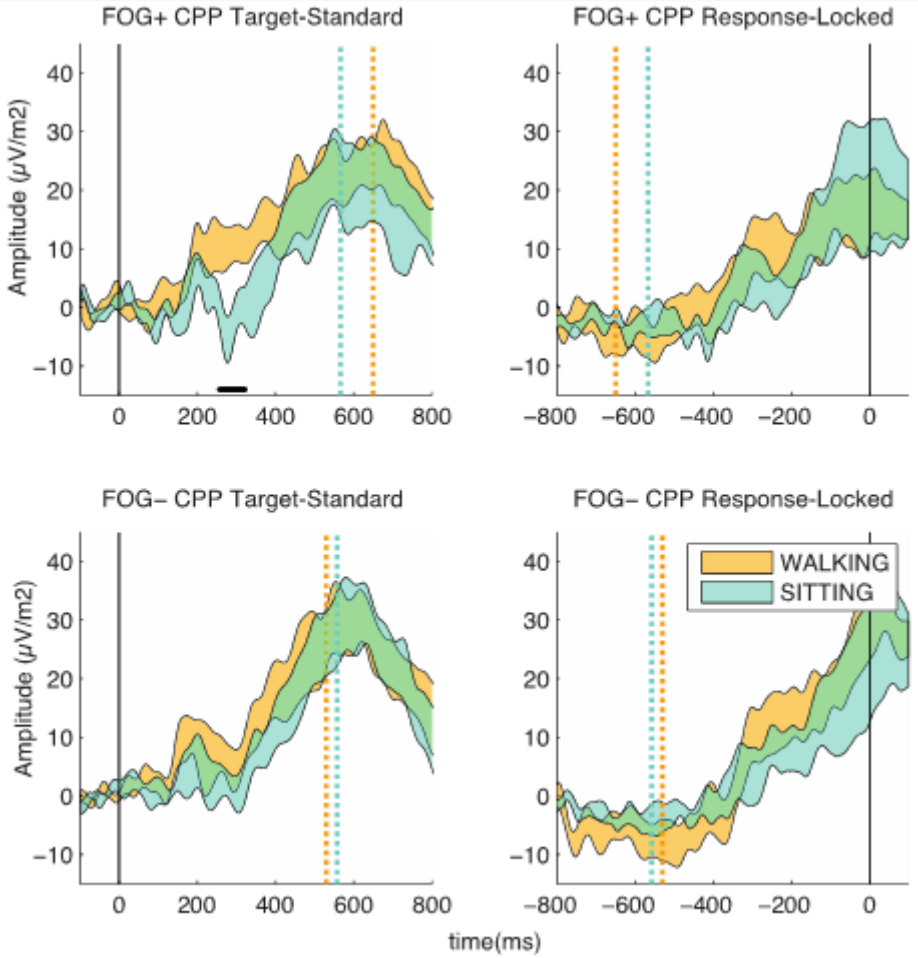
Significant interaction of Response Times for group (FOG-, FOG+) and condition (SIP, SIT)

Standard vs Target



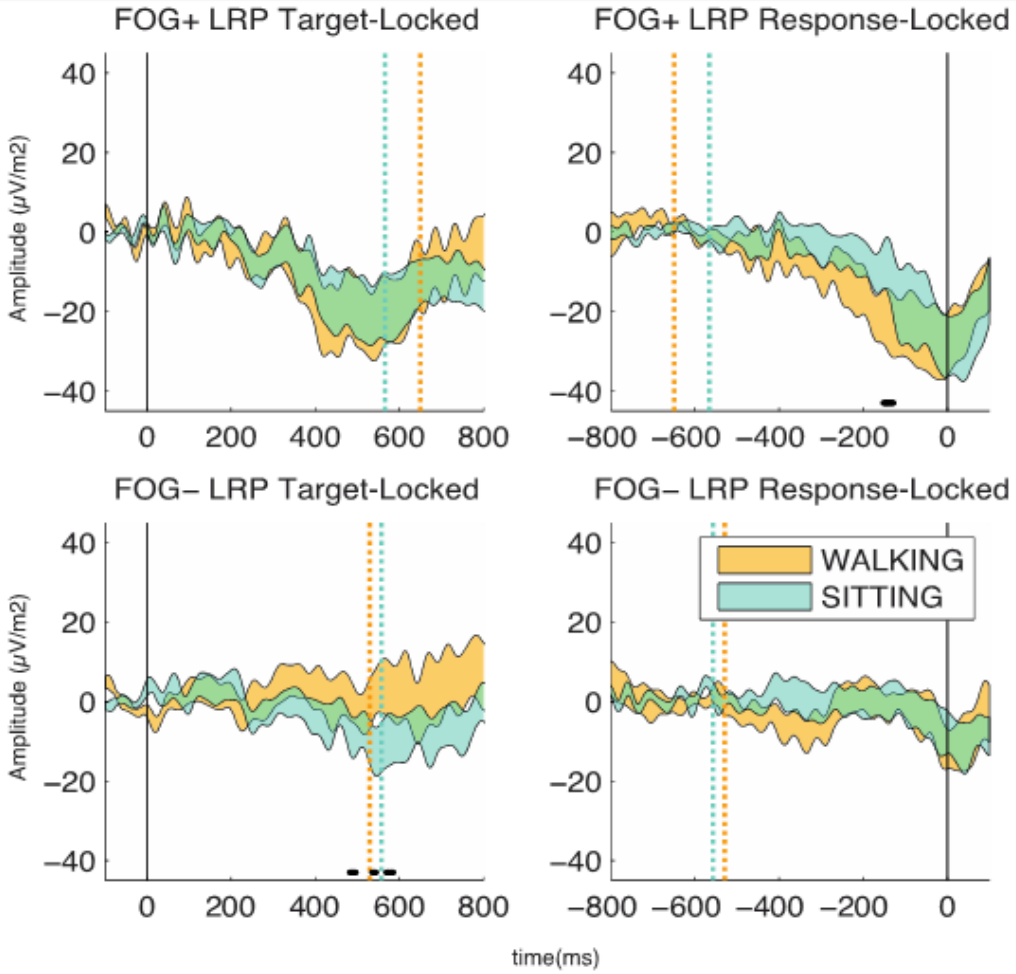
Relatively clean data for both sitting and stepping in place

N2 and CPP



N2 is absent in FOG+ while stepping in place

Readiness Potential



Earlier onset and larger LRP response for the FOG+ group

Summary IV

- With the added load of stepping in place FOG+ response times were slowed
- Absence of N2 suggests that early "automatic" resources are being re-allocated
- The larger and earlier onset of the LRP while walking illustrates the recruitment of resources to perform the task

Conclusion

- Relative sensory processing differences in PD and correlates with years with symptoms.
- LRP is a marker of differences in motor preparation with respect to FOG status even in the absence of differences in standard clinical measures of motor processing (reaction time and UPDRS).
- Taken together these findings explore sensitive and subtle sensory and motor biomarkers of PD and FOG for early intervention, even possibly in the preclinical phase of the disease.

Thank you again

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Conor Fearon
Tim Lynch