On the nature of Rhythm, Time & Memory

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Outline

- Timing substrates
- Timing mechanisms
- Rhythm and Timing
- Unified timing model
- Memory for Time[NEW]

Timing Substrates

Timing in the brain

Cerebellum

Neuropsychological work in patients with cerebellar degeneration (Ivry):

- **Patient groups:** Unilateral/bilateral CB lesions; Parkinson's patients; Ataxics
- **Timing tasks:** Motor: Finger tapping, circle drawing
  Perceptual: duration discrimination
- **Response Measure:** Variability – motor vs. clock (c.f. Wing & Kristofferson, 73)
- **Timing mechanisms:** Event-based (tapping) vs. Emergent (cont. circle) timing
- **Results:** CB patients impaired on event-based timing tasks
  PD patients impaired on emergent timing tasks

CB and Timing

- Involved in sub-second and not supra-second time perception
- Critical for behaviour requiring real-time prediction
- CB: error-based learning (climbing fiber as teaching signal)
- CB: instantiates an internal forward model

➢ **CB as a dedicated (event-based) timing system**

Basal ganglia

Neuropsychological work in patients (Artieda/Pastor/Harrington):

Parkinson's patients impaired on time perception and production tasks, implicating the nigrostriatal dopaminergic system.

Neurophysiological work in animal models with lesions/pharmacology (Meck):

- **Timing tasks:** Peak-interval timing
- **Response Measure:** Gaussian PI response function (mean & precision)
- **Timing mechanisms:** Striatal Beat Frequency model (Matell and Meck, 2004)
- **Results:** PI response function shifts horizontally with DA +/- (i.e., internal clock speeds up or down)

Magnitude of leftward shift α DA (+) dose
Magnitude of rightward shift α DA (-) affinity to D2 receptor

BG and Timing

- Dorsal striatum (putamen and caudate) key for time perception
- Role of striatum in timing is dopamine dependent (nigrostriatal dopamine)
- Striato-frontal network (BG-SMA-PMC-DLPFC) key for timing
- BG computations based on dopamine-dependent reinforcement learning

➢ **Dorsal striatum as a possible substrate for an internal clock**

Cortex and Hippocampus

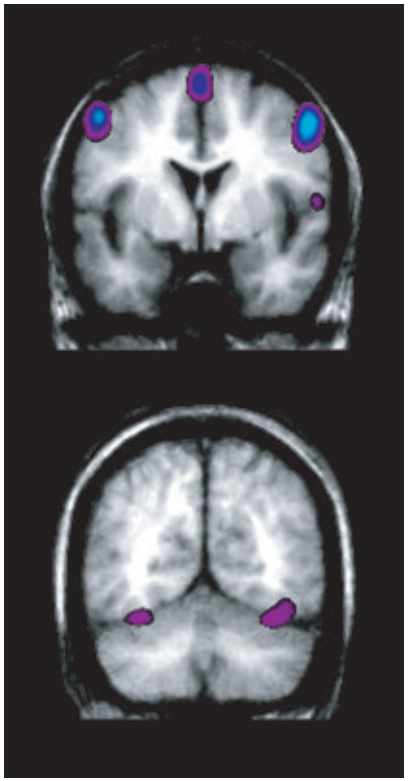
- Lesions of nucleus basalis (cholinergic input to frontal cortex) -> rightward shift
- Lesions of medial septum (cholinergic input to hippocampus) -> leftward shift

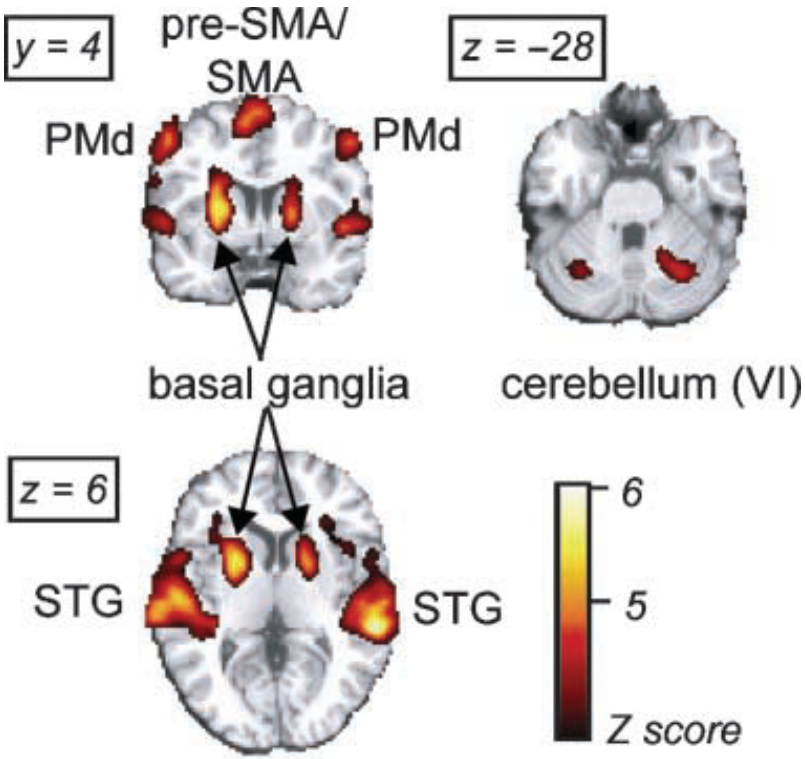
- Timing effects after cholinergic lesions take several sessions to build up unlike effects of dopaminergic lesions, suggesting changes in the encoding of temporal memories rather than speed of the internal clock.

- Frontal cortex (e.g. DLPFC) mediates working memory and attention, which are recruited during timing of supra-second intervals.

➢ **Modulatory role for cortex/hippocampus in interval timing**

Recent neuroimaging evidence





Listening to rhythms recruits several regions of the brain:

Cerebellum, basal ganglia; pre-SMA/SMA, pre-motor; STG, prefrontal

Bengtsson, Chen, Grahn et al.

Timing Mechanisms

Timing classifications

- **Sub-second** vs. **Supra-second timing**
- **Event-based timing** vs. **Emergent timing**

Ivry et al.

- **Implicit** vs. **Explicit timing**

Coull et al.

- **Automatic** vs. **Cognitive timing**

Lewis and Miall

- **Duration-based** vs. **Beat-based timing**

Griffiths et al.

Timing Mechanisms

- **Relative, beat-based timing:**

  Timing of intervals relative to a regular beat (ΔT_i / T_{beat})

- **Absolute, duration-based timing:**

  Encoding absolute duration of individual time intervals (ΔT_i)

Beat-based timing

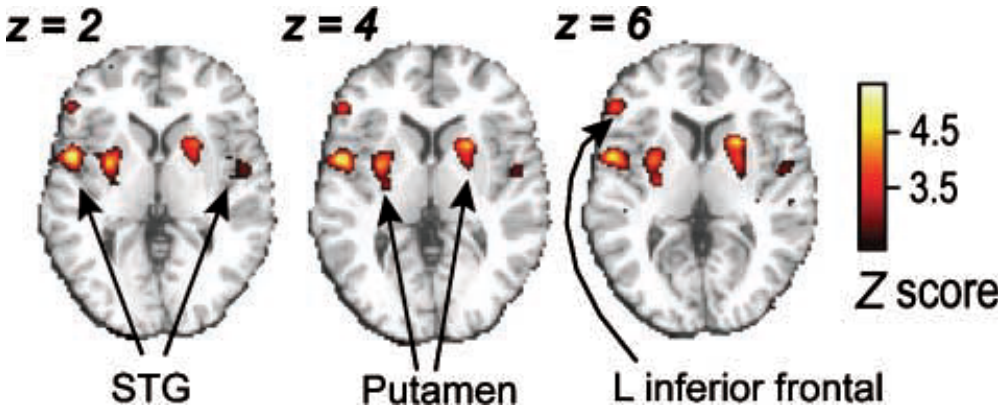
A regular beat offers beneficial temporal cues in perceptual timing

(Povel & Essen, 1985)

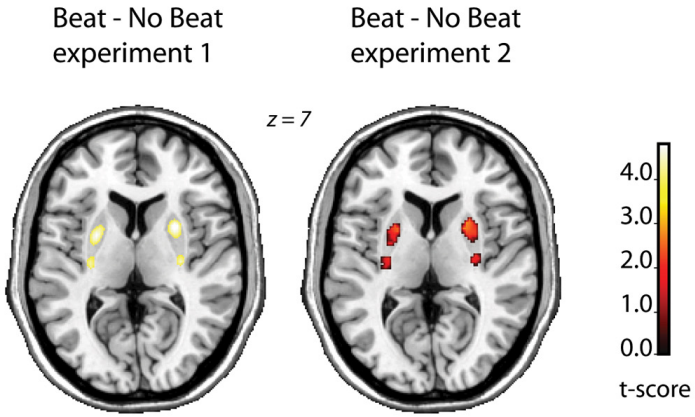
Parkinson's patients show deficits in perceptual timing tasks.

(*Artieda et al. 1992, Harrington et al. 1998, Grahn & Brett, 2009)*

Beat-based timing



Grahn and Brett, 2007



Grahn and Rowe, 2009

Basal ganglia, pre-SMA/SMA, and pre-motor cortex

implicated in perception of beat-based and metrical rhythmic sequences.

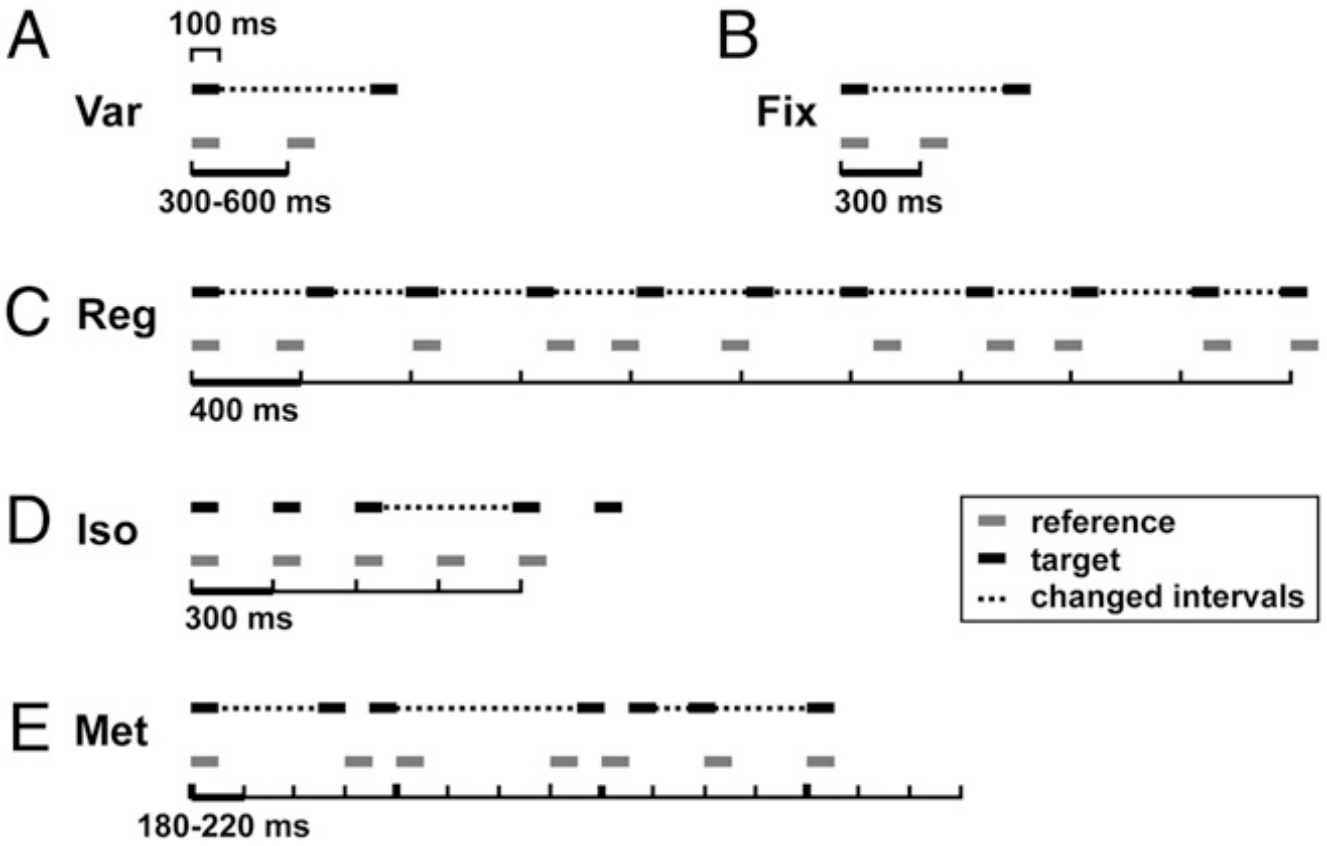
Duration-based timing

Cerebellum: **Encoding of absolute duration of discrete time intervals.**

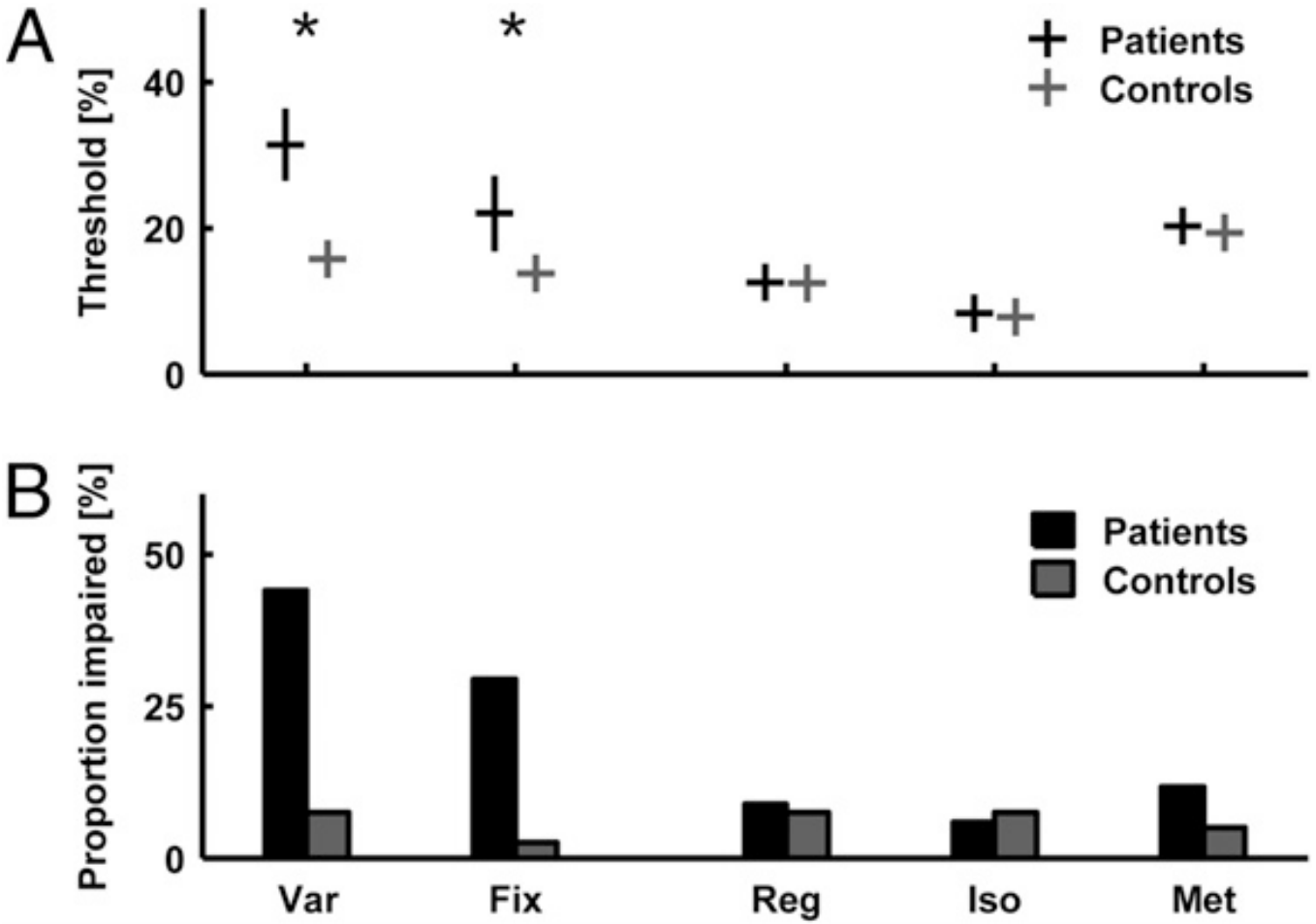
(Ivry)

Duration-based timing

Patients with Spino Cerebellar Ataxia type 6:



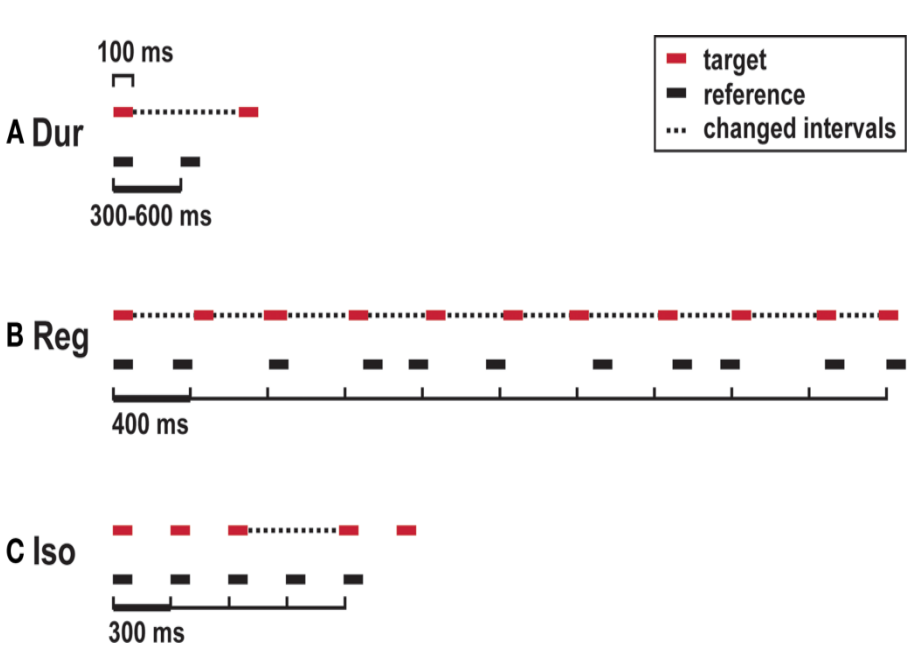
Duration-based timing

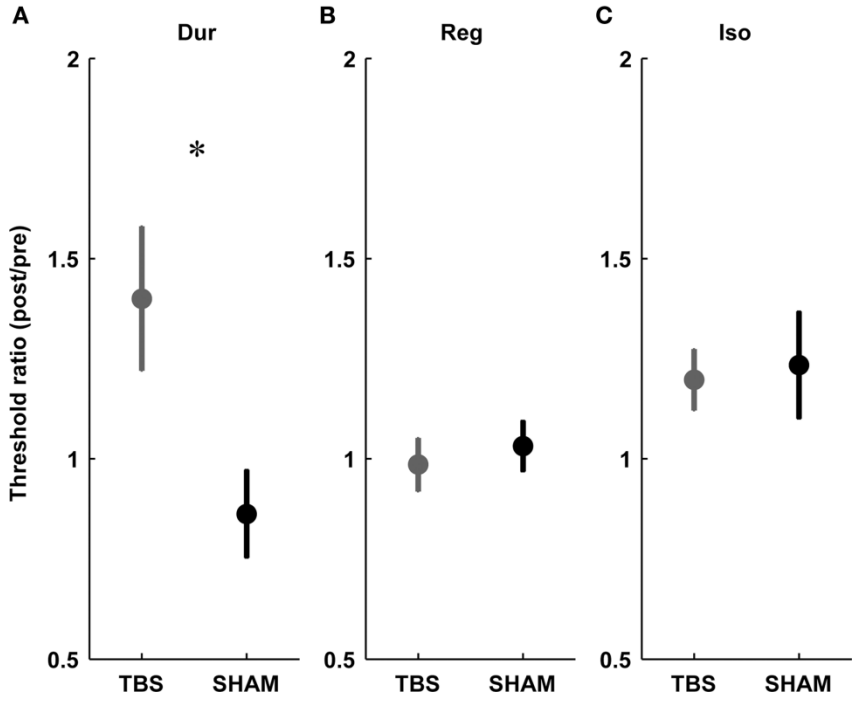


(Grube et al., 2010: PNAS)

Duration-based timing

Normal subjects with TMS over medial cerebellum:





(Grube et al., 2010: Frontiers)

Rhythm & Time

fMRI study

Aim: Test for dissociation between the timing functions of cerebellum and basal ganglia according to the rhythmic context of time intervals.

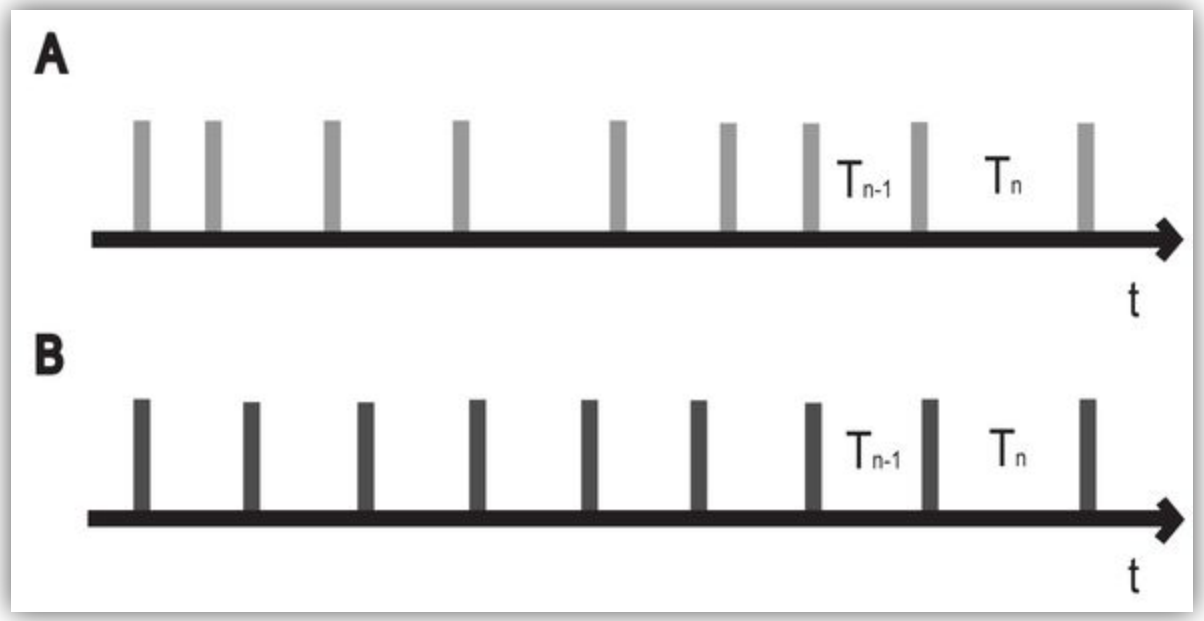
Hypotheses:

H1: Beat-based timing more accurate than duration-based timing

H2: Cerebellum more involved in absolute, duration-based timing

H3: Basal ganglia more involved in relative, beat-based timing

Stimulus and Task

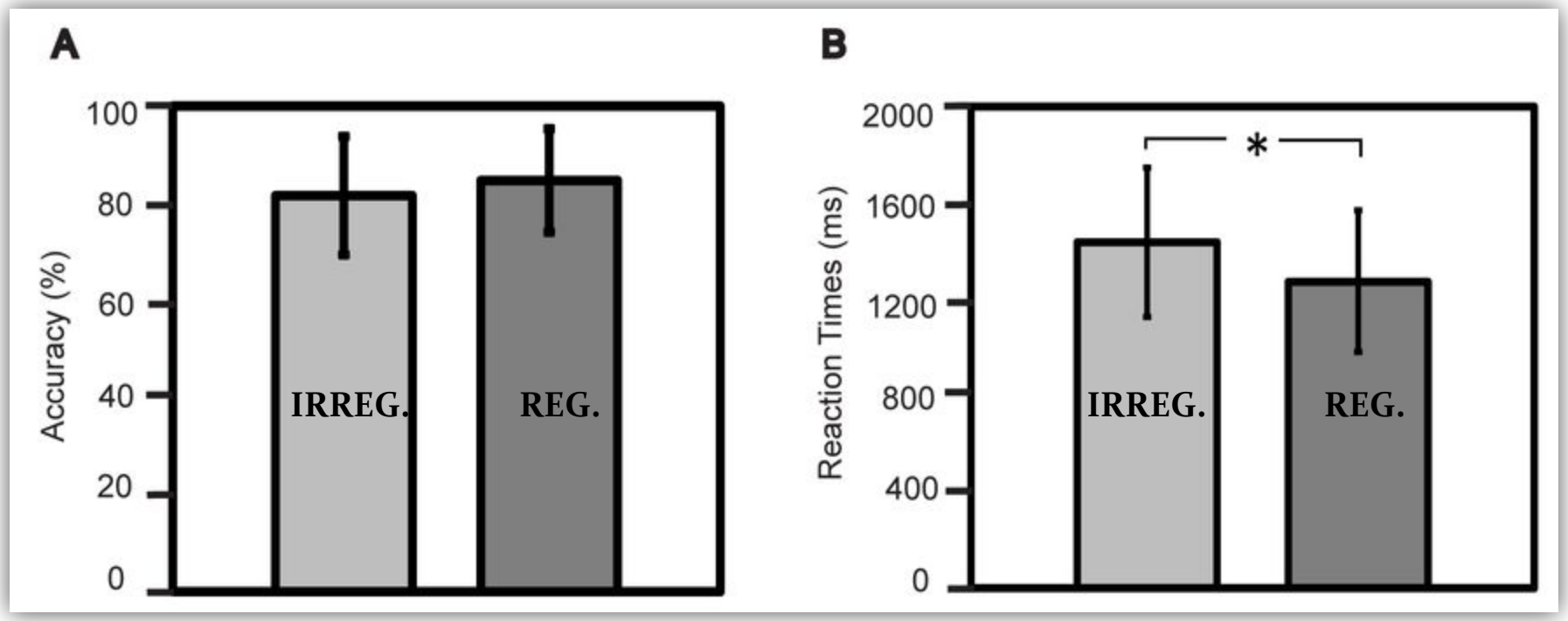


- ***Judge the duration of the final compared to the penultimate interval***
  T_n > / < T_{n-1}

Sequence A: Irregular with 15% average jitter

Sequence B: Regular with an isochronous beat

Behaviour in scanner



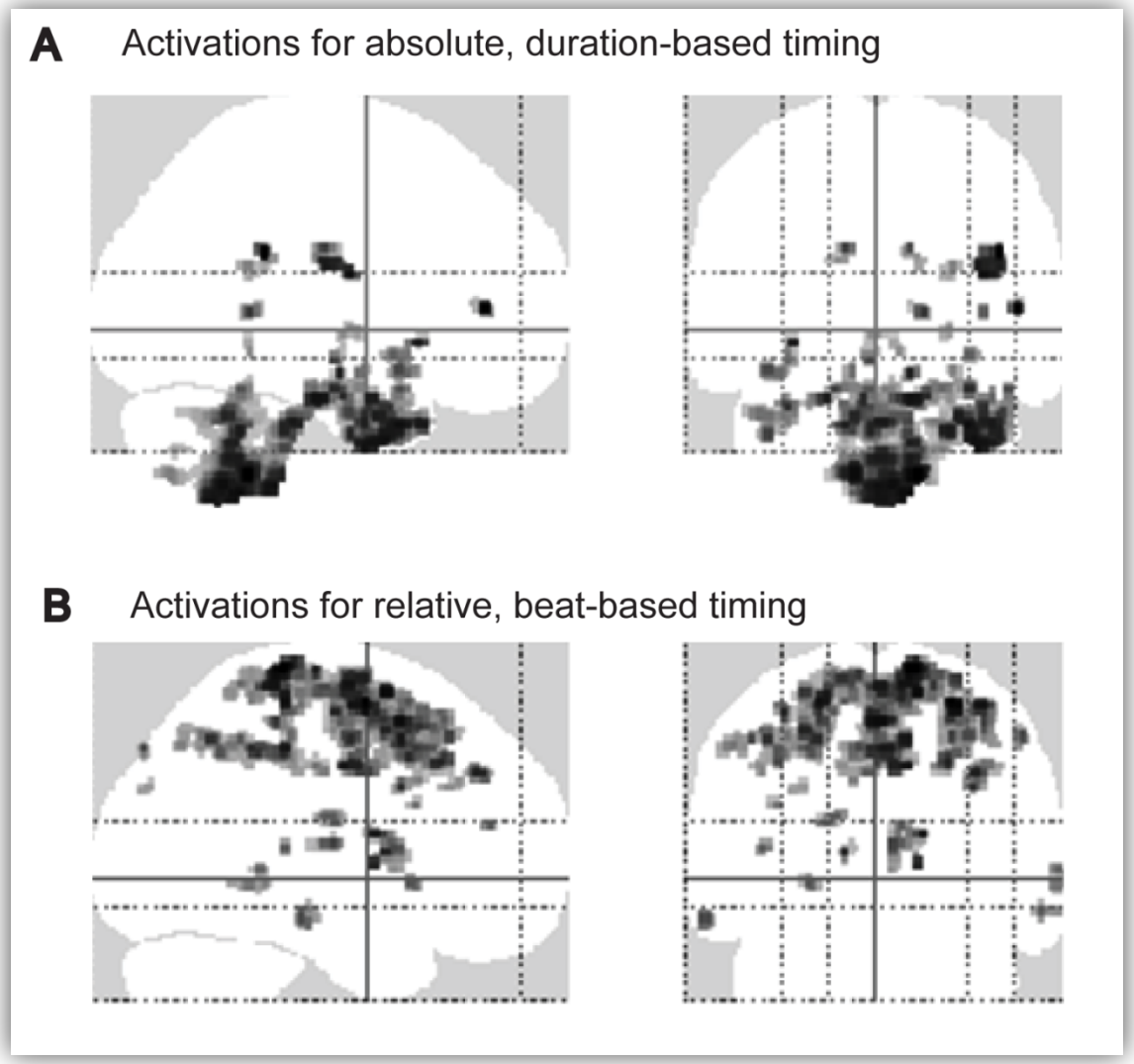
81.53% ± 12.28%

84.72% ±10.64%

1438 ± 297 ms

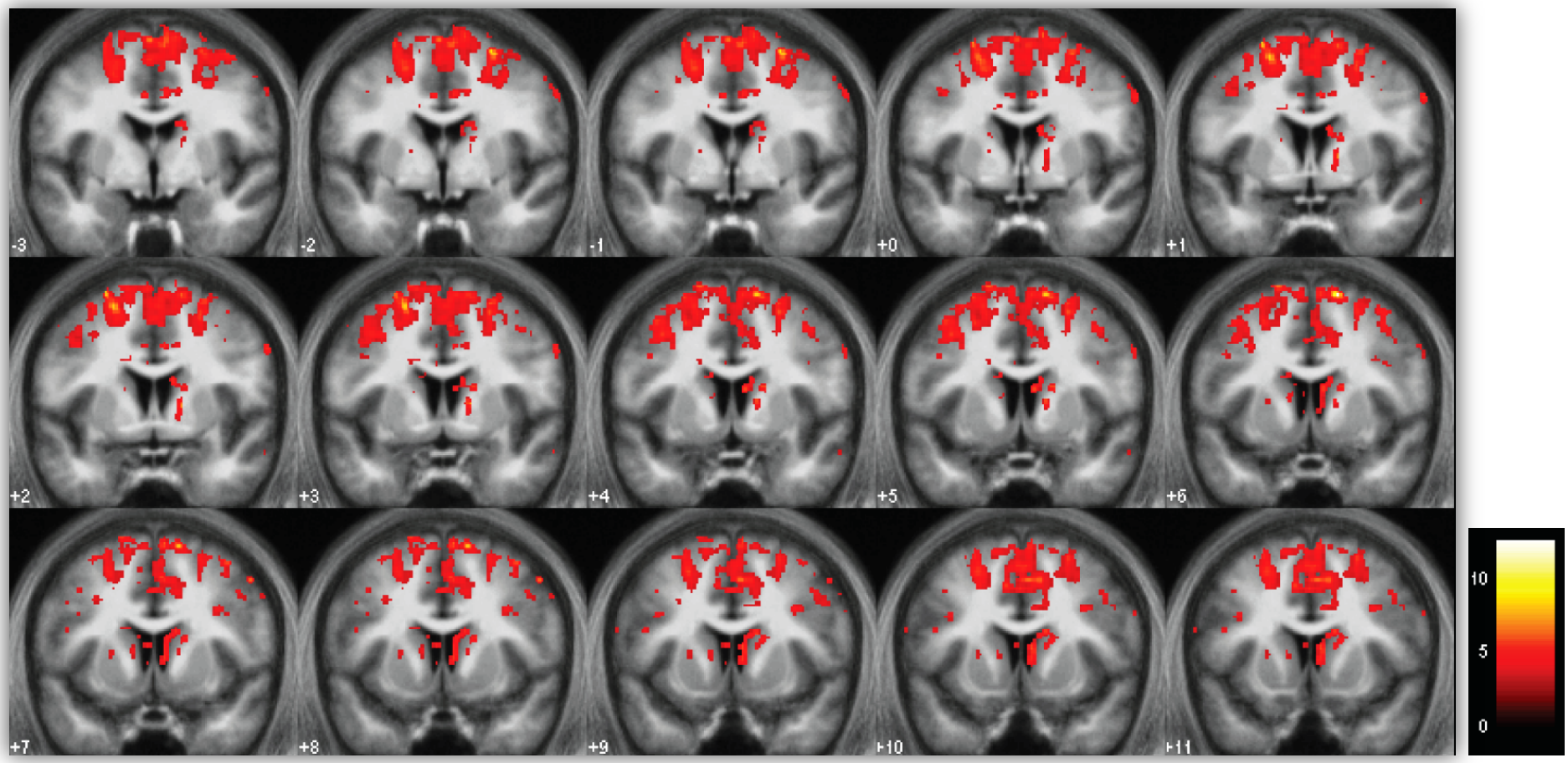
1275 ± 312 ms

fMRI Results



MNI space; t-value > 4.00 and extent threshold > 10 voxels

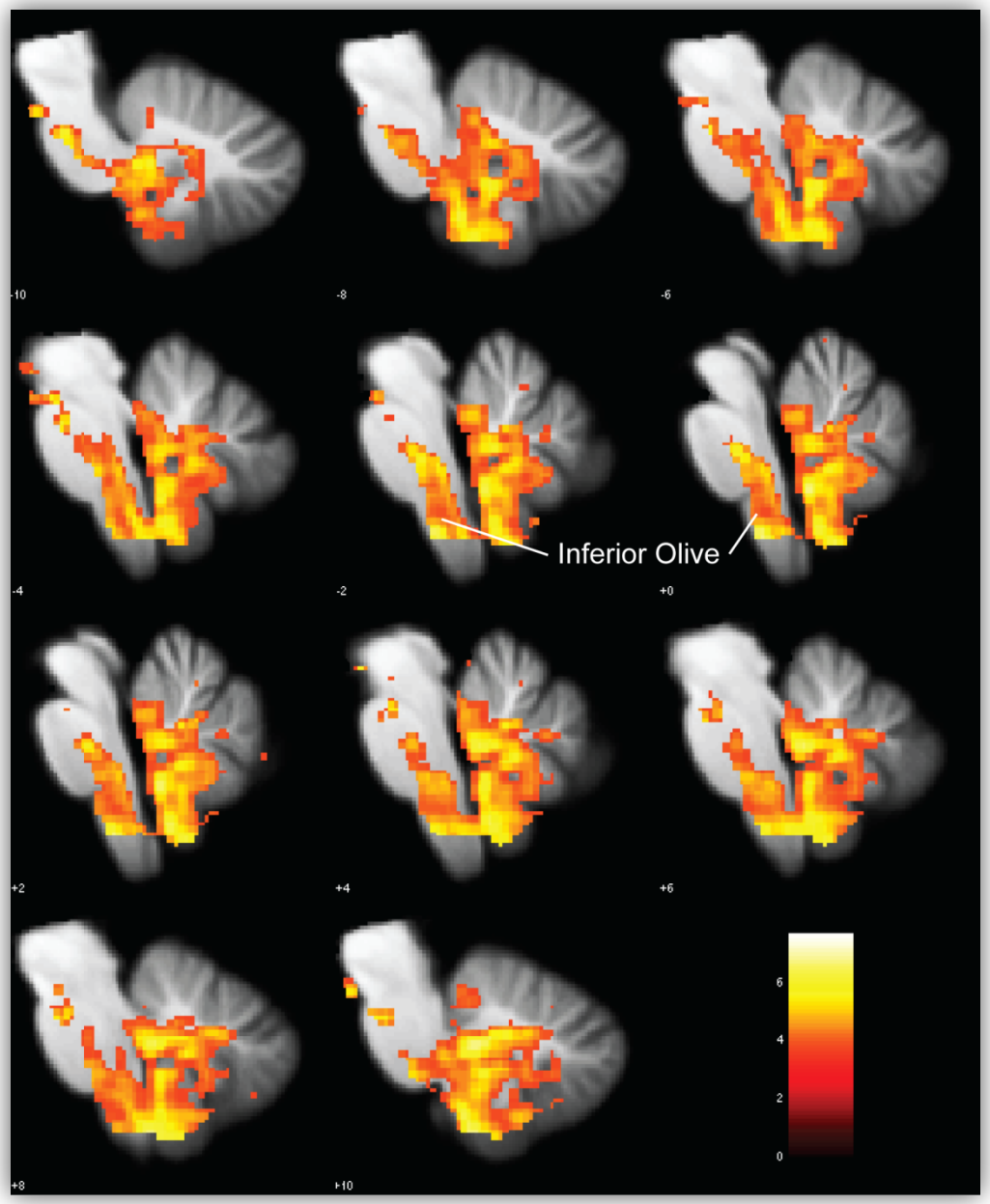
Striatal, premotor and prefrontal activations



x = -3 mm to + 11 mm

p < 0.001 (unc.)

Olivocerebellar activations



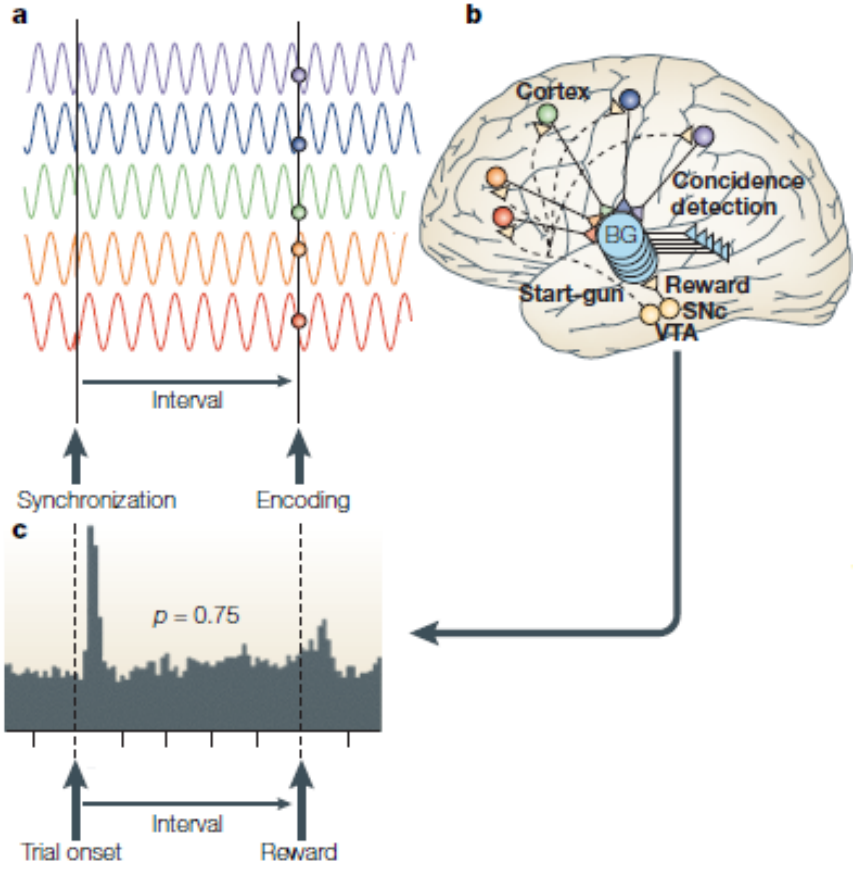
p < 0.001 (unc.)

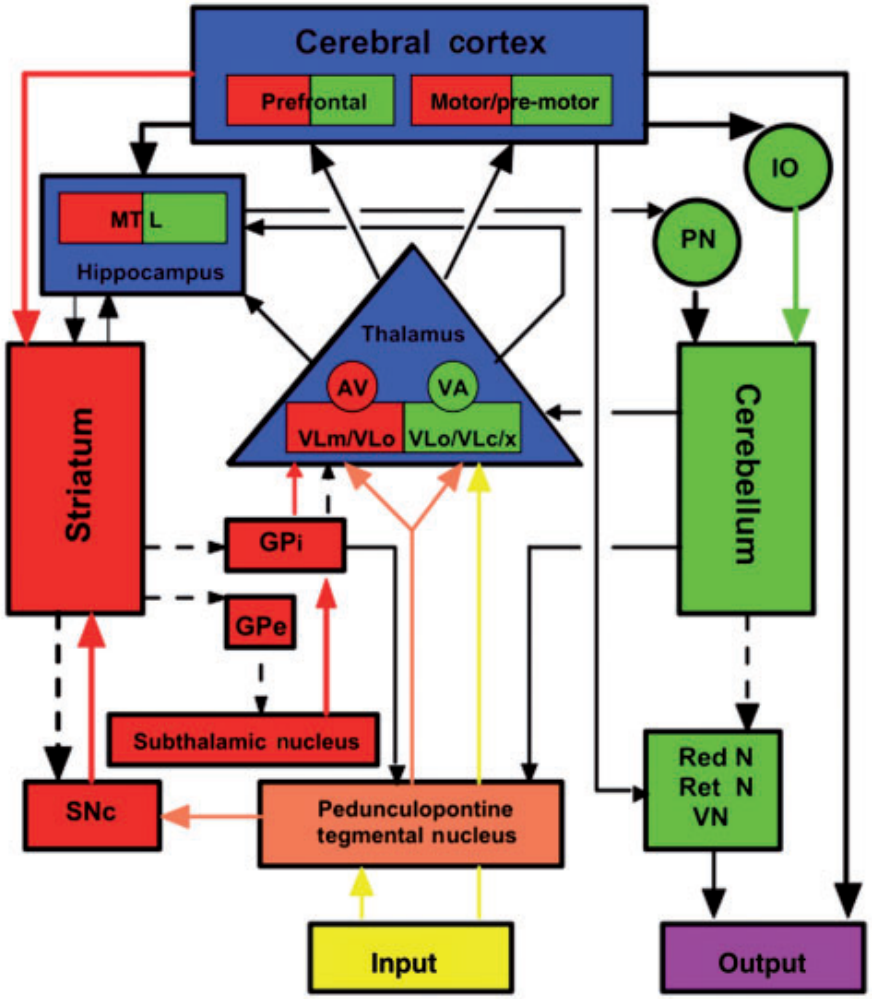
x = -10 to +10 mm

Teki et al., 2011
J Neurosci

Timing models

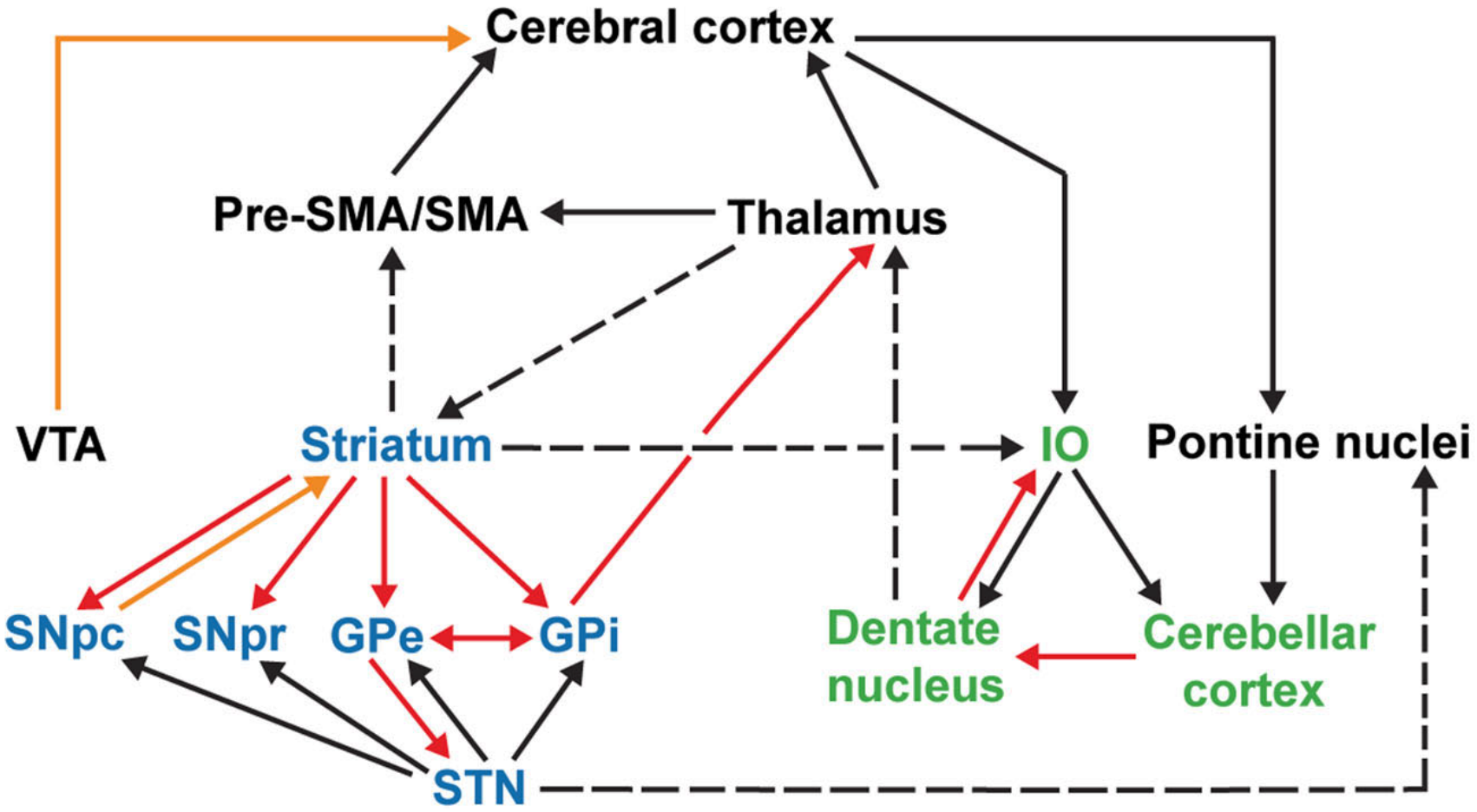
Striatal Beat Frequency Model





Matell and Meck, 2004; Meck, 2005; Allman and Meck, 2011

Unified model



Teki et al., 2012
Frontiers

Features

- Motor structures specialized for timekeeping in the brain
- Timing functions of BG and CB not necessarily independent
- BG network timing signal based on SBF model
- CB network timing signal based on known neurophysiology
- The two key networks interact to improve the accuracy of the timing signal

Assumptions:

- Striatum serves as default/central timekeeper
- Beat-based clock operates for timing stimuli in predictable, beat-based context
- Duration-based clock more active for stimuli in irregular, isolated context

Anatomy

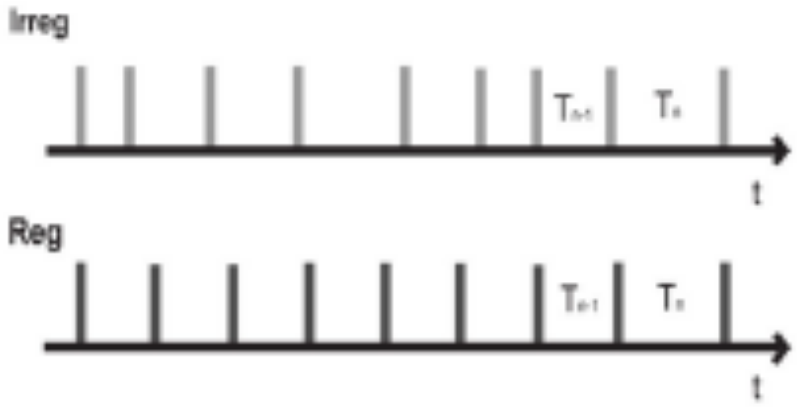
- BG network based on known anatomy (SBF model)
- CB network based on known anatomy
- **Novel connections:**

  Interconnections between striatal and cerebellar networks (c.f. Strick):

  - Dentate => Thalamus => Striatum
  - STN => Pontine nuclei => Cerebellar cortex

Timing

- **Function**: beat-based timing with error-correction by duration-based clock



Regular context:
beat-based clock produces less errors in predicting next time intervals =>
less error-correction required and lesser contribution of CB clock

Irregular context:
beat-based clock produces larger errors in predicting next time intervals =>
greater error-correction required and more contribution by CB clock

Empirical support

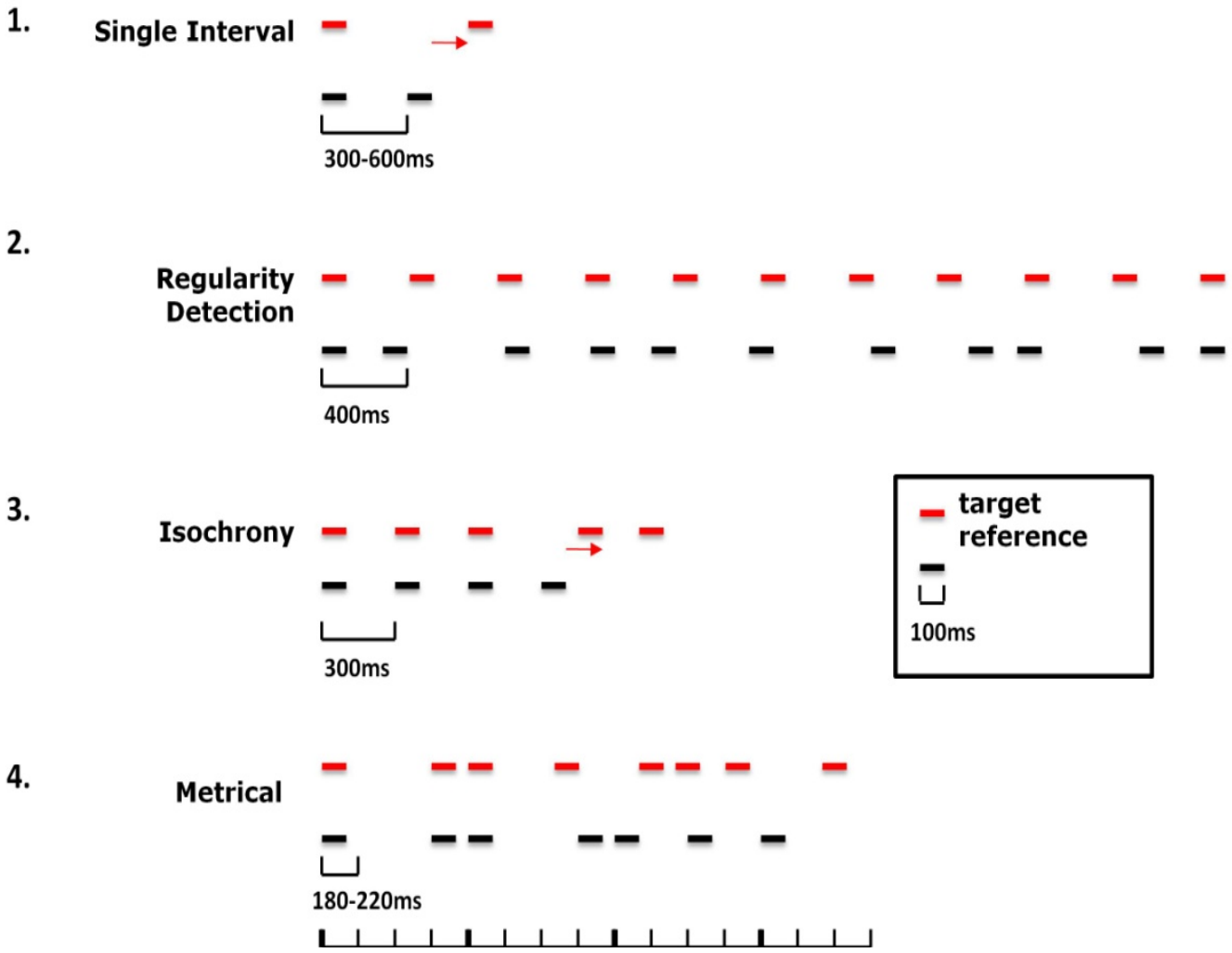
Is a functional dissociation possible?

- CB lesions do not affect relative timing (Grube) or emergent timing (Ivry)
- Striatal lesions affects both relative and absolute timing:

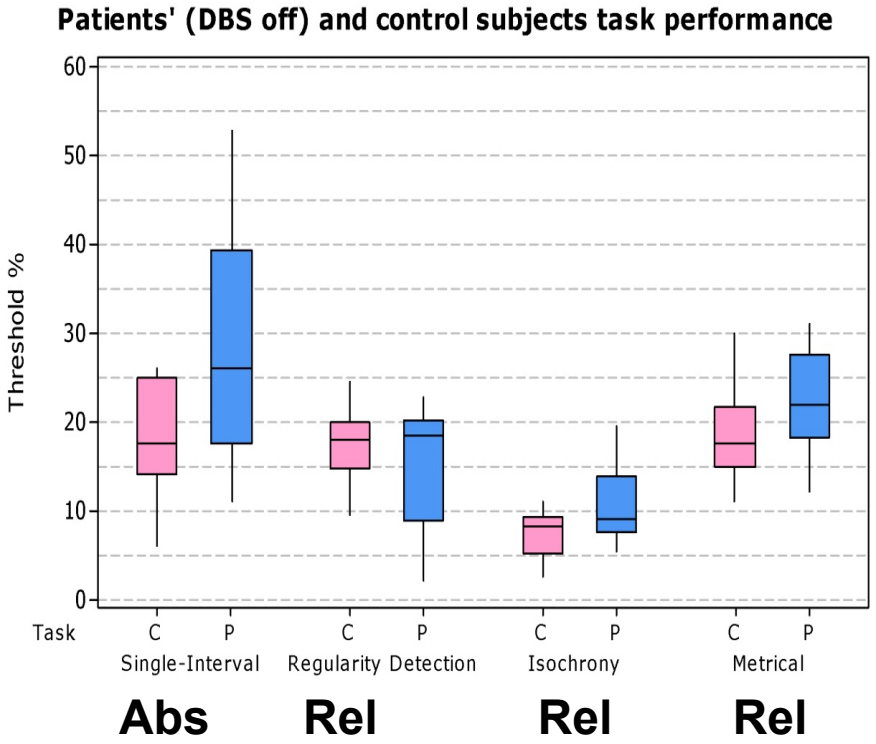
    1) **Parkinson's disease**

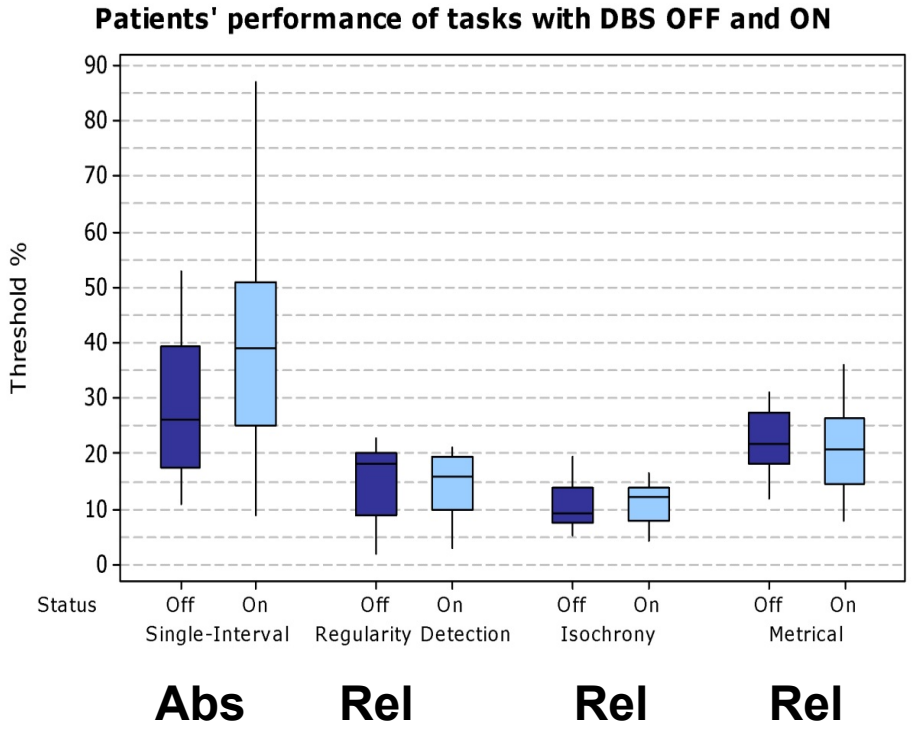
    2) **Huntington's disease and Multiple Systems Atrophy**

I. PD patients



I. PD patients



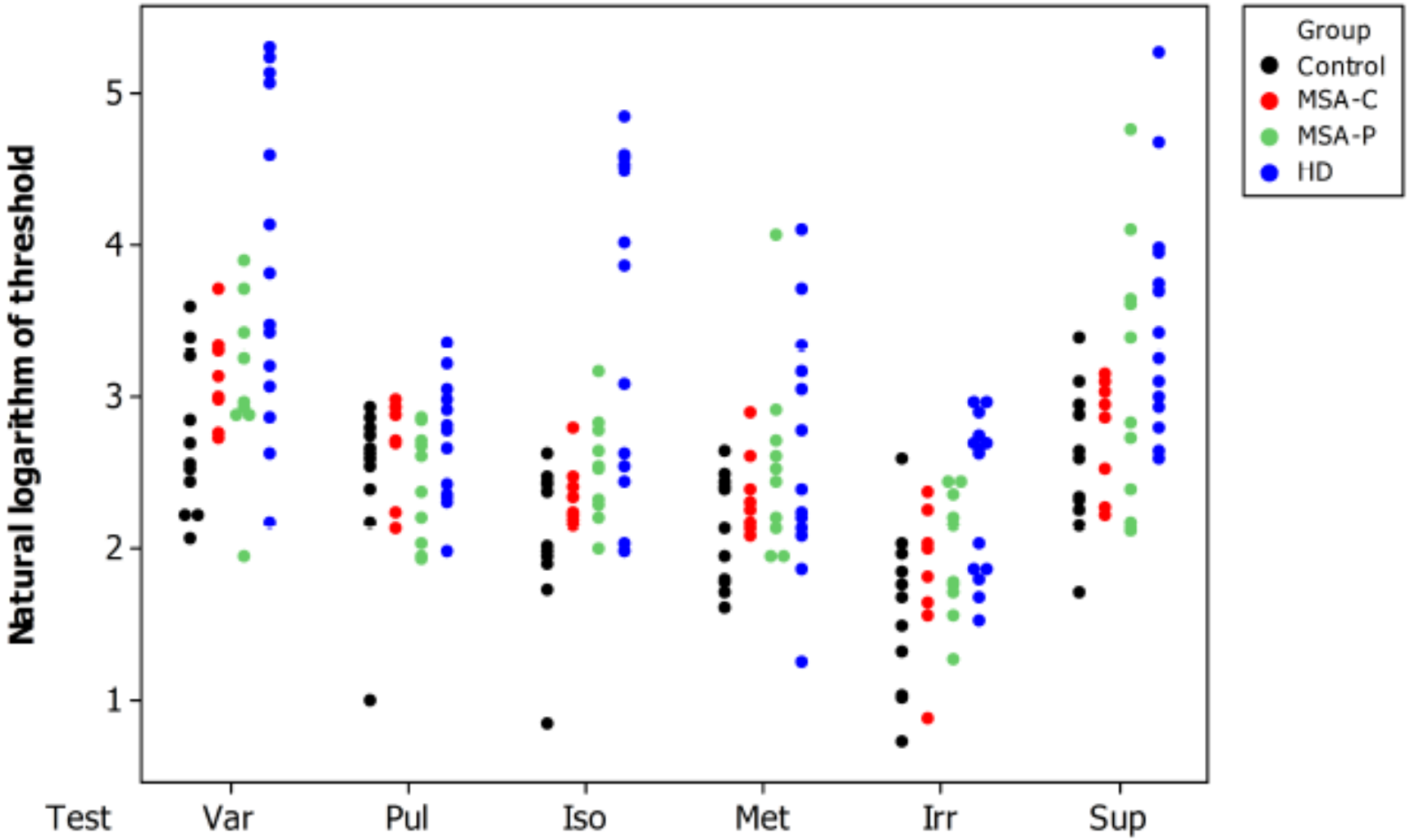


- PD (DBS OFF) worse than controls on single-interval discrimination (abs task)
- PD (DBS ON) worse than PD (DBS OFF) on same absolute timing task

➢ **PD patients also impaired on absolute timing tasks**

Mandal et al., (in prep.)

II. HD/MSA patients



Timing: **Abs** **Rel** **Rel** **Rel** **Abs** **Abs**

II. HD/MSA patients

Figure 2: Mean thresholds by group and task

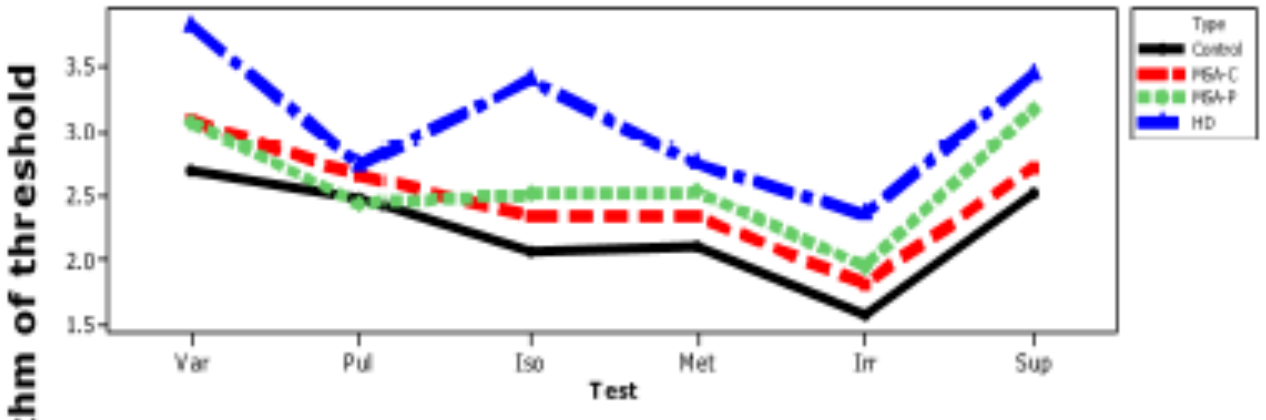
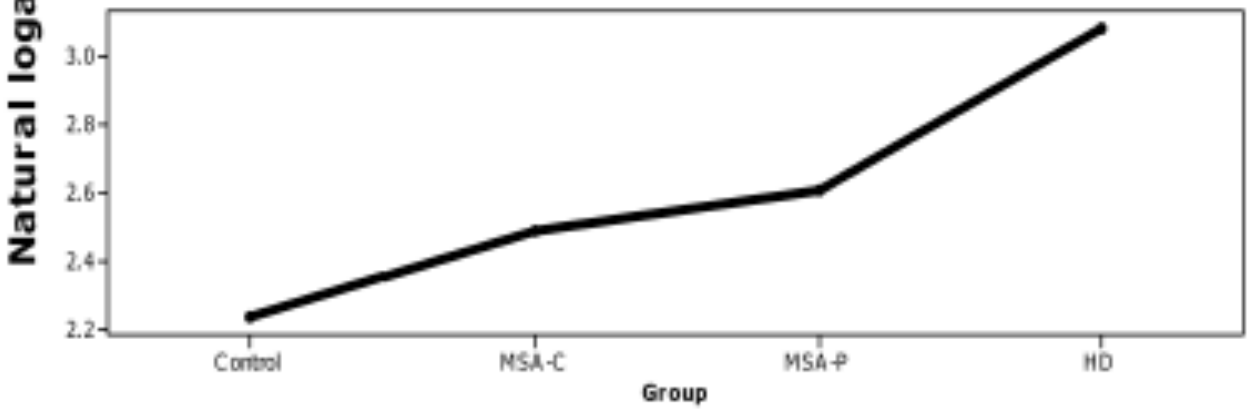


Figure 3: Mean threshold main effects by group



- HD patients significantly worse than controls on absolute and relative timing tasks
- MSA-P also significantly worse than controls on absolute and relative timing tasks

Cope et al., (in prep.)

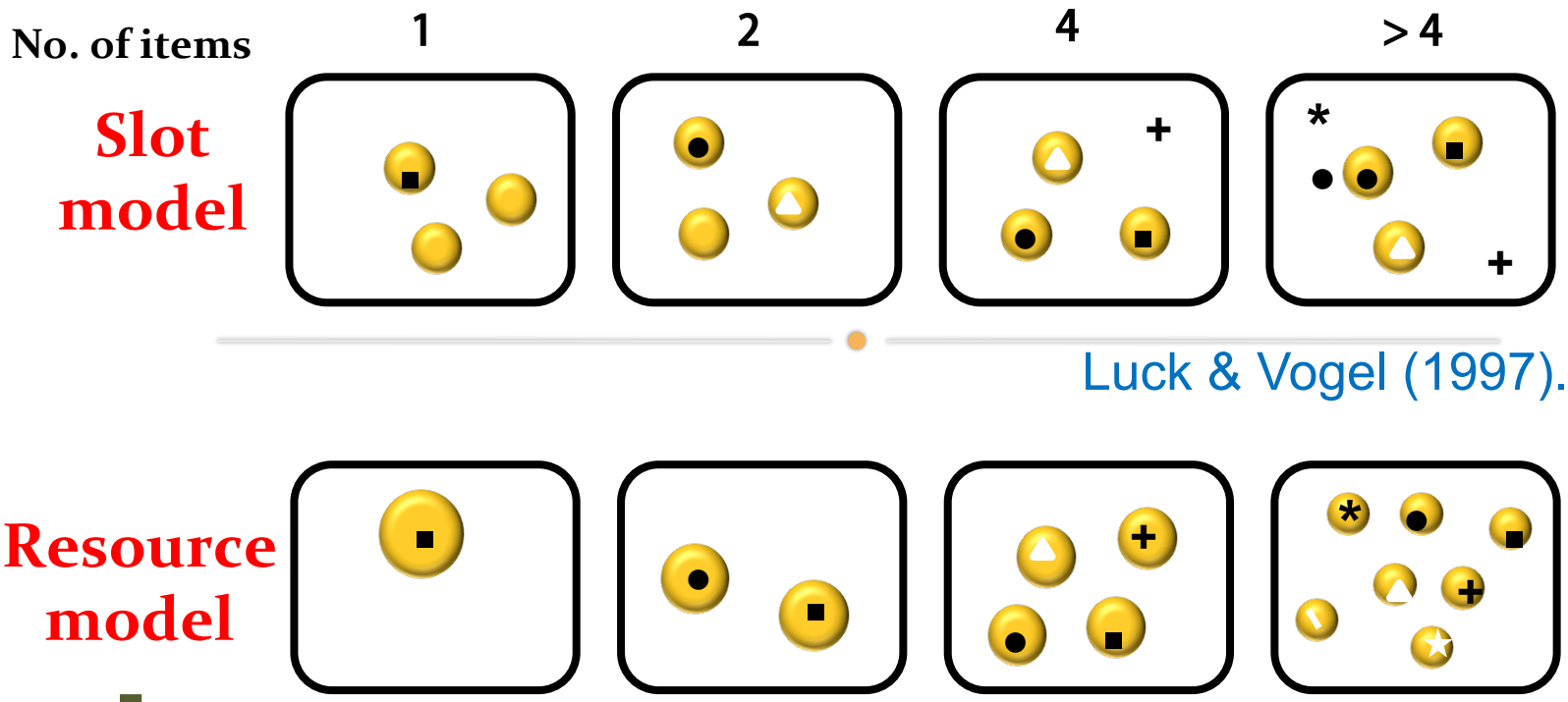
Model summary

- Unified model emphasizes projections between CB and BG which were earlier looked at in isolation wrt interval timing
- Model is asymmetrical in that BG clock (and relative timing) is default mode
- Patients with striatal lesions (PD, HD, MSA-P) impaired on both absolute and relative timing tasks
- Patients with CB lesions impaired only on event-based and not emergent timing tasks
- Understanding timing through such disorders may provide key insights.

Time & Memory

Models of Working memory

Working memory is a limited resource



Luck & Vogel (1997). *Nature*

Working memory for time?

Bays & Husain (2008) *Science*
Bays et al (2009) *J Vision*
Gorgoraptis et al (2011) *J Neurosci*

Working memory tasks

Traditional ways of testing: shorter or longer?

e.g. Rao et al., 2001

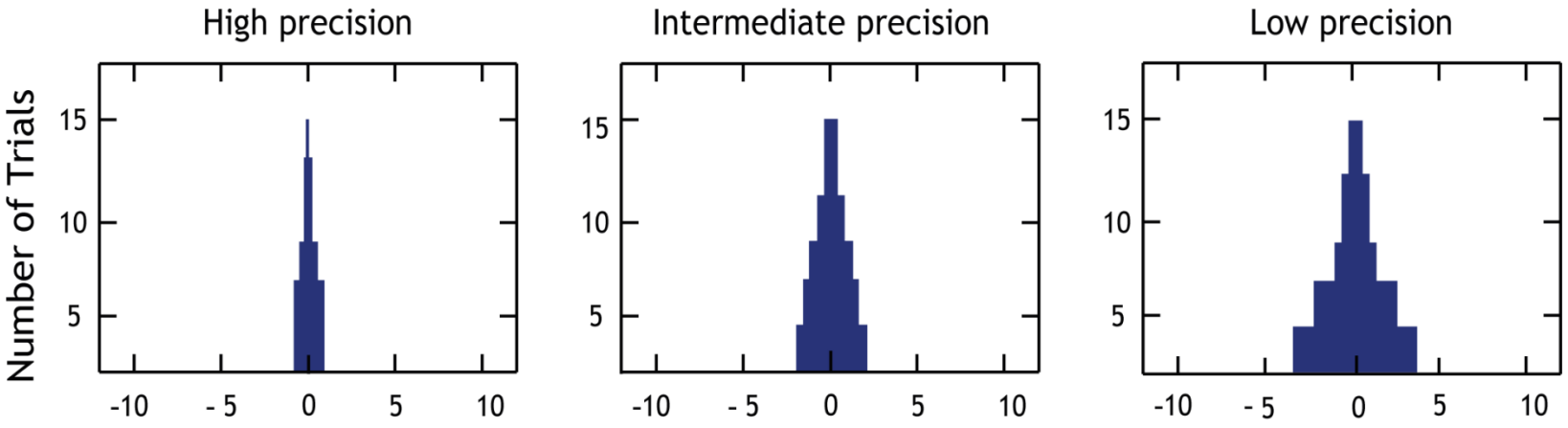
→ no variation of memory load

→ binary/categorical measures

Precision of Memory

A more informative method: quantifying the fidelity of WM

Precision = 1/STD



Paradigm

RT BLOCK: Estimate median RT

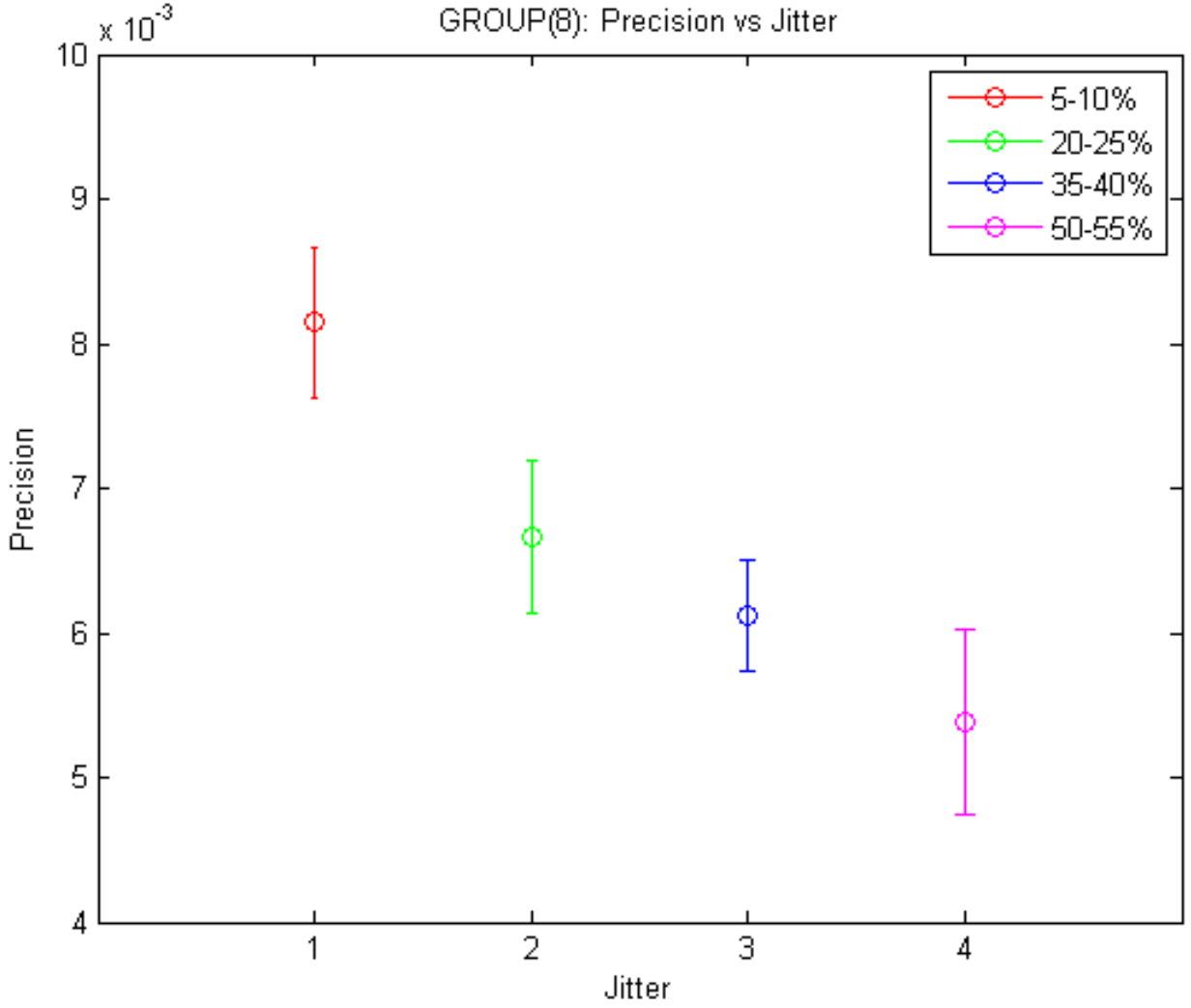
TIMING BLOCK: Timing response for probed interval duration

Perceptual time matching response = reproduced time – response time

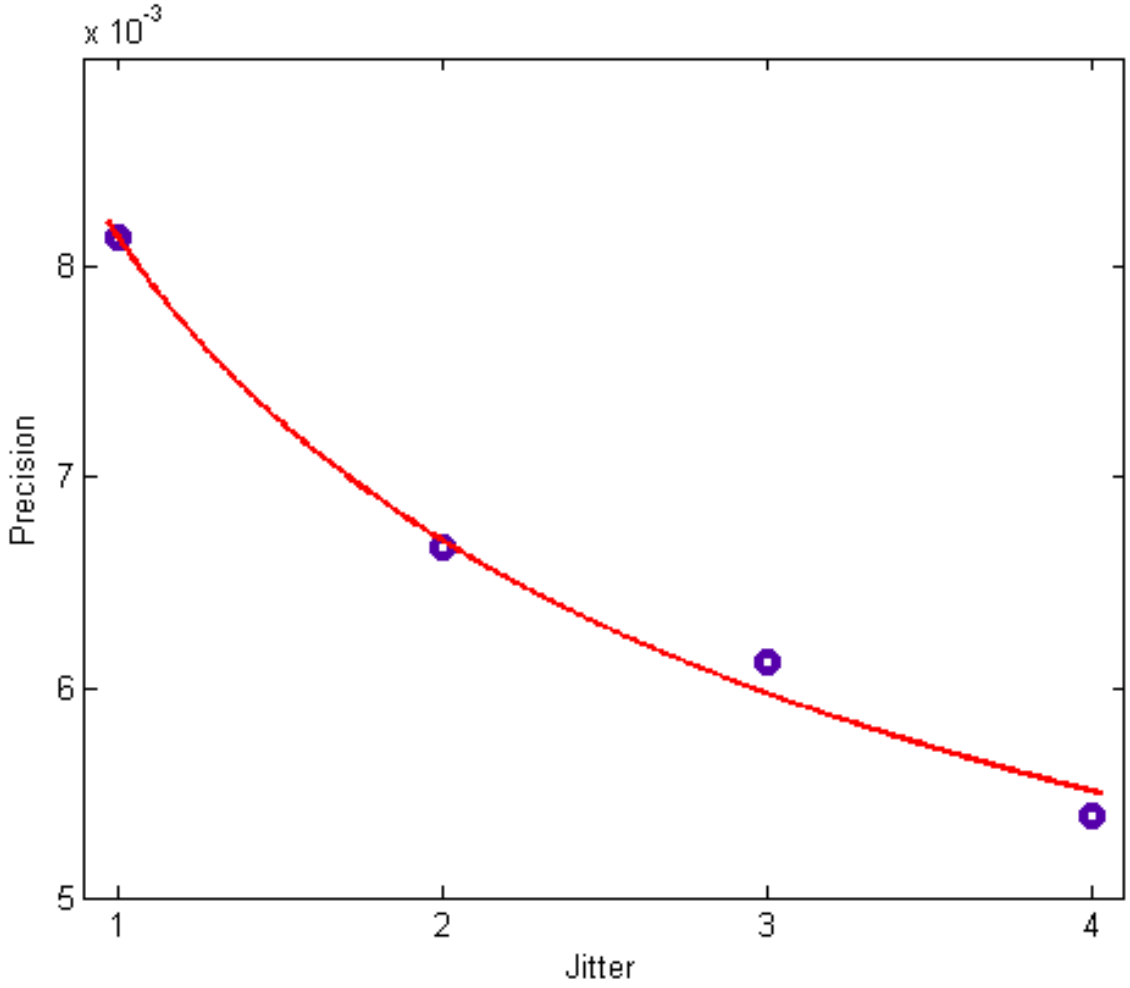
Error response = Time matching response - Duration of probed interval

Precision of WM for time = 1/STD (Error response)

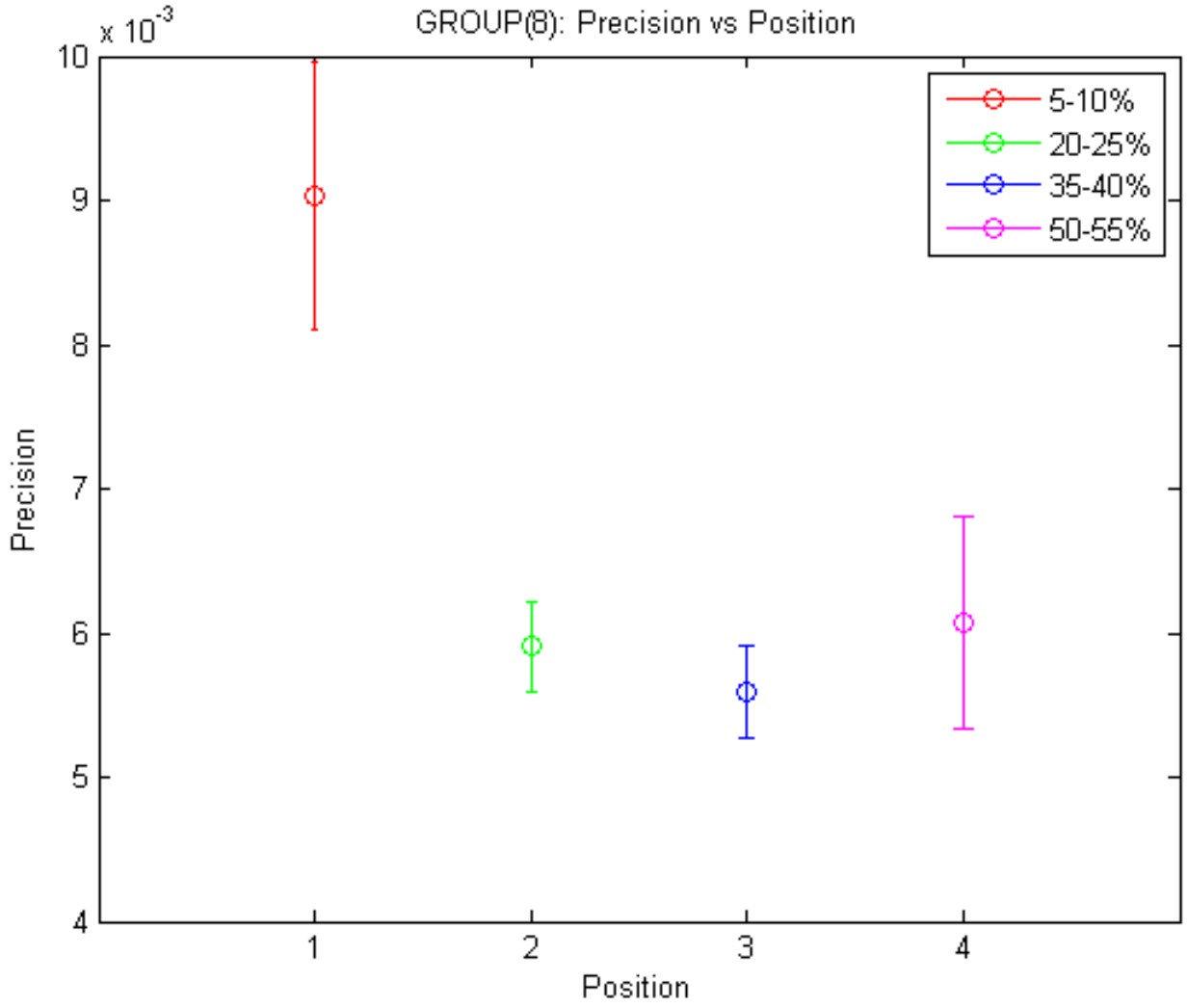
I. Precision vs. Jitter



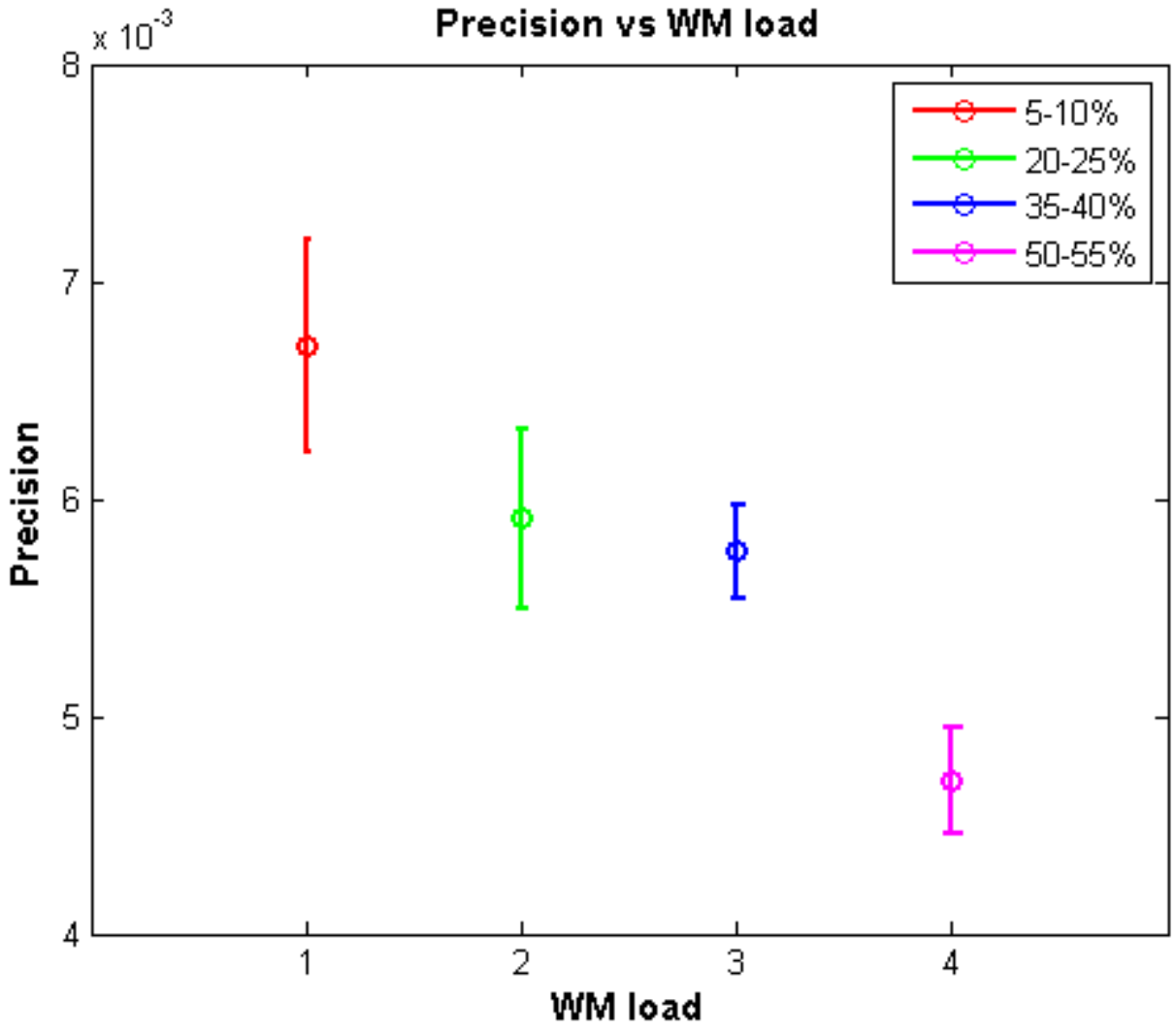
Power fit



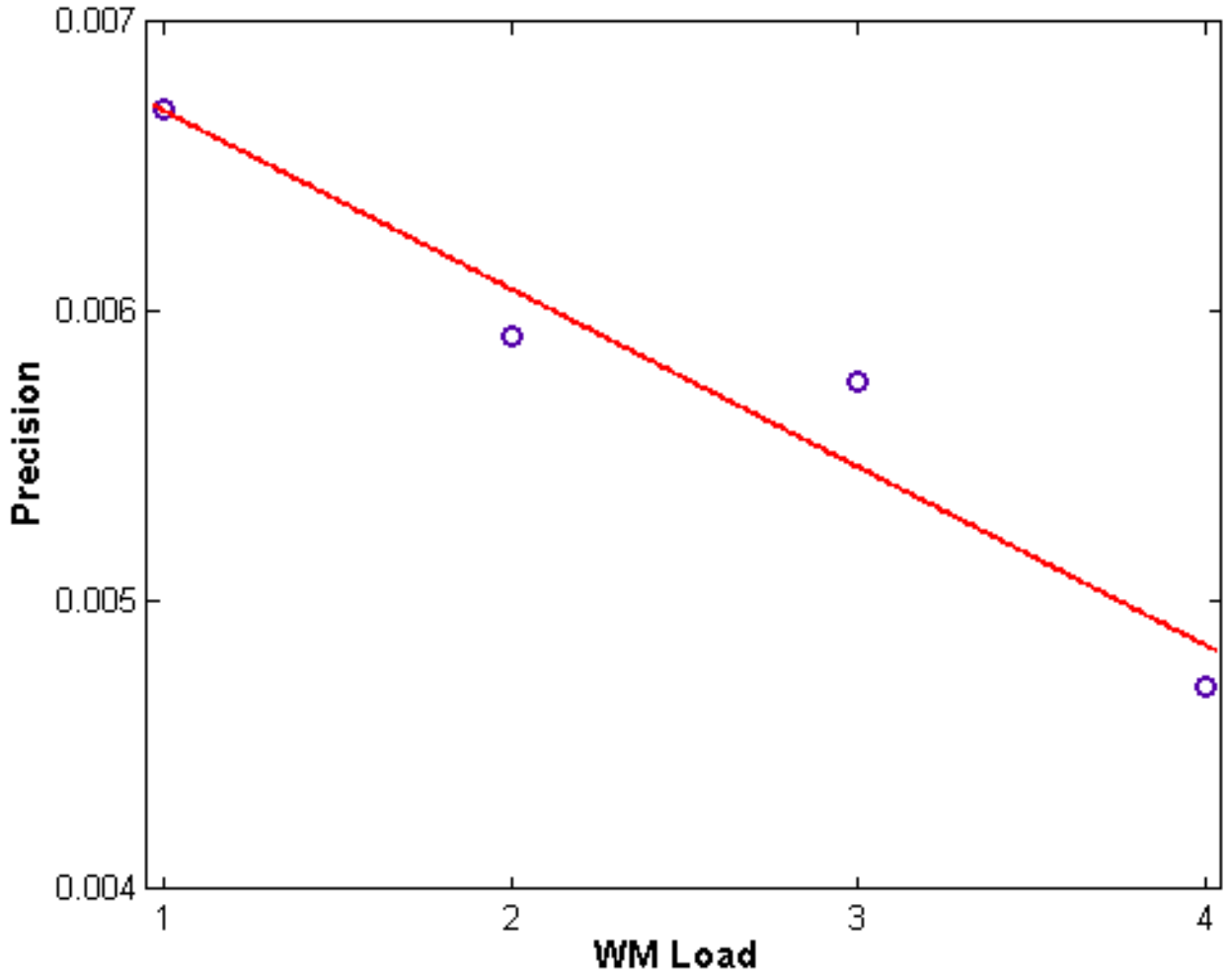
Precision vs. Position



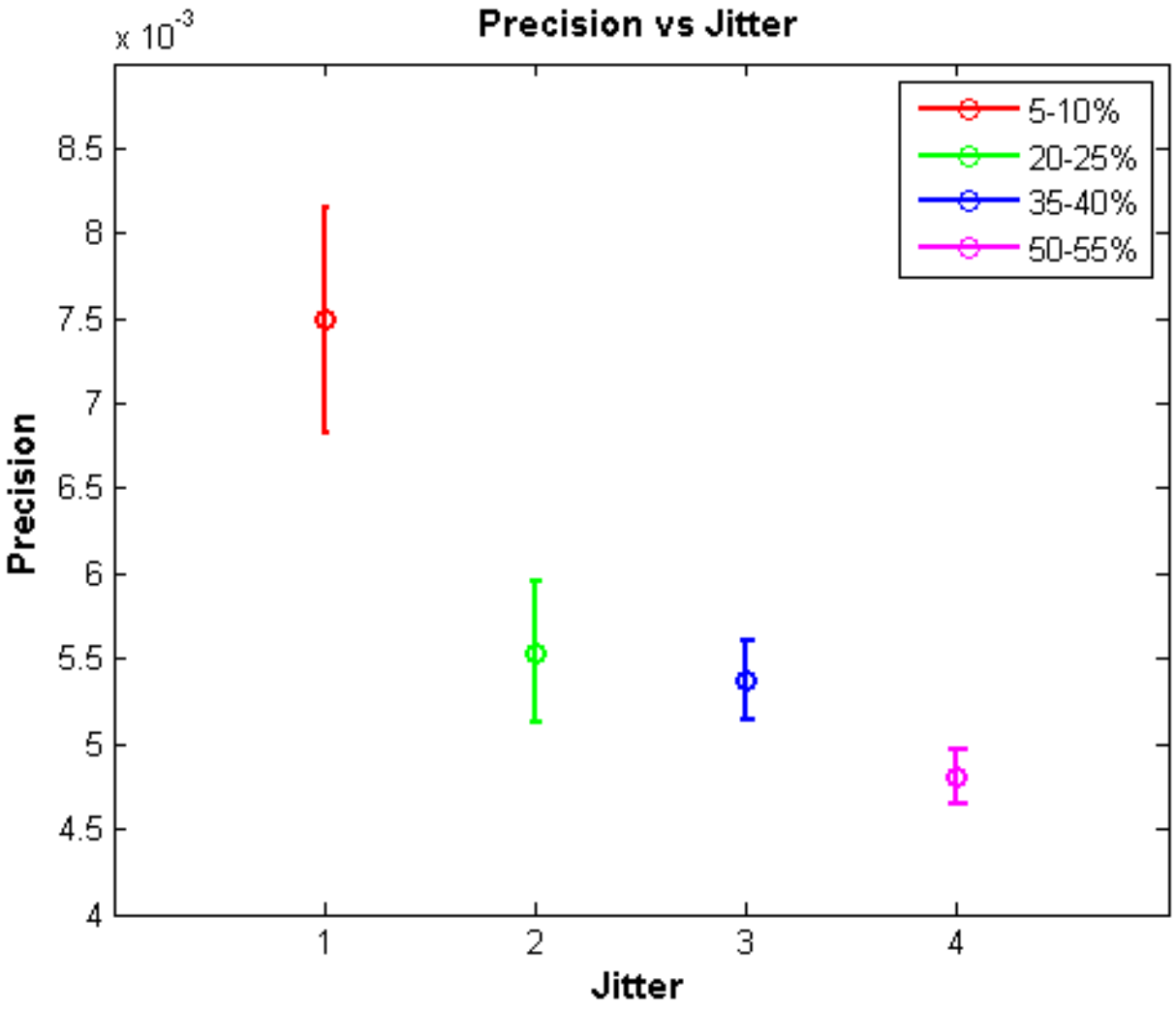
II. Precision vs. WM load



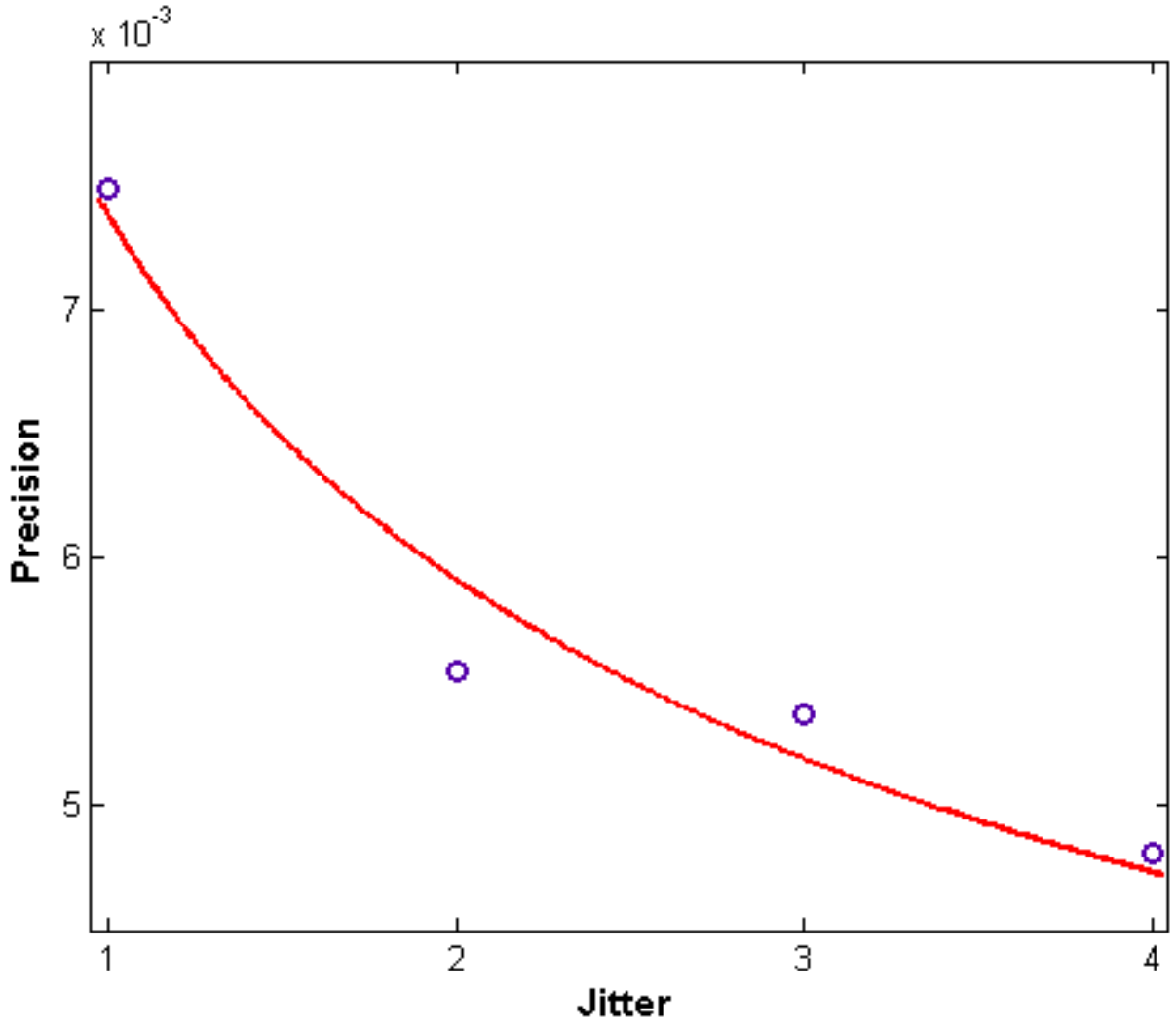
II. Linear fit



II. Precision vs. Jitter



II. Power fit



Overall summary

Time is a distributed property of brain circuits but certain structures are specialized for temporal processing.

Rhythmic structure of time intervals is an important dimension in the analysis of time intervals, especially in auditory domain for signals such as speech and music.

Substrates involved in timing may have separate roles (attention/memory) but the dorsal striatum appears to be vital for supporting core timing functions.

Disorders that are associated with impairment in timing analysis can give us a view into the systems level deficits.

Memory for time not studied for intervals embedded in the context of sequences with different rhythmic structure. A new paradigm and measure of temporal memory as proposed can offer new insights.

Acknowledgments

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wellcome trust