THE DIFFERENTIAL EFFECTS OF MILD TBI ON NEUROCOGNITIVE FUNCTIONING: WHY NO TWO "MILD" BRAIN INJURIES ARE THE SAME

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CONFLICT OF INTERESTS

MY ONLY FINANCIAL RELATIONSHIP WITH A COMPANY ARE ROYALITES FOR SCIENTIFIC BOOKS: OXFORD UNIVERSITY & CAMBRIDGE UNIVERSITY PRESSES.

THE CLINICAL CHALLENGE

- **How to treat cognitive/behavioural dysfunction after TBI in the most effective way possible**
- **You can't rehabilitate what you don't know**
- **Ergo, the first step in the treatment and management of traumatic brain injury is knowledge and correct diagnosis and description**
- **TBI IS NOT A SIMPLE DISORDER**

MY CONCLUSIONS IN ADVANCE

- **TBI research indicates the need for improved phenotyping (sub-grouping) of patients**

- **Rationale: specific treatments may work only in certain groups of patients. That is, there is variability among individuals - group variability**

- **The objective of understanding group variability is to develop stratified subgroups based on rational principles. Phenotyping can be anatomical, behavioural, genetic…**

WHY IS THIS IMPORTANT?

- **Perhaps too many failures in rehabilitation and treatment, certainly in clinical “trials”, derived from not accepting that there are sub-groups within what seemed to be a single disorder**

EFFECTIVE REHABILITATION

- **RIGHT PERSON –** directed to a well-characterized subgroup in which the intervention is effective: *IMPLICATION* – solve group heterogeneity

- **RIGHT TREATMENT** – theoretically driven, validated and tested approach, continually updated and refined as knowledge changes: *IMPLICATION* – excellent science

- **RIGHT TIME –** given at the right time: *IMPLICATION* – longitudinal studies

- **Ultimately, this is "personalized medicine"**

OUTLINE – TWO SECTIONS

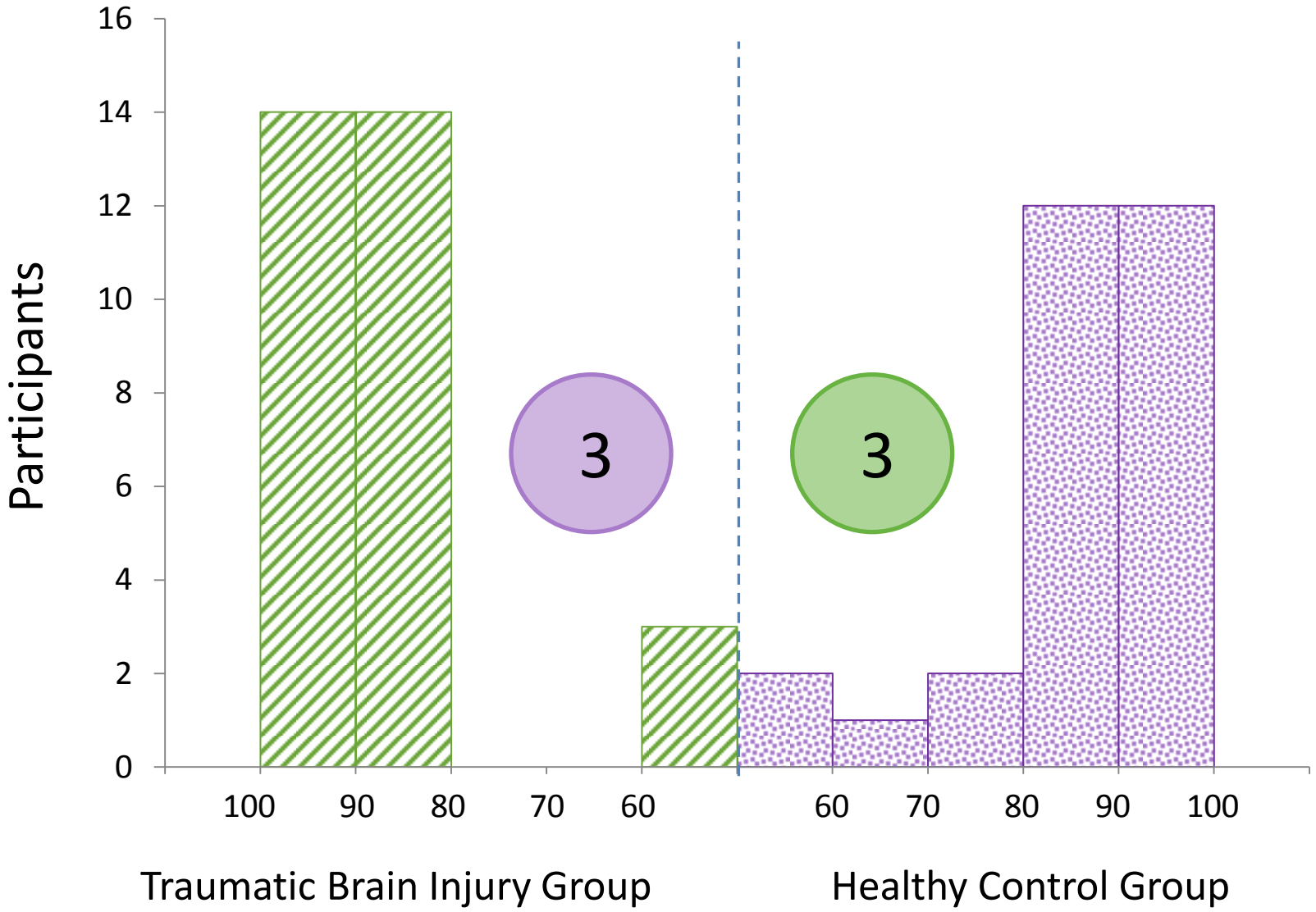
- **What you can learn by understanding and harnessing group variability – examples from TBI and frontal lobe research**

- **What is the value of defining sub-groups of individuals with TBI?**

TBI EXAMPLE # 1

- **TBI patients had “good recovery”, and were comparable to matched control individuals on standard measures such as WMS, IQ.**
- **Continued to have vague complaints**
- **Discriminant Functional Analysis noted that two key measures differentiated the groups at a high significance level**
- **BUT classification into appropriate group was not 100%**

Classification By Performance in TBI vs Healthy Control Group



WHY?

- KEY MESSAGE – There is variability of recovery within the "defined" group – did I not define sufficiently well?
- - Dissociating causes of variability is an important factor
- in deciding on treatment, care, rehab

- SEARCH FOR REASONS
- - not litigation
- - not TBI severity
- - and I was not smart enough to have other measures
- Ask **WHY**

- THE GOAL - **PRECISION REHABILITATION/TREATMENT**

TBI EXAMPLE # 2-A

- **Prospective study of the acute recovery period after TBI**

  - Daily measures of the recovery of memory and attention

EXPERIMENTAL DESIGN – PATIENTS

- **Hospitalization required >100 participants**
- **Mild, Moderate, Severe – defined by GCS at 6 hours**
- **Prospective:**

  - patients assessed asap after hospitalization

  - tested daily at bedside with simple tests

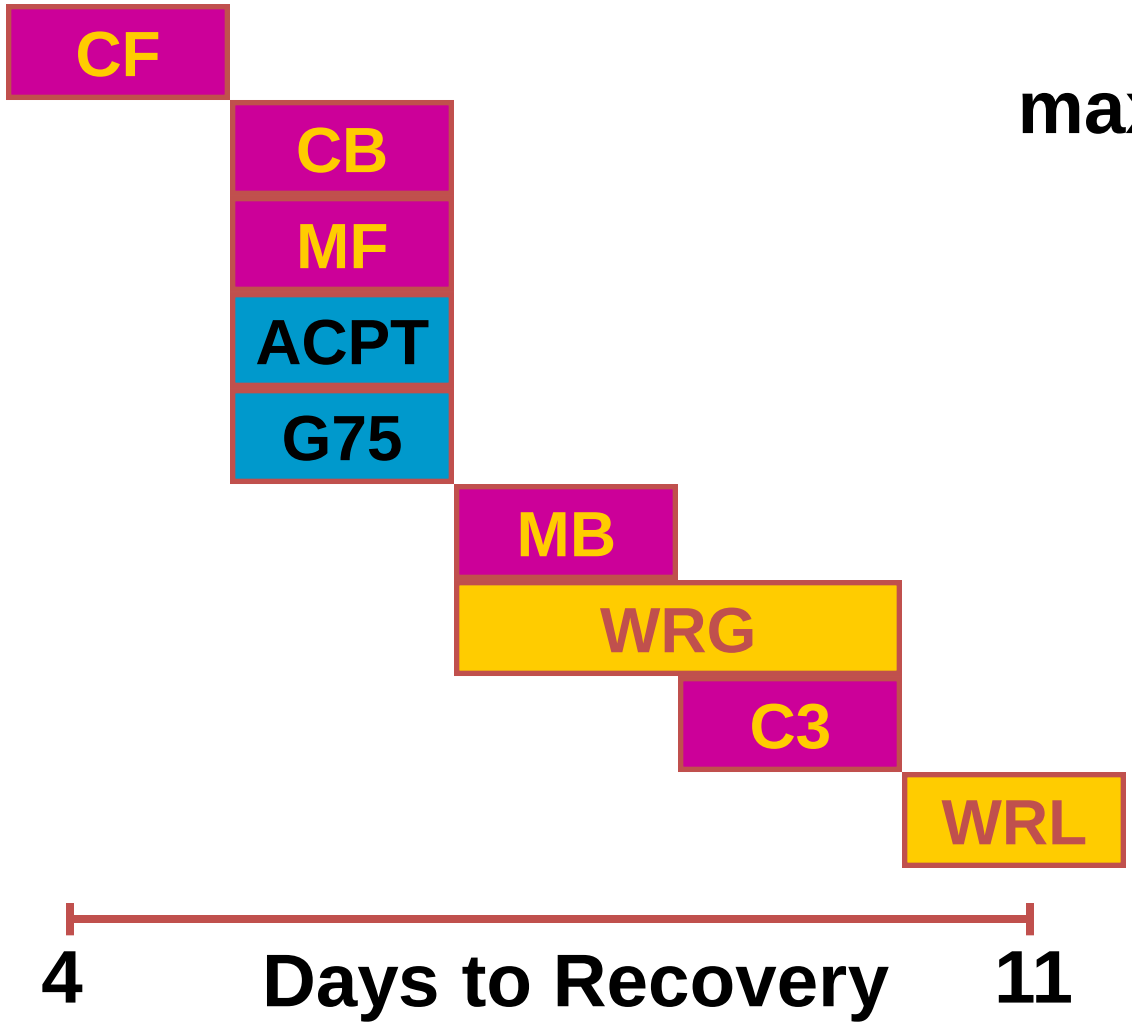
EXPERIMENTAL DESIGN – TESTS

- **Tests: memory and attention, varying in task demands, appropriately randomized**

- **Attention\working memory:**
  - **Count forwards and backwards by 1 – and by 3**
  - **Months forwards and backwards**
  - **Auditory Continuous Performance Test**

- **Memory**
  - **Galveston Orientation and Amnesia Test**
  - **Three word/figures encoding and 24 hour recall/recognition**

STAGES of RECOVERY
MILD

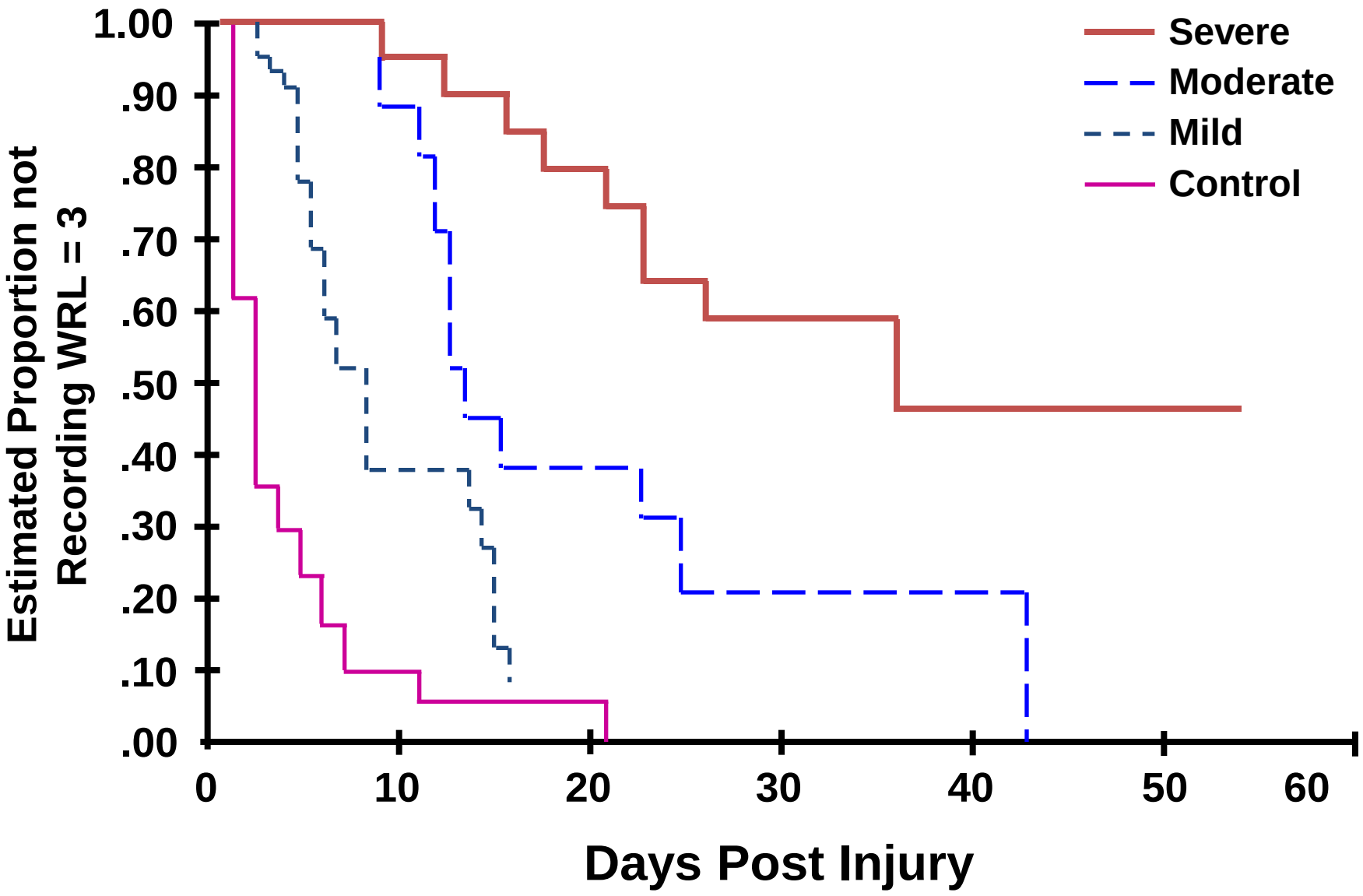


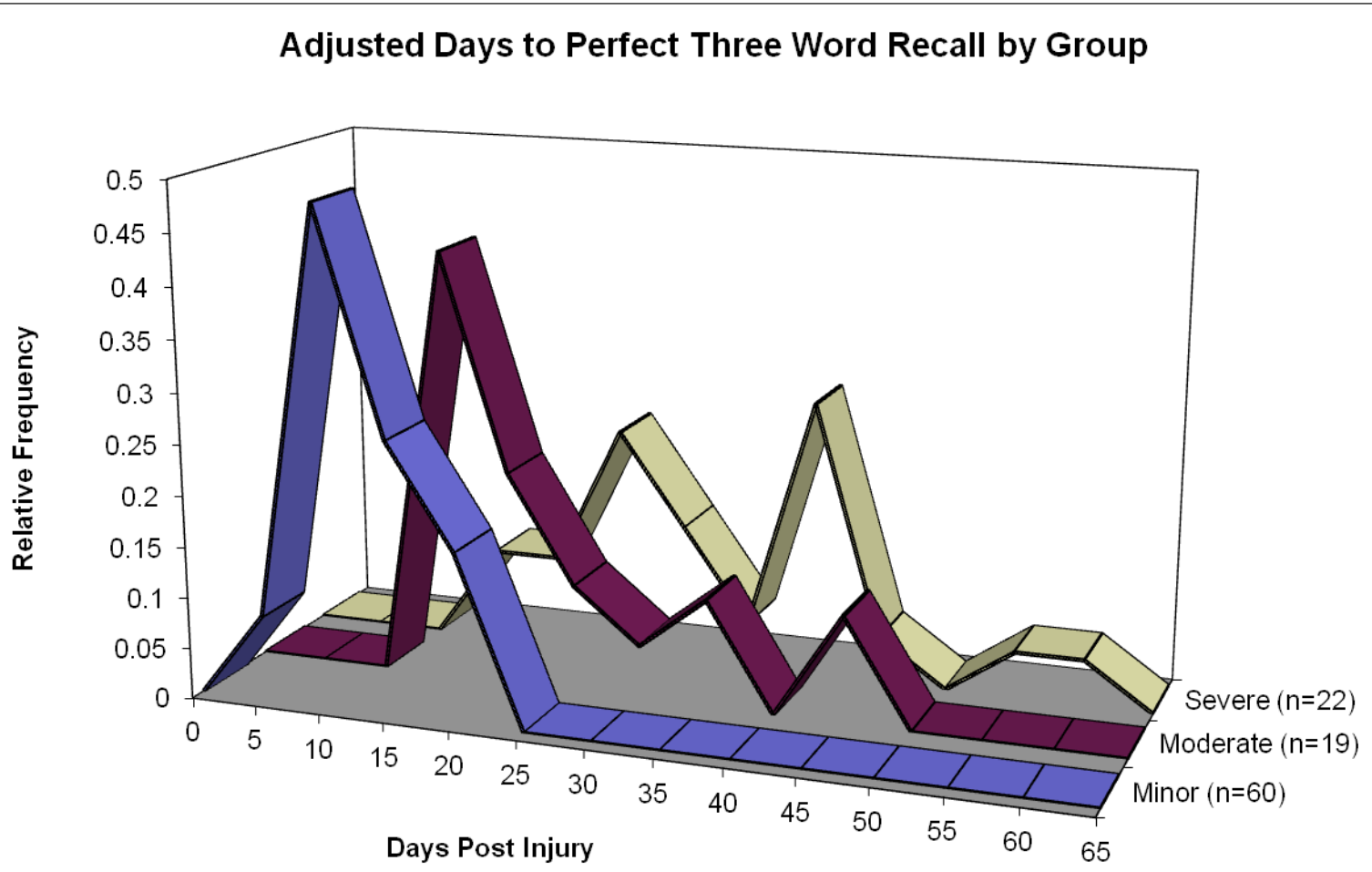
TBI EXAMPLE – #2-B

- **Prospective study of the acute recovery period after TBI**

  - Prediction of Recovery from Post-Traumatic Amnesia

THREE WORD RECALL




Adjusted Days to Perfect Three Word Recall by Group
Relative Frequency
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
5
10
15
20
25
30
35
40
45
50
55
60
65
Days Post Injury
Severe (n=22)
Moderate (n=19)
Minor (n=60)

VARIATION IN OUTCOME - WHY?

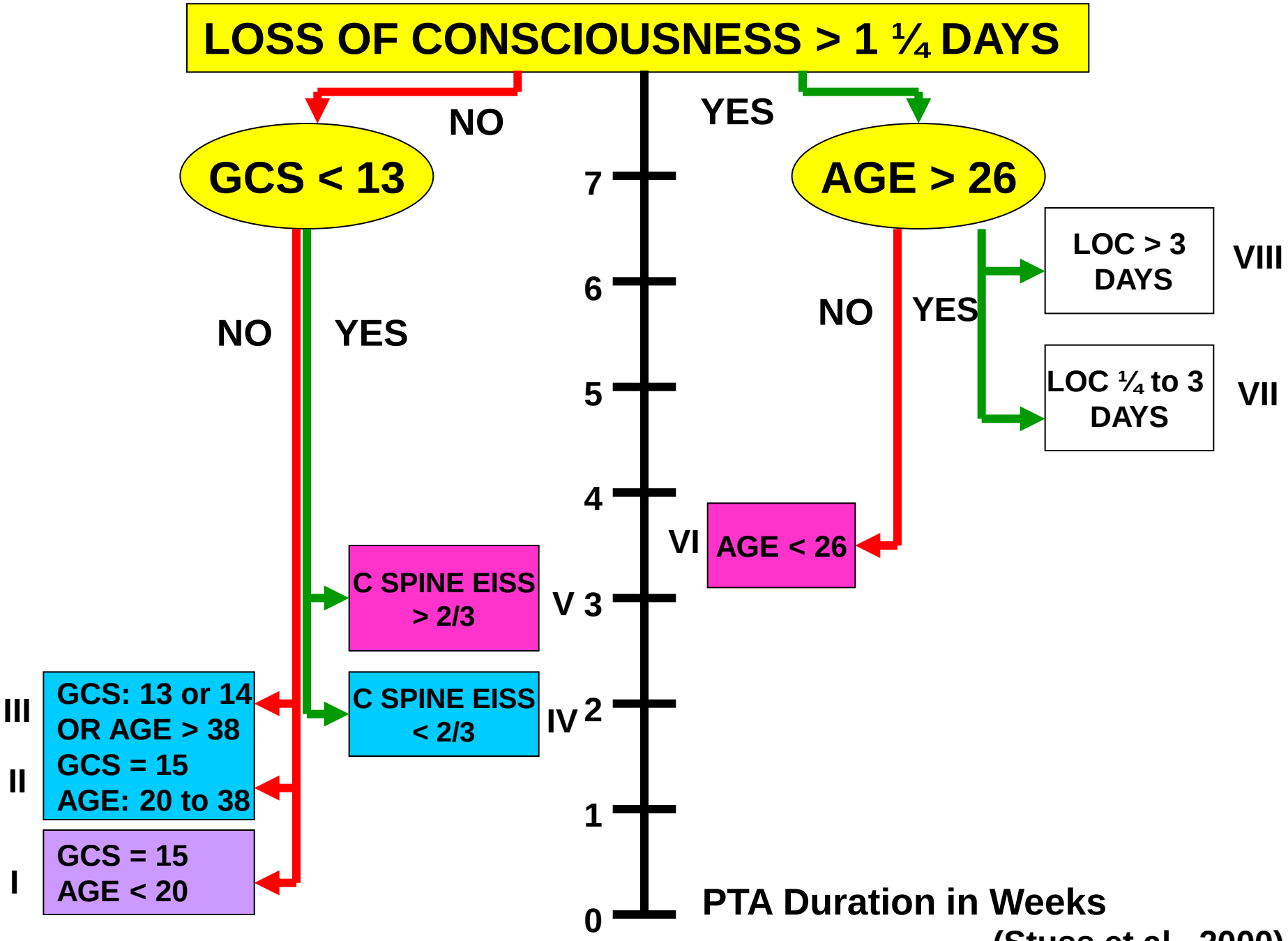
- **Use a statistical method that analyzes different factors that might impact outcome**

CLINICAL IMPORTANCE

- **More accurate prediction of recovery of continuous memory to benefit patient acute care management, including planning of discharge timing**

- **What types of factors would be important predictors?**

  - severity of injury (e.g., GCS, LOC duration)
  - capacity – what inherent resources to achieve recovery, measured by premorbid IQ (education) and age)
  - head and neck injuries compared with other soft tissue damage


LOSS OF CONSCIOUSNESS > 1 ¼ DAYS
NO
YES
GCS < 13
AGE > 26
NO
YES
NO
YES
LOC > 3 DAYS
VIII
LOC ¼ to 3 DAYS
VII
VI
AGE < 26
C SPINE EISS > 2/3
V
C SPINE EISS < 2/3
IV
III
GCS: 13 or 14
OR AGE > 38
II
GCS = 15
AGE: 20 to 38
I
GCS = 15
AGE < 20
7
6
5
4
3
2
1
0
PTA Duration in Weeks
(Stuss et al., 2000)

CONCLUSIONS AGAIN

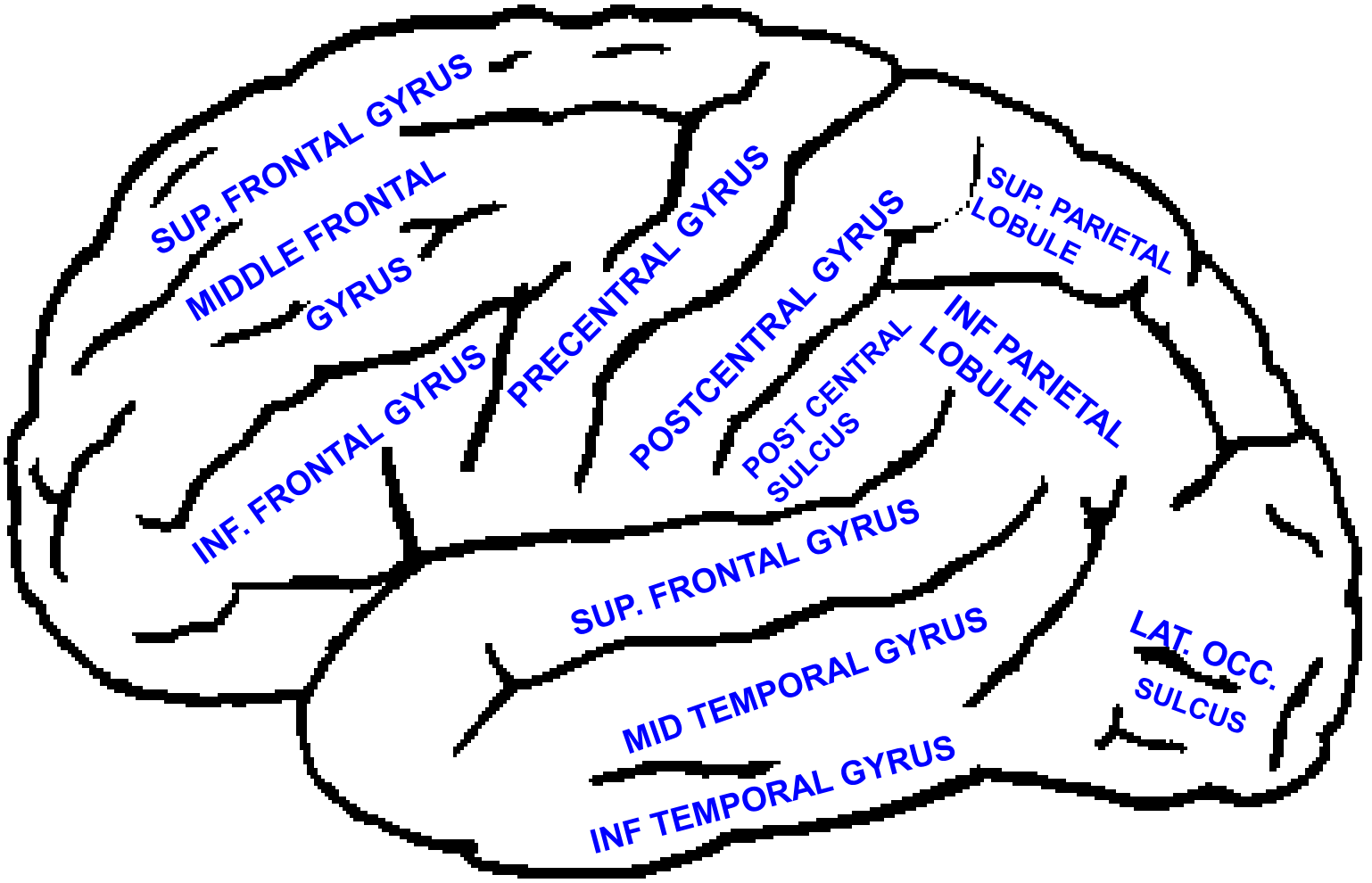
- **TBI research indicates the need for improved phenotyping (sub-grouping) of patients**

- **Rationale: specific treatments may work only in certain groups of patients. That is, there is variability among individuals - group variability**

- **The objective of understanding group variability is to develop stratified subgroups based on rational principles. Phenotyping can be anatomical, behavioural, genetic…**

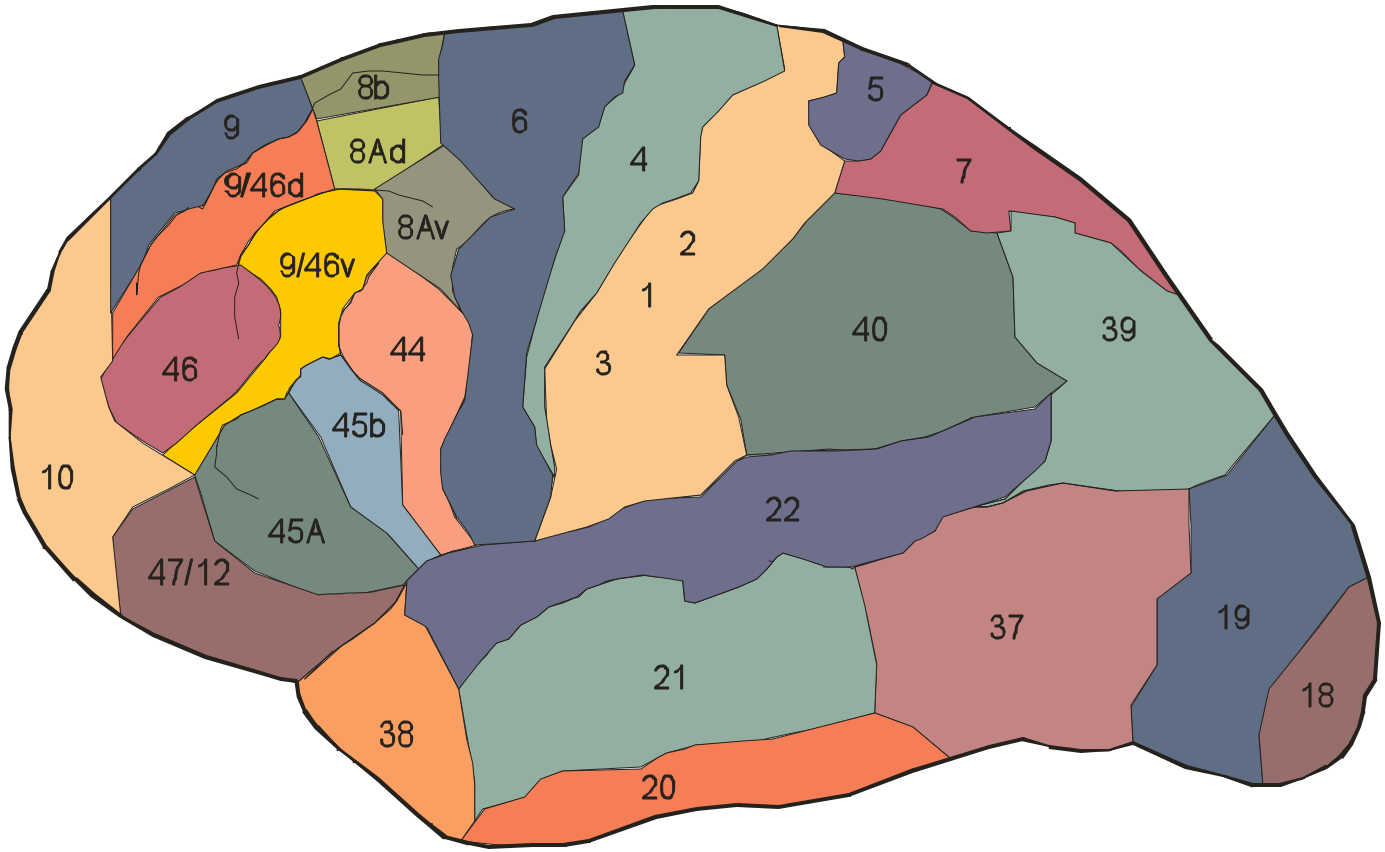
FRONTAL LOBE EXAMPLE

- **Functions of the frontal lobes were described in general "unitary" terms such as executive, or supervisory**


SUP. FRONTAL GYRUS
MIDDLE FRONTAL GYRUS
INF. FRONTAL GYRUS
PRECENTRAL GYRUS
POSTCENTRAL GYRUS
POST CENTRAL SULCUS
SUP. PARIETAL LOBULE
INF PARIETAL LOBULE
SUP. FRONTAL GYRUS
MID TEMPORAL GYRUS
INF TEMPORAL GYRUS
LAT. OCC. SULCUS

FRONTAL LOBE EXAMPLE

- **Unitary?**
- **But in reality there are multiple functions related to different regions of the frontal lobes**


8b
9
8Ad
6
4
5
9/46d
7
8Av
2
9/46v
1
40
39
44
3
46
45b
10
22
45A
47/12
37
19
21
18
38
20

FOUR CATEGORIES OF FRONTAL LOBE FUNCTION

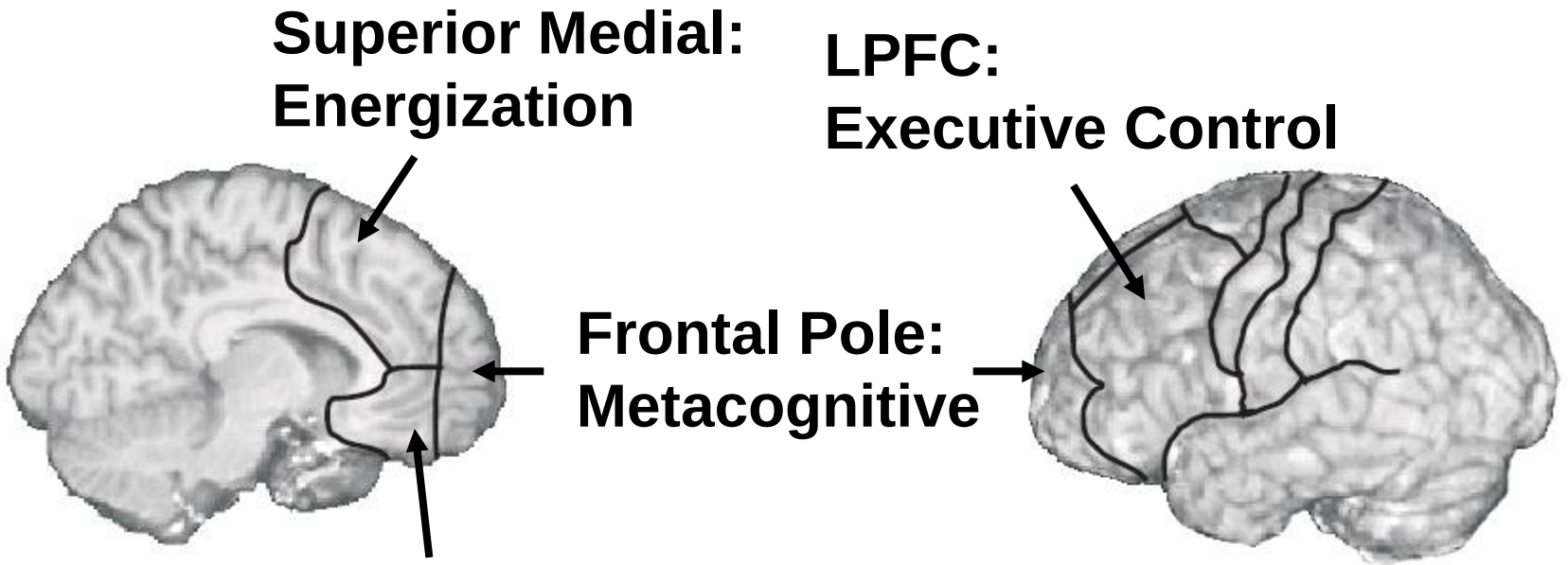
- **There are at least four separate categories of frontal lobe functions. Only one can be labeled as executive.**
  - **Energization (initiation and sustaining of behaviour)**
  - **Executive**
  - **Behaviour/Emotional Self-Regulation**
  - **Metacognition (Theory of Mind)**

THE FOUR RELATE TO DIFFERENT FRONTAL REGIONS

- **The four categories of frontal functions map onto general anatomical localization based on principles of anatomical development and connectivity**
  - **Energization: Superior medial frontal, ACG**
  - **Executive: Lateral prefrontal cortex**
  - **Behaviour/Emotional Self-Regulation: Ventral medial, orbitofrontal prefrontal cortex**
  - **Metacognition (Theory of Mind): polar**

Stuss, 2007, 2011

OVERVIEW OF FL FUNCTIONS



OUTLINE – TWO SECTIONS

- **What you can learn by understanding and harnessing group variability – examples from TBI and frontal lobe research**

- **<u>What is the value of defining sub-groups of individuals with TBI?</u>**

  - **Improved diagnosis**

  - **Targeted rehabilitation**

THE OBVIOUS IMPLICATION

- **Individuals with traumatic brain injury often are considered to have frontal lobe damage, also called "executive dysfunction"**
- **BUT the conclusion is too general…**
- **What does frontal lobe damage mean?**
  - **Not all individuals with TBI have the same pattern of problems**
  - **The frontal lobes constitute 25-33% of the entire brain. And we just learned that there are different functions related to different frontal regions**

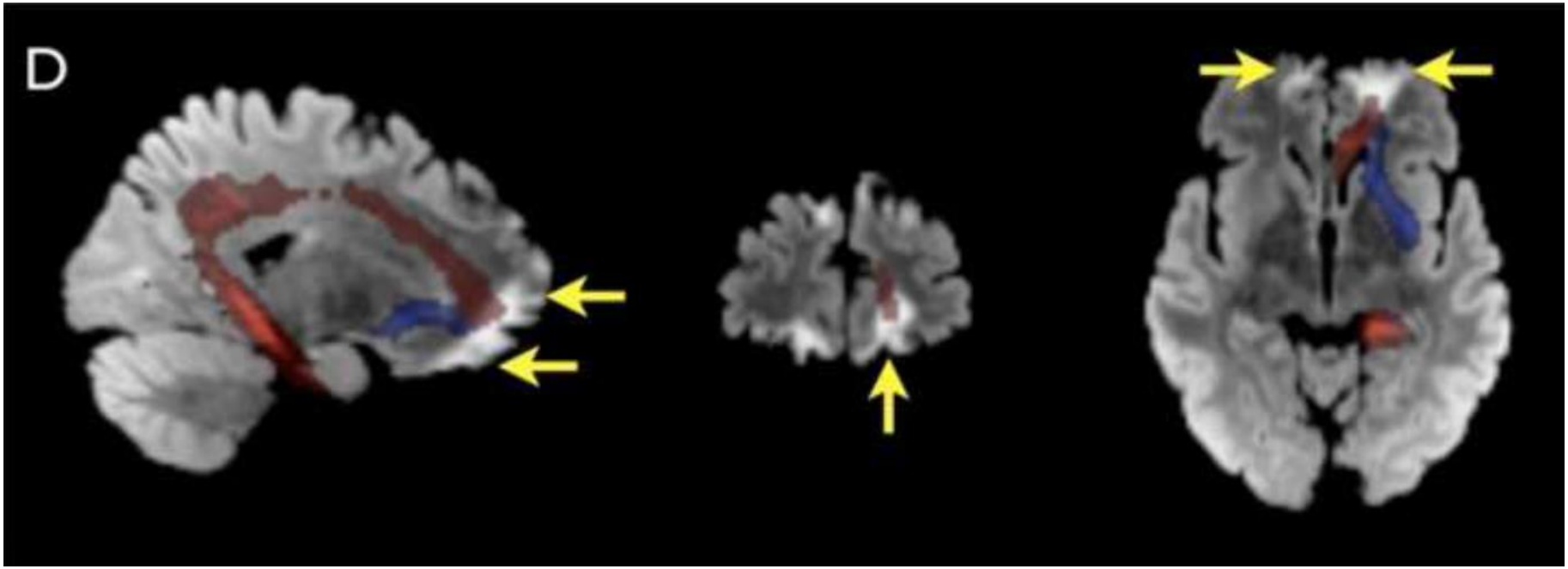
IMPROVED DIAGNOSIS

- **Three patterns of dysfunction in TBI**
  - **Abulic**
  - **Dysexecutive**
  - **Behavioural**
- **Each associated with a different FL region**

Zappala et al., Cortex, 2012
Stuss, Current Opinions in Neurology, 2011

TBI ABULIC SYNDROME

- **Primary Localization: medial frontal, including anterior cingulate and superior medial frontal regions**
- **Behaviours: slowness of processing, lack of activation and initiative, apparent disinterest, and lethargy**
- **"Pseudodepressed"**
- **Measures: observation, RT measures**

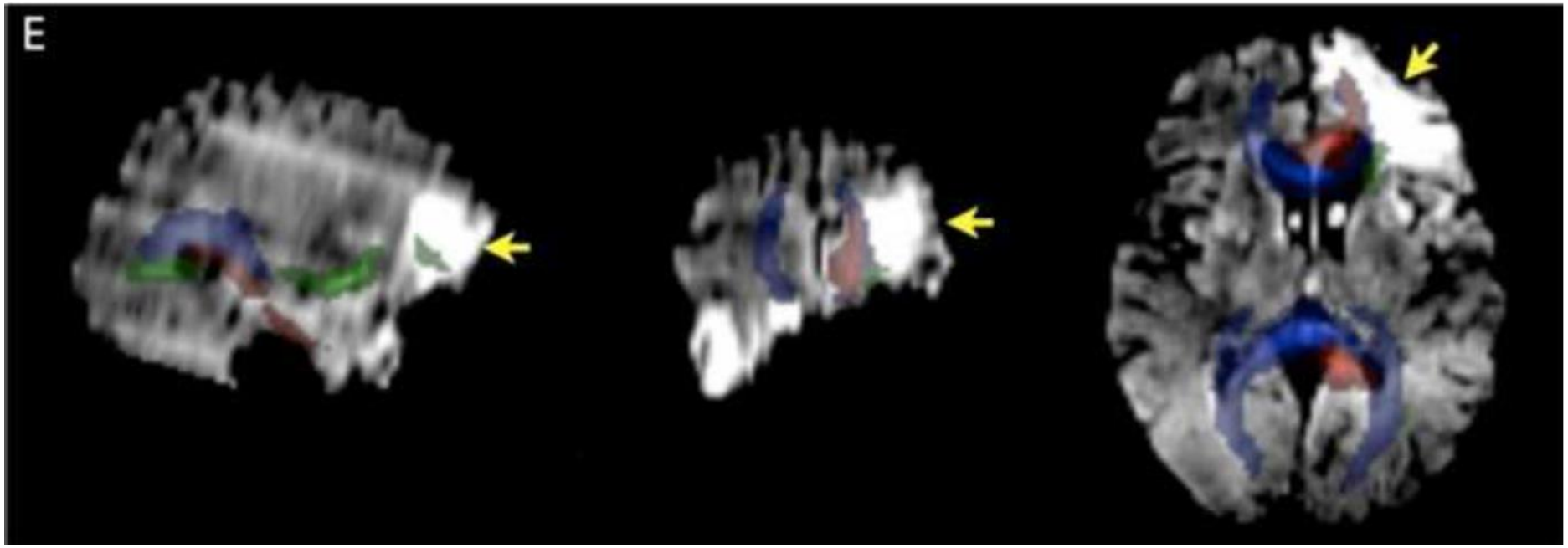


The overlap of the MRI scan with a probabilistic atlas of the white matter pathway suggests an impairment of *left anterior cingular cortex* (red) and left uncinate fasciculus (blue) (D).

Zappala et al (2012)

TBI DYSEXECUTIVE SYNDROME

- **Primary localization: more laterally involving ventro- and dorsolateral FL regions**
- **Behaviours: Impaired organization, planning, reasoning, set-shifting, and monitoring**
- **"Pseudo-dementia", when severe**
- **Measures: many standard FL tests**

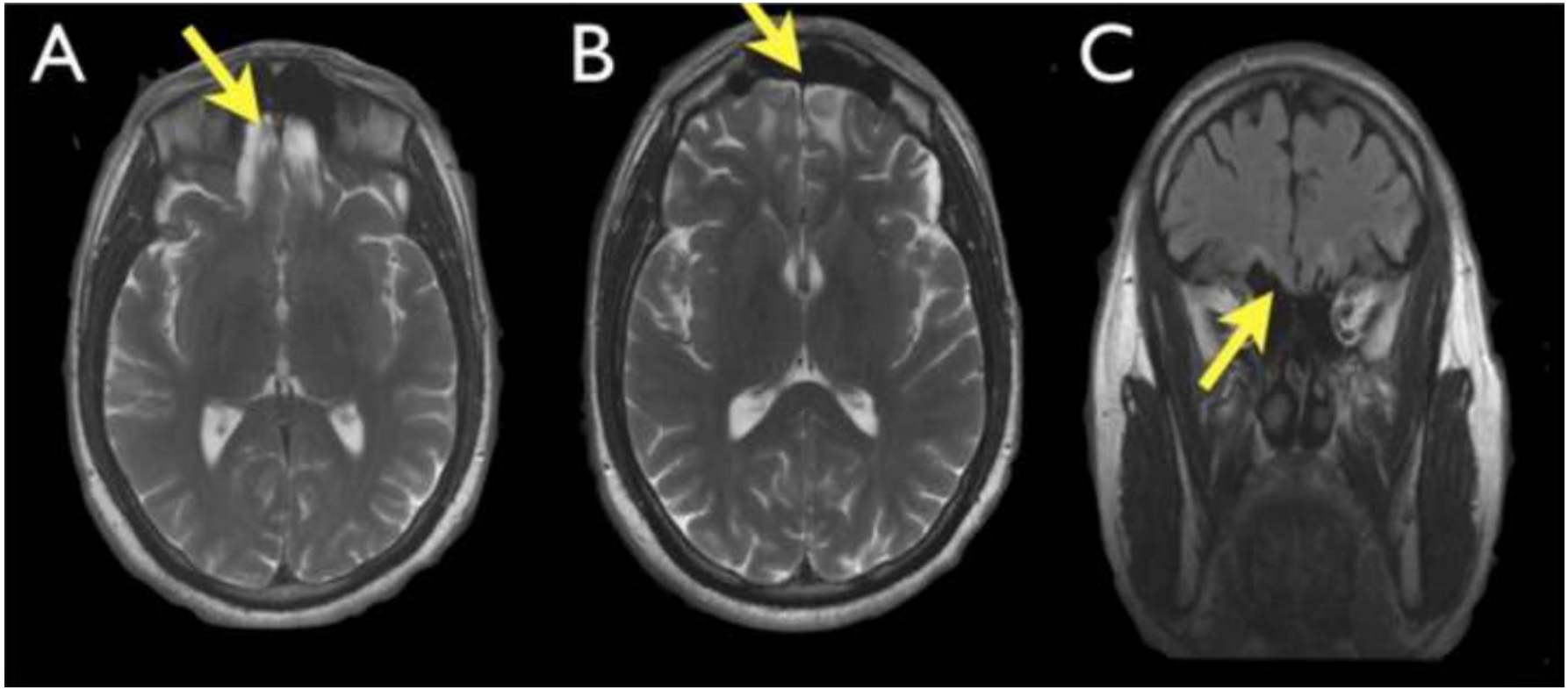


The overlap of the MRI scan with probabilistic atlas of the white matter pathway suggests an impairment of *left anterior cingular cortex* (red), *anterior corpus callosum* (blue) and *inferior fronto-occipital fasciculus- IFOF* (green).

Zappala et al (2012)

TBI BEHAVIOURAL SYNDROME

- **Primary localization: orbitofrontal/ventro medial FL regions**
- **Behaviours: disinhibition, childishness, aggressive and abusive behaviour, selfishness, impulsivity, etc.**
- **"Pseudopsychopathic" when severe**
- **Measures: observations, gambling tasks**



A case of minor TBI with a behavioural syndrome. Conventional MRI scans illustrating the identifiable damages (yellow arrows) using T1 (A and B) T2 (C) contrasts.

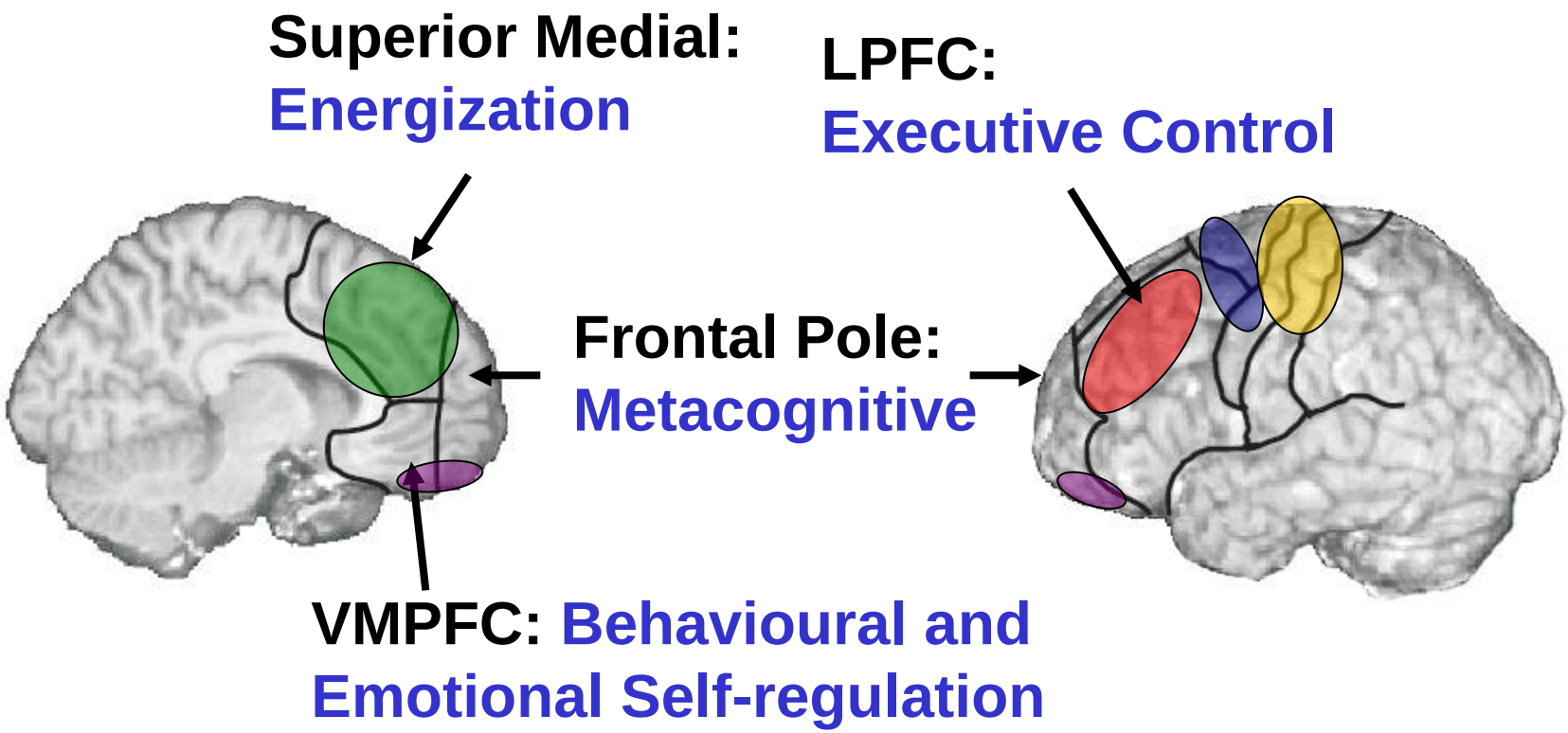
Zappala et al (2011)

COMMENTS

- **TBI syndromes clearly map onto FL fractionation framework:**

  - Abulic — - Energization
  - Dysexecutive — - Executive
  - Behavioural — - Behavioural regulation

- **What of Polar Area 10, since is frequently damaged in TBI: - only recently has Area 10 dysfunction been reported (see Stuss & Knight, 2012, Oxford University Press)**


Superior Medial:
Energization
LPFC:
Executive Control
Frontal Pole:
Metacognitive
VMPFC: Behavioural and
Emotional Self-regulation

BUT DOES THIS APPLY TO MILD TBI?

- **Mild TBI primarily affects white matter connectivity**

- **True – but different WM tracts get affected in TBI depending on the acceleration/deceleration forces**

- these involve to a greater degree the frontal WM pathways, and these derive from the frontal regions which have specific functions

Lateral/Medial Orbitofrontal Circuit

Origin:
Lateral & orbital 12

Superior Medial Circuit

Origin:
AC & SM

Dorsolateral prefrontal-subcortical circuit

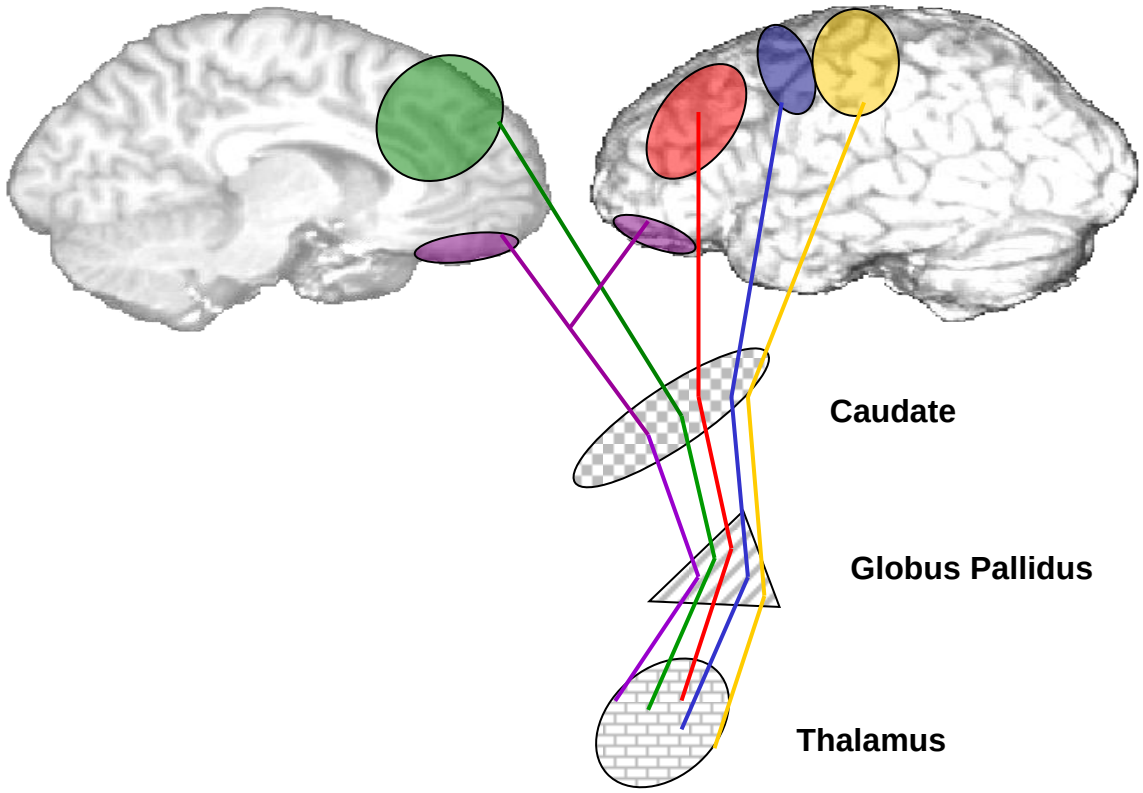
Origin:
9, 46

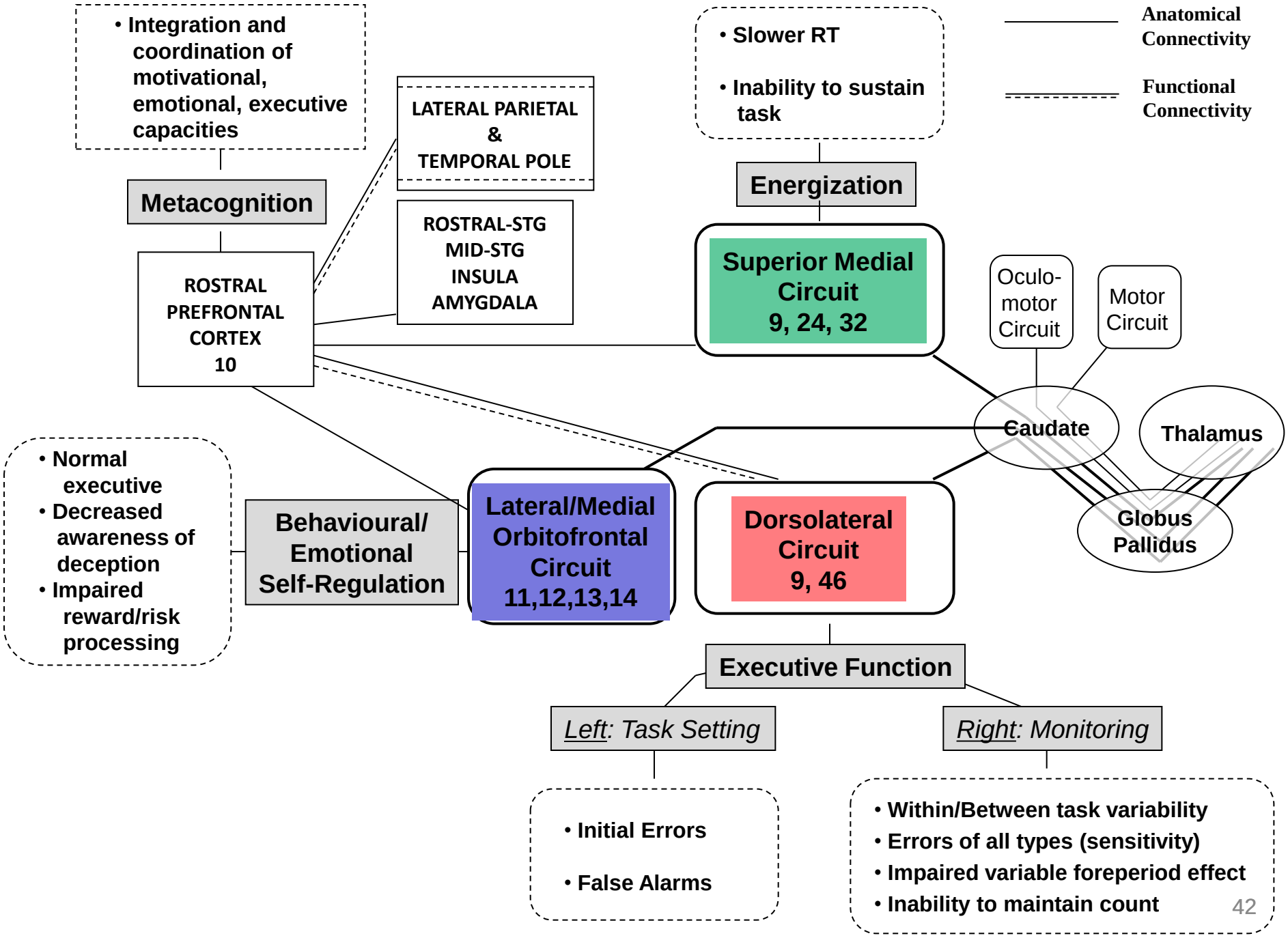
Oculomotor Circuit

Origin:
8

Motor Circuit

Origin:
Motor Cortex




• Integration and coordination of motivational, emotional, executive capacities
Metacognition
ROSTRAL PREFRONTAL CORTEX 10
LATERAL PARIETAL & TEMPORAL POLE
ROSTRAL-STG
MID-STG
INSULA
AMYGDALA
• Slower RT
• Inability to sustain task
Energization
Superior Medial Circuit 9, 24, 32
Anatomical Connectivity
Functional Connectivity
Oculo-motor Circuit
Motor Circuit
Caudate
Thalamus
Globus Pallidus
• Normal executive
• Decreased awareness of deception
• Impaired reward/risk processing
Behavioural/ Emotional Self-Regulation
Lateral/Medial Orbitofrontal Circuit 11,12,13,14
Dorsolateral Circuit 9, 46
Executive Function
Left: Task Setting
Right: Monitoring
• Initial Errors
• False Alarms
• Within/Between task variability
• Errors of all types (sensitivity)
• Impaired variable foreperiod effect
• Inability to maintain count

CAUTIONARY NOTES

- **Presentation of a single syndrome after TBI is uncommon, most patients having mixed presentations**

- **Value of framework is not just diagnostic differentiation, but in recognition of the potential diversity of clinical problems for understanding and treatment**

OUTLINE – TWO SECTIONS

- **What you can learn by understanding and harnessing group variability – examples from TBI and frontal lobe research**

- **What is the value of defining sub-groups of individuals with TBI?**

  - **Improved diagnosis**

  - **Targeted rehabilitation**

TARGETED NEUROREHABILITATION

- **For reviews and elaboration of concepts, see**

  - **Cicerone et al., 2006**
  - **Levine, Turner & Stuss, 2008**
  - **Stuss, 2008**
  - **Stuss, 2011**

REHABILITATION of FUNCTION

Energization

- **Externally cuing initiation** (Sohlberg et al., 1988)
- **Pharmacological dopamine agonist** (Powell et al., 1996)

Task Setting

- **Simplification of complex problems** (Von Cramon et al, 1991)
- **Cueing and feedback** (Fox et al., 1989)

Executive Functions

- **Goal Management Training** (Levine et al, 2000, 2007)

Behavioural/Emotional Self-Regulation

- **Prompts/rewards – Monitoring – Control** (Alderman et al, 1995)

Meta-cognitive Processes

- **Problem solving and role play** (Ownsworth et al, 2000)
- **Modifying people's predictions, not behaviour** (Rebmann & Hannon et al, 1995) (Youngjohn & Altman, 1989)

FRONTAL FRACTIONATION AND REHABILITATION

Oliver Zangwill Centre, Cambridgeshire Community Services, NHS Trust Used Frontal Lobe fractionation model to direct rehab

- **In TBI, found dissociable patterns of outcome based on the model**
- **Developed targeted rehabilitation based on behavioural patterns**

CONCLUSIONS

- **Current rehabilitation of individuals with traumatic brain injury may not be targeting the most pertinent problems**
- **Assessment of such individuals must cover all categories of frontal lobe functions.**
- **Standard test of many of these frontal lobe dysfunctions do not yet exist.**
- **The clinical needs suggest the use of experimental measures at this time**

CONCLUSIONS

- **The value of the framework is that it is a theoretical model grounded in anatomy, brain-behavior relations, and understanding of network connectivity.**

- **As such it provides an improved ability to differentiate the potential causes underlying dysfunction after TBI, and to target rehabilitative efforts**

LET'S GO BACK TO WHY

- **ARE THERE OTHER FACTORS TO CONSIDER BESIDES PATHOLOGY, SEVERITY, AGE?**

OTHER POTENTIAL FACTORS AFFECTING OUTCOME

- **Pain**
- **Depression**
- **Anxiety**
- **Sleep**
- **Alcohol use**
- **Stress**
- **Vestibular, cerebellar problems**
- **Psychosocial environment**

SUMMARY

- **Understanding and differentiating the different types of factors affecting an individual may be an important key to target the type of rehabilitation**

- **Current rehabilitation of individuals with TBI may not be targeting the most pertinent problems**

THANK YOU