



**Clinicians Beware!**  
**Appearances May Be Deceiving**

Donald T. Stuss, PhD,  
 Founding President and Scientific  
 Director  
 Ontario Brain Institute




**Financial Disclosure**

I have no financial relationships to disclose:

**ACKNOWLEDGMENTS**


- Mick Alexander, Tim Shallice, Terry Picton,
- Antonio Valesi - fMRI
- Susan Gillingham, and a host of others
- Funders: CIHR, OMHF



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**Overarching Objective**


- Share with you for consideration and discussion some 35 years of lessons learned in the study of individuals with frontal lobe dysfunction on why to be wary when you study, diagnose and treat such individuals



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**Specific Learning Objectives**

- Identify and differentiate the four major categories of frontal lobe functioning
- Map the relationship between anatomical development and connectivity to frontal lobe functions
- Identify how “basic” research can be used for the development of neurorehabilitation techniques to patients with frontal lobe dysfunction



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**OUTLINE**

- Examples of the “Mystery” of the Frontal lobes
- Research findings that shed some light
- The value of these findings to clinical application
- Summary of the Lessons



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## THERE IS A REASON WHY THE FRONTAL LOBES WERE CALLED A MYSTERY

- Clinical investigation of the frontal lobes has led to many “teachings” that we use for diagnosis
- Using clinical examples, will highlight the reasons for wariness in diagnosis and indeed even understanding the frontal lobes – perhaps because we view the individuals through our cognitive and clinical models
- Through this, will summarize lessons learned

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### MYSTERY # 1 - GAGE ET AL.

- “No longer Gage” – “the equilibrium ..between his intellectual faculty and animal propensities, seems to have been destroyed.”
- Ackerly & Benton (1947) – congenital bilateral prefrontal lesion. As he grew, significant problems in emotional control

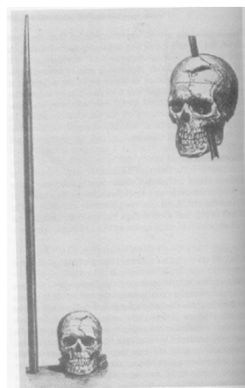
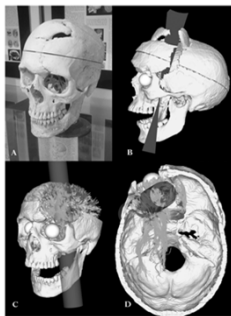


Figure 1. Modeling the path of the tamping iron through the Gage skull and its effects on white matter structure.



Van Horn JD, Irimia A, Torgerson CM, Chambers MC, et al. (2012) Mapping Connectivity Damage in the Case of Phineas Gage. PLoS ONE 7(5): e37454. doi:10.1371/journal.pone.0037454  
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0037454>



### EARLY REPORTS – BUT...

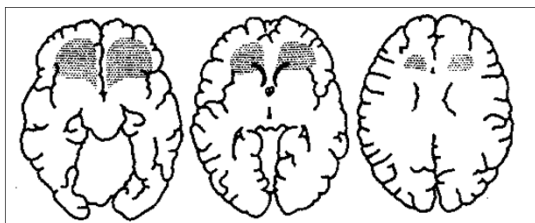
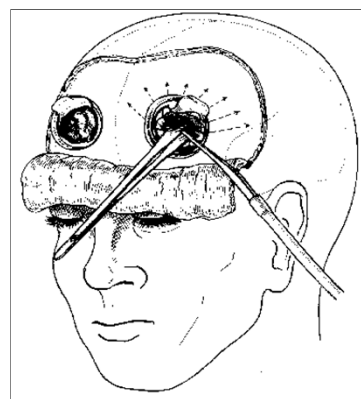
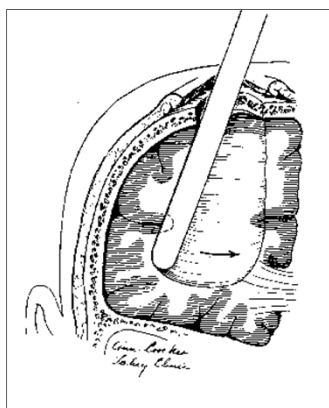
- Gage
  - a) The most dramatic changes occurred in early stages post-injury, and decreased
  - b) Many of the reports apparently exaggerated (Macmillan)
  - c) Gage could hold a job – *but not consistently*
- Ackerley & Benton – patient could hold a job *under certain circumstances*

### IMPLICATIONS

- There are subtleties to study and understand, which are important for rehabilitation and management
- Context (time since injury, environmental circumstances) appears particularly relevant

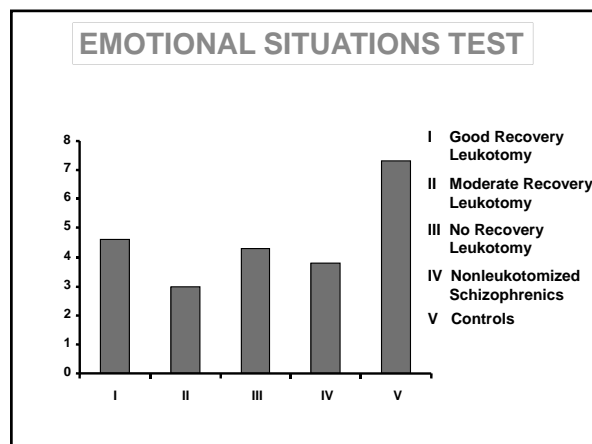
### MYSTERY # 2 – LEUCOTOMY STUDIES

- In the mid 1970s we studied the effects of pre-frontal leucotomies 25 years post-surgery



### GROUP DESCRIPTIONS

- Five groups of individuals were studied:
- Matched control group
- Four patient groups from the same hospital, diagnosed by the same physicians as psychotic
- Three groups had received a frontal leucotomy as treatment; sub-divided into three groups based on degree of recovery: good, moderate, poor
- The fourth – no surgery even though one had been prepped



- ### LEUCOTOMY IMPACTS SOCIAL BEHAVIOURS - BUT....
- The Boston bus station
  - Going dancing
  - Catatonia and a sense of humour
  - Changing neuropsychological examiners - a lesson about social behaviour

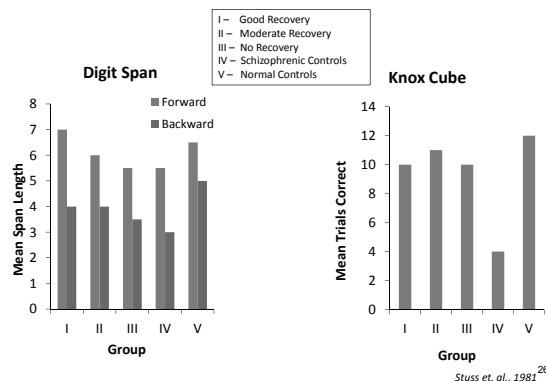
- ### IMPLICATIONS
- Social changes are not an all-or-nothing phenomenon
  - There are qualitative differences in abnormal social responsiveness
  - Context again is important

- ### MYSTERY # 3 – MORE LEUCOTOMY
- During the leucotomy research, DF Benson was on sabbatical at the Maudsley in the UK
  - The Context
  - My Response:– even though I had not analyzed the data, I had been working with these individuals for months. I was trained as a clinical psychologist before neuropsychology – I was a confident observer and diagnostician.
  - FRANK, TRUST ME – the major deficit after frontal leucotomy is a severe attentional deficit

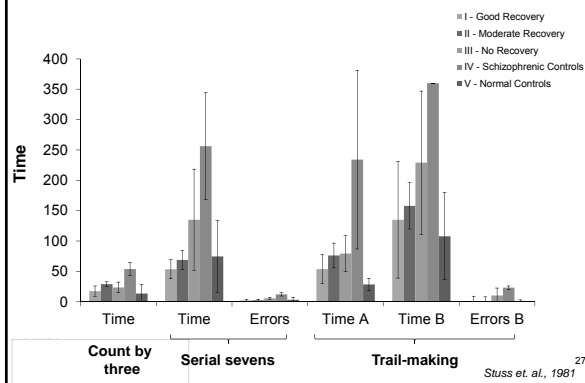
**BUT...**

- THEN – I ANALYZED THE DATA

## SPAN TESTS



## ATTENTION MEASURES



## IMPLICATIONS

- What you see is not necessarily indicative of the actual abilities; it may represent the unfolding of abilities under certain contexts
- You can become the frontal lobes of the patient, compensating for the problems – and this itself is a type of context

## MYSTERY # 4 – PSYCHOSIS OR NOT

- Canadian volunteer to US Army in Vietnam way discharged for psychiatric reasons
- One year later – recalled
- The day before recall – ended up in hospital with tentative diagnosis of acute psychotic reaction with catatonic symptoms
- Description of patient examination
- Lesion – small left posterior frontal ventrolateral lesion

## IMPLICATIONS

- One more lesson on the importance of understanding context when you examine a patient
- Lesion location within the frontal lobes is important

### MYSTERY # 5 - TBI CASE STUDY

- Patient suffers mild-moderate TBI. After initial recovery, has normal intelligence, attention, language, relatively good ability to learn new information, good visual-spatial skills, good general knowledge of the world.
- BUT – has lost all episodic memory. That is, he has no memory of his personal past, but can remember all factual information.

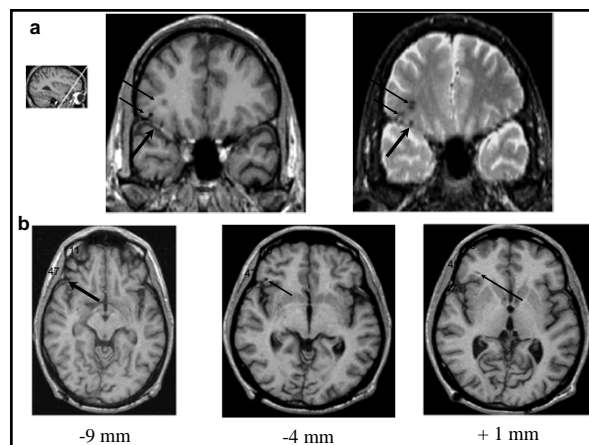
### MYSTERY # 5 – CLINICAL FACTS

- TBI – loss of all pre-injury personal memories, but semantic memories intact
- Post injury, he could remember past memories, but devoid of emotion
- Questions: malingerer? If a real deficit, how to explain?

### BUT...

- More recent research indicated importance of right frontal lobe to a) retrieval; b) self-awareness and episodic memories
- Hypothesis: if right frontal lobe important to self-awareness and episodic memories, a focal lesion disconnecting RFL could theoretically result in a) lost of pre-injury episodic memories because could not retrieve; b) post-injury lost of “episodic” (warm, personal) nature of memories

(Levine et al., Brain, 1998, 121)
















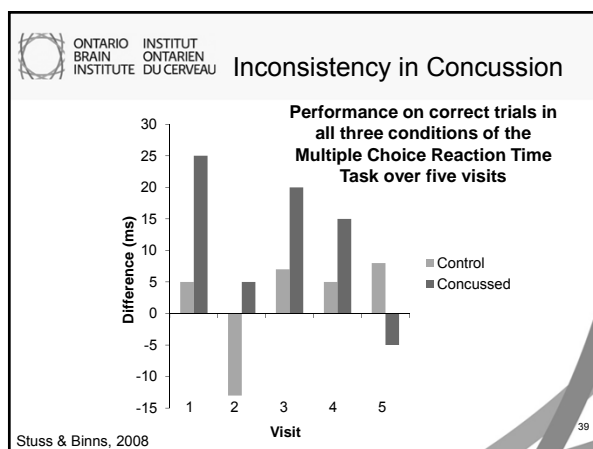
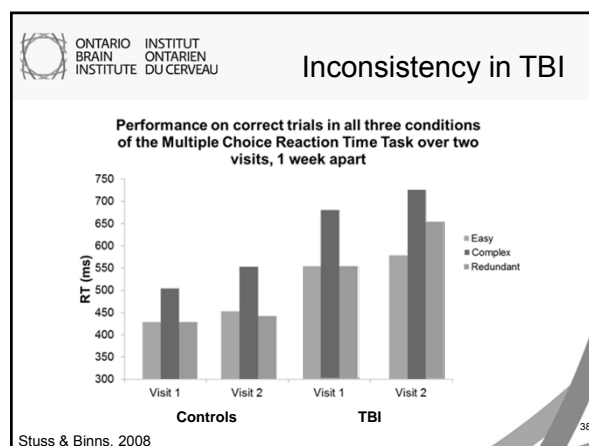
### IMPLICATIONS

- You need both anatomy and cognitive theory to understand the functions of the frontal lobes

### MYSTERY # 6 – TBI and FL Dysfunction

- Experimental attempt to demonstrate focused attention deficit after TBI
- Moderate to severe TBI group compared to matched control group
- Procedure was developed to isolate the process of focused attention
- And – to show that effect was reliable, groups were tested twice, same time of day, one week apart

FEATURE INTEGRATION TEST		
Test	Target	Distractors
Simple		none
Easy Choice		  
Complex Choice	 blue	 red  yellow  blue
Redundant Choice	 yellow	 red  green  blue



### LESSON

- Had to use my own frontal lobes to break my mental set from training as experimental psychologist which suggests that if results are not replicable, they are not valid; the results are “noise”
- Had to think as a clinician and listen to patients
- And one can show that variability itself is reliable in its own way
- But what causes variability? We postulated some “type” of frontal lobe control dysfunction

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### IMPLICATIONS

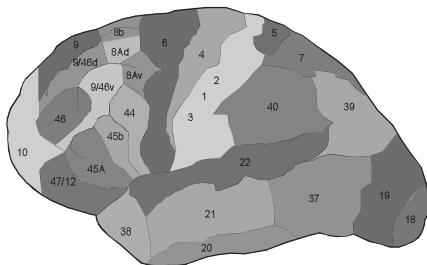
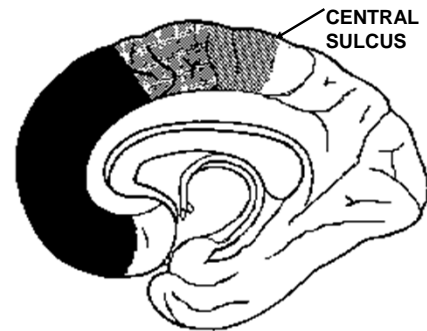
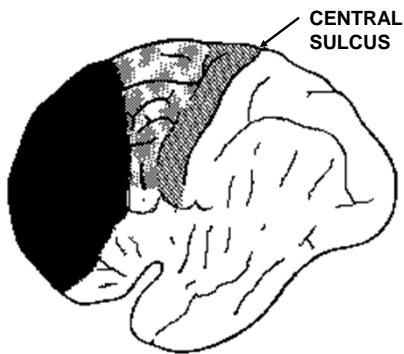
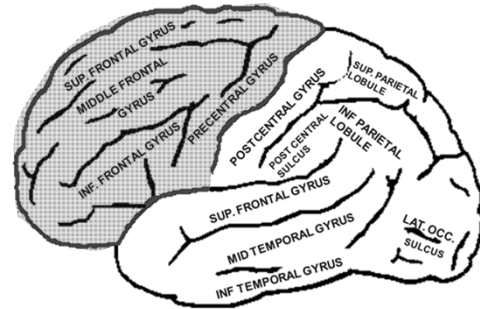
- The variability WAS THE DATA

### MYSTERY # 7 –FRONTAL LOBE ANATOMY

- We use the terms “frontal functions” or “frontal dysfunction”

BUT....

- Look at the anatomy



SURFACE	REGION	CYTOARCHITECTURE
POLAR	Superior	10
	Inferior	10
ORBITO-FRONTAL		14, 11, 13, 47/12
LATERAL	Dorsolateral	9, 46, 9/46d, 9/46v, 8b, 8Ad, 8Av, 6a, 4
	Ventrolateral	47/12, 45a, 45b, 44, 6b, 4
SUPERIOR MEDIAL	Superior Anteromedial	8b, 9
	Superior Posteromedial	6a, 4
	Paracingulate	32
	Cingulate	24
INFERIOR MEDIAL	Ventromedial	14
	Paracingulate	32
	Cingulate	24, 25

Stuss et al., 2002



## Summary of Lessons

- The reason that it is difficult to understand the functions of the frontal lobes is that one has to consider many factors:
  - functional/anatomical specificity
  - context of different types
  - the sophistication of cognitive theory
  - possible different types of control
  - the effect of disturbance in control on consistency of performance

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- Research findings that shed some light
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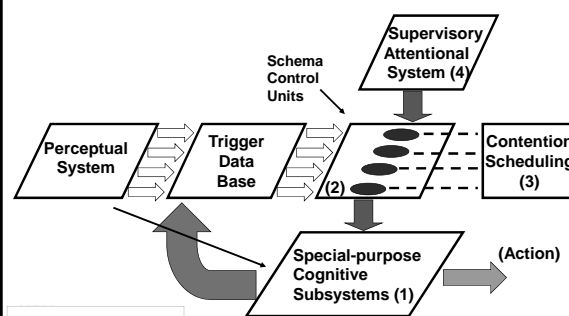
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## QUESTION

- If the frontal lobes have a dominant central organizing role, is this system unitary (an “executive”) or fragmented (a series of domain general control processes)?
- Frame within the role of the frontal lobes in “attention”

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## ANTERIOR ATTENTIONAL SYSTEM Shallice (1991)



## WE STARTED FROM SCRATCH

- Shallice, Alexander, Picton and myself
- Start with patients with focal lesions, to evaluate which brain regions are necessary for functions
- Differentiated “task” from “process”
- Differentiated “descriptive term” from “fundamental process”
- Scaffolded difficulty - why? – to demonstrate that frontal lobe patients could do simple tasks, and highlight at which level of difficulty problems arose

## WITH THIS APPROACH

- We proposed five different frontal attentional processes, related to different frontal regions
- These processes are fundamental, in that they can explain performance on a series of different tasks
  - Energization
  - Inhibition
  - Contention Scheduling (setting of)
  - Monitoring
  - Logic – adjusting goals and energization based on monitoring (setting the task)

(Stuss et al., ANYAS, 1995, 769)

### LET'S START WITH ATTENTION

- There are (at least) three separate processes related to attention within the frontal lobes, each related to a different frontal region
- Energization
- Task Setting
- Monitoring

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### STRUCTURE of DATA PRESENTATION

- TOP: Bar graph by coarse lesion localization:
  - RL – right lateral;
  - LL – left lateral;
  - SM – superior medial;
  - IM – inferior medial
- BOTTOM: Architectonic localization

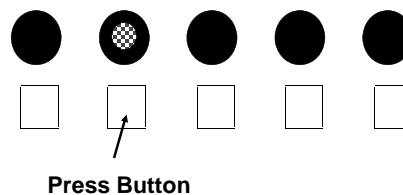
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### TELL THEM

- ENERGIZATION
  - “The process of initiation and sustaining of any response made”

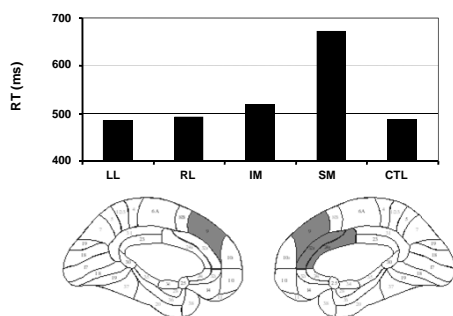
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### ENERGIZATION CONCENTRATE (ROBBIA)



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### ENERGIZATION CONCENTRATE (ROBBIA)



Stuss et al., 2005;  
Stuss & Alexander, 2007 59

### IMPLICATIONS

- Frontal processes are important even for simple tasks – have to rethink idea of complexity

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## IMAGING EVIDENCE of ENERGIZATION

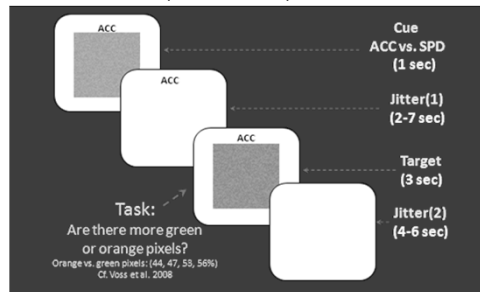
### Experimental Aim:

- to investigate the brain mechanisms and associated distinct processes related to the regulation of speed-accuracy strategy trial-by-trial by using fMRI.

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## METHOD: Speed/Accuracy Tradeoff

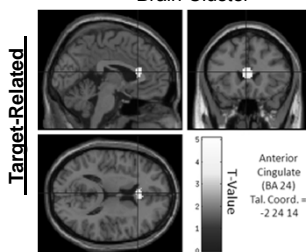
- Participants: 12 right-handed healthy subjects (6 F; mean age: 24 years, range: 19-37).
- Session: 6 runs (6 practice and 40 test trials per each run), preceded by two practice runs with feedback (on the 0 T scanner).



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## RESULTS

### Brain Cluster



The Anterior Cingulate was mostly activated when it was necessary to sustain a speeded response (no-switch SPD trials), consistently with a role in energization (Paus, 2001; Stuss et al., 2005).

Vallesi et al., 2012



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## TASK SETTING

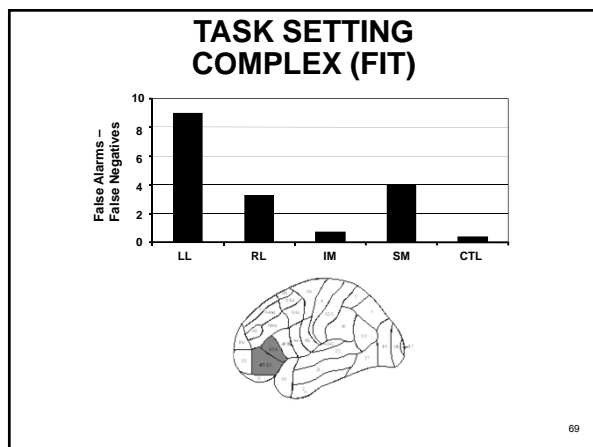
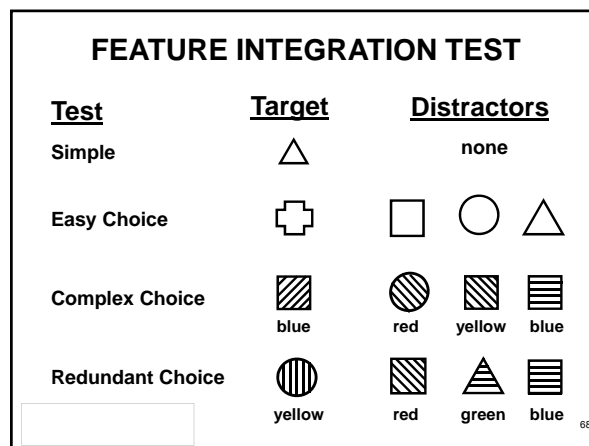
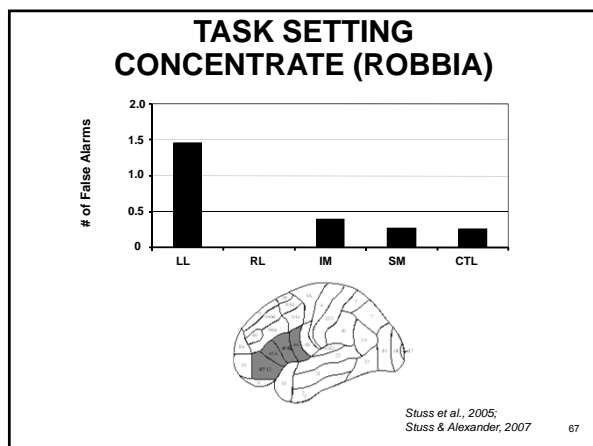
- “The ability to establish a stimulus-response relationship”, requiring formation of a criterion to respond to a defined target with specific attributes, organization of the schemata to do a task, and adjustment of contention scheduling

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## TASK SETTING

- Can also be seen as a “sculpting” activity (Fletcher et al., 2000; Frith, 2000), where surface material to be carved represents a prepotent habitual response that needs to be overcome
- Emerging shape is the new strategy, or S-R association

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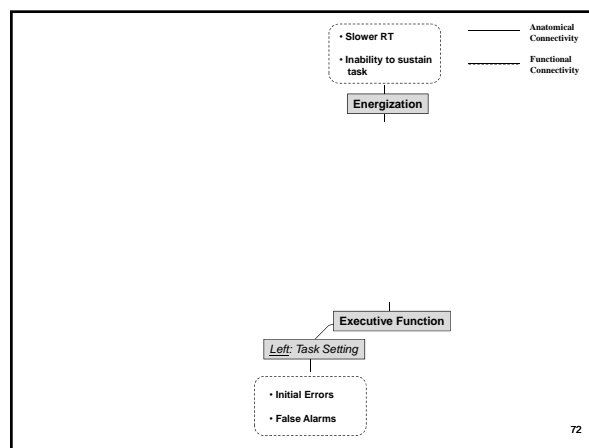
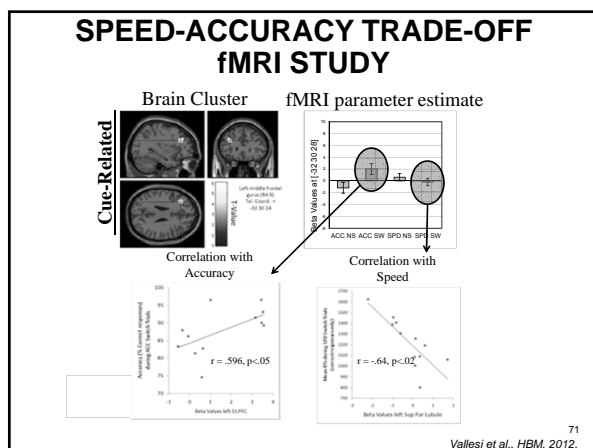


### TASK SETTING IMAGING EVIDENCE

**Experimental Aim:**

– Speed-accuracy trade-off

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## MONITORING

- “The process of checking the task over time for ‘quality control’ and the adjustment of behaviour ”

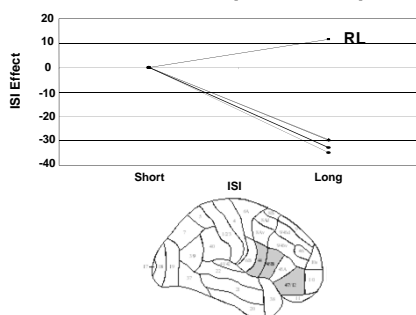
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## MONITORING SIMPLE RT (ROBBIA)

- 5 different Inter-stimulus Intervals (ISI) (3,4,5,6, or 7 seconds), each occurring 10 times randomly
- Short ISI = 3 and 4 seconds
- Long ISI = 6 and 7 seconds

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## MONITORING SIMPLE RT (ROBBIA)



Stuss et al., 2005;  
Stuss & Alexander, 2007

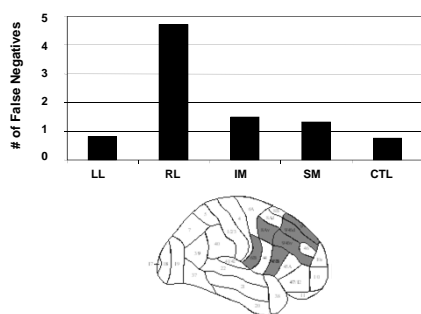
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## FEATURE INTEGRATION TEST

Test	Target	Distractors			
Simple		none			
Easy Choice					
Complex Choice					
Redundant Choice					

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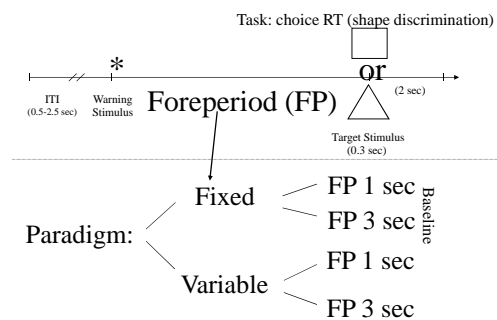
## MONITORING COMPLEX (FIT)



Stuss et al., 2005;  
Stuss & Alexander, 2007

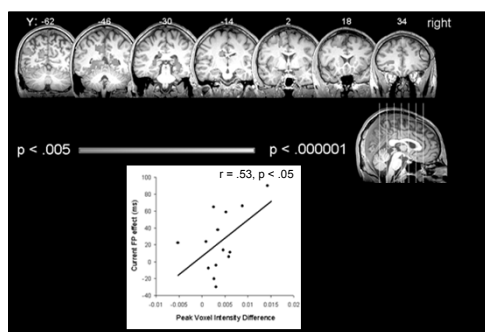
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## MONITORING FOREPERIOD & fMRI



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## MONITORING FOREPERIOD & fMRI



Vallesi, McIntosh, Shallice & Stuss, J Cog Neurosc, 2009

• Slower RT  
• Inability to sustain task

Energization

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

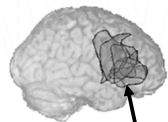
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LEFT LATERAL

RIGHT LATERAL



Task Setting



Monitoring

Energization

R

L

SUPERIOR MEDIAL

81 81

## THREE FRONTAL LOBE ATTENTIONAL CONTROL PROCESSES

- There are (at least) three separate processes related to attention within the frontal lobes, each related to a different frontal region
- Energization
- Task Setting
- Monitoring

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## LET'S RETURN TO VARIABILITY

- Can the three separate processes related to attention within the frontal lobes, explain variability
- Examine response to errors within a task;
- The common response in a reaction time task is often to speed up over time, and then when an error is made, slow down for the to trial to adapt to the situation and not make another error

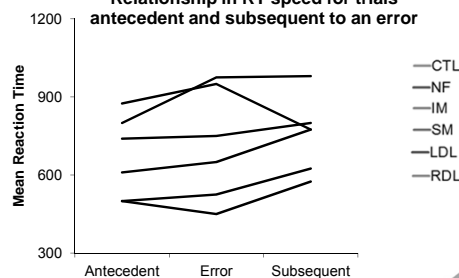
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## Frontal Processes Underlying Variability

Relationship in RT speed for trials antecedent and subsequent to an error



Stuss et al., 2003

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## Observations on Variability

- Individual variability can be caused by impairment in different control processes
- These different control processes are revealed by examining performance under a specific context – reaction to making an error
- The observation, the measurement of variability, is not the process; one has to unveil the process to develop focused rehabilitation

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## FROM ATTENTION TO EMOTIONS AND META-COGNITION

- Let's look at possible other functions associated with the frontal lobes
  - Behavioural/emotional self-regulation
  - Meta-cognition/integration

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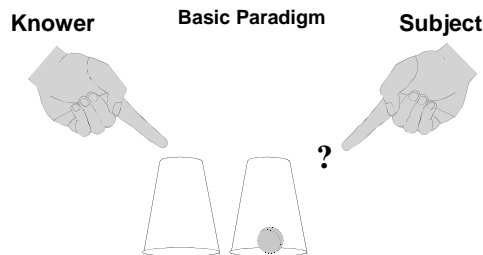
## BEHAVIOURAL/EMOTIONAL SELF-REGULATION

- Emotional Processing:
  - ✦ Difficulty in understanding the emotional consequences of behaviour
- Behavioural Self-Regulation:
  - ✦ Required in situations where cognitive analysis, habit, or environmental cues are not sufficient to determine the most adaptive response

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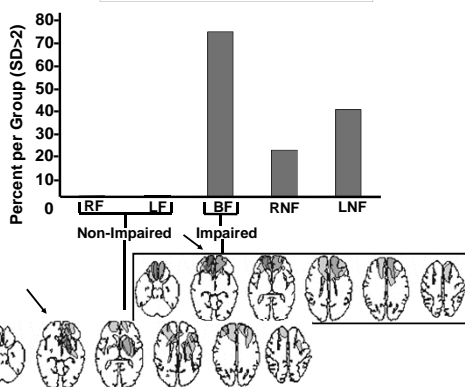
## BEHAVIOURAL/EMOTIONAL SELF-REGULATION

### Deception Task

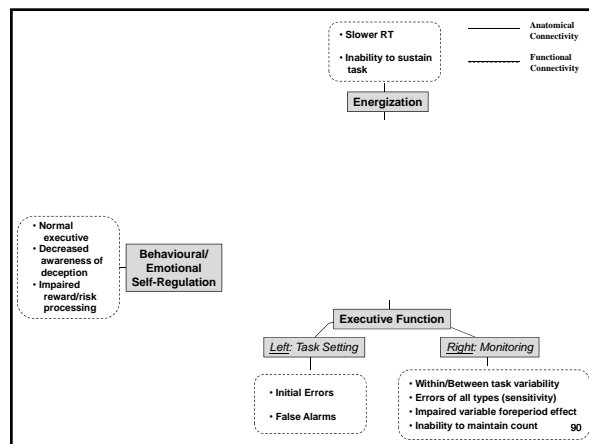


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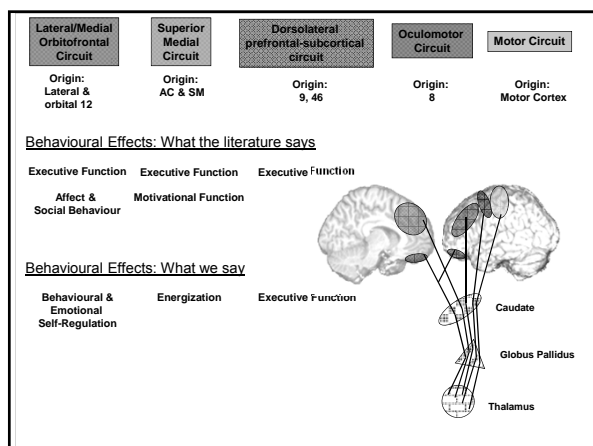
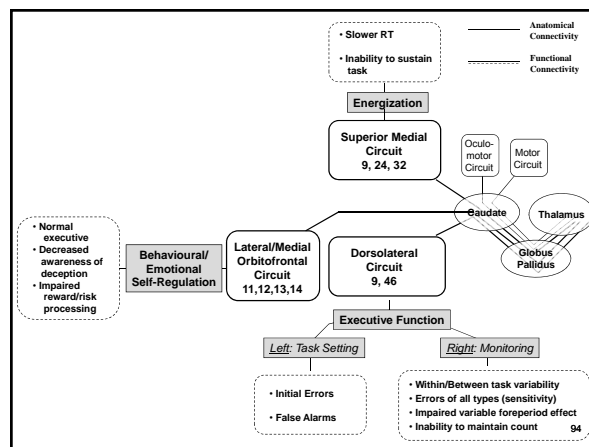
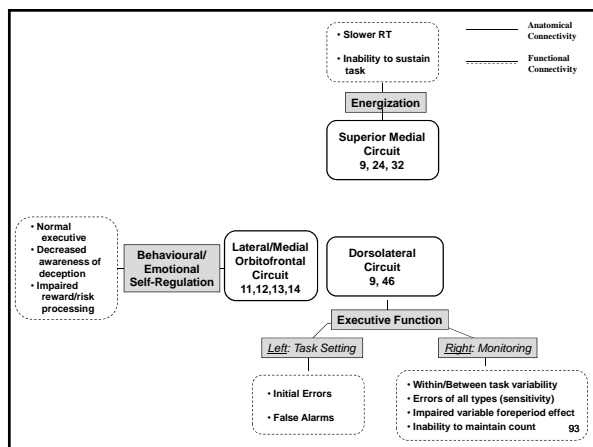
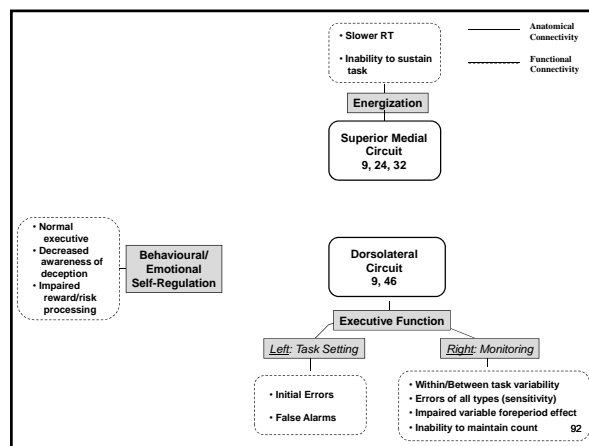
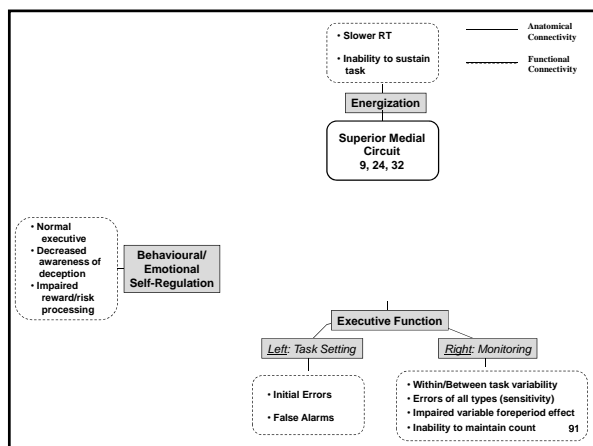
## DECEPTION TASK



89 89



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## METACOGNITIVE PROCESSES

- A reflective representation of one's own mental states, beliefs, attitudes and experiences
- Affects ability to make inferences about the world, to empathize with and understand the actions of others, and to serve as a base for appropriate social judgments



## METACOGNITIVE PROCESSES

### Humour Study – Is this funny?

- Paris Hotel-  
“Leave your values at the front desk”
- Hong Kong Dentist-  
“Teeth extracted by the latest Methodists”
- Bangkok Cleaners-  
“Drop your trousers here for best results”

Shammi &amp; Stuss, 1999

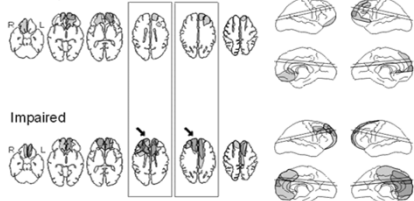
97 97

- In a Rhodes tailor shop-  
“Order your summers suit. Because is big rush we will execute customers in strict rotation.”
- In a Bangkok temple-  
“It is forbidden to enter a woman even a foreigner if dressed as a man.”
- In a restaurant in Paris-  
“Lunch will be served to patrons between noon and 3 p.m.”

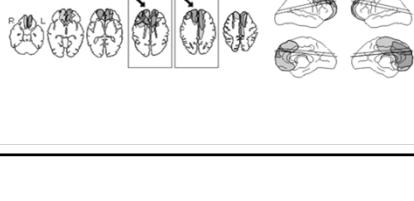
## METACOGNITIVE PROCESSES

### Difference Between Rating of Humorous and Neutral Items

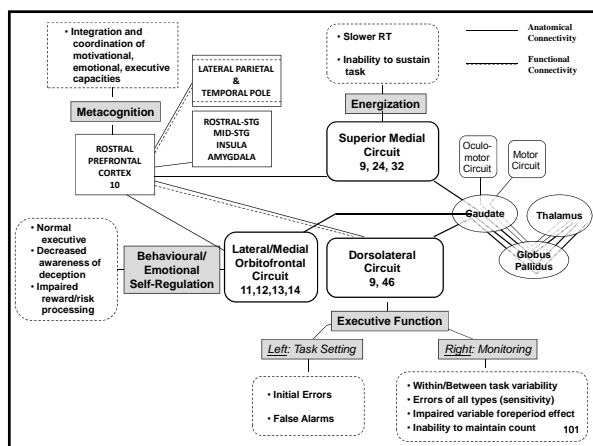
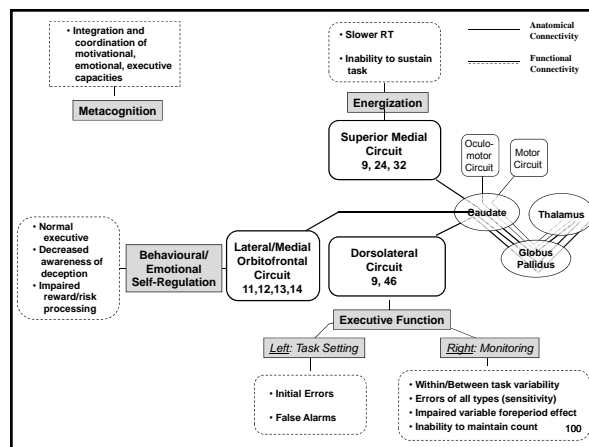
Non-Impaired



Impaired



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## PROPOSAL – THERE ARE FOUR CATEGORIES OF FL DYSFUNCTION

- The four categories of frontal functions map onto general anatomical localization based on principles of anatomical development and connectivity

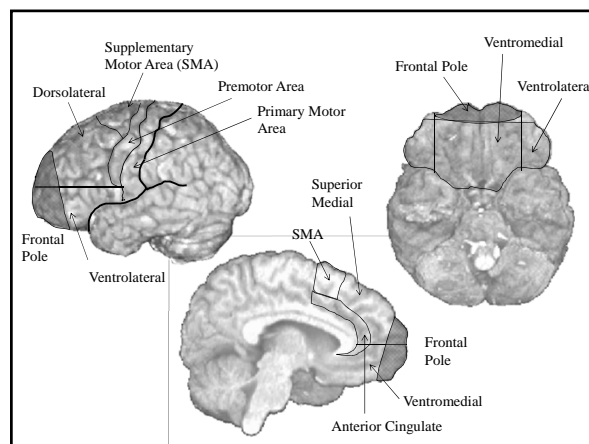
- ♦ **Energization:** Superior medial frontal
- ♦ **Executive:** Lateral prefrontal cortex
- ♦ **Behaviour/Emotional Self-Regulation:** Ventral medial prefrontal cortex
- ♦ **Metacognition (Theory of Mind):** polar

(Stuss, JINS, 2011)

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### ASSESSMENT: FOUR DOMAINS

- A. Energization/regulation: superior medial
- B. Executive/cognitive: lateral
- C. Metacognitive: frontal poles, primarily right
- A. Behavioural Self-regulatory: orbital/ventromedial



### THIS CATEGORIZATION is COMPATIBLE with ANATOMY and CONNECTIVITY

- Two major divisions are based on evolution of cortical architectonics (e.g., Sanides; Pandya; Stuss & Levine, 2002)
  - Dorsolateral: from hippocampal, archicortical trend
    - Spatial and conceptual reasoning: executive cognitive
  - Ventral(medial): from olfactory, paleocortical trend
    - Emotional processing: behavioural self-regulatory
- Network connectivity (Alexander et al., 1986) – adds action regulation (e.g., energization)
- Metacognitive – role of area 10 in frontal interconnectivity

### CONCLUSIONS

“The frontal lobes do not equal a central executive. Executive functions represent only one functional category within the frontal lobes. These frontal functions are domain general, possibly because of the extensive reciprocal connections with virtually all other brain regions, integrating information from these regions. Further integration of these processes with emotional and motivational processes allows the most complex behaviors.”

Stuss (2011). JINS, p.763

### IMPLICATION

- The frontal lobes are not a monolith. There are at least four functional categories within the frontal lobes.
- There are likely subdivisions within the categories; e.g., different types of monitoring (Petrides, in Stuss & Knight, 2012); potential hierarchies of “task setting” (D’Esposito); fractionation of area 10 (Burgess, in Stuss & Knight, 2012).



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### OUTLINE

- Examples of the “Mystery” of the Frontal lobes
- Research findings that shed some light
- The value of these findings to clinical application
- Summary of the Lessons

## WHY IS FRACTIONATION RELEVANT?

- This is the era of neural networks, inter-connectivity, system analysis –  
- fractionation is so old school
- **ANSWER:** I can work on rehabilitation and treatment of separate processes, the outcome of which I can measure on its effect on the system network – but I don't know how to rehab a system without understanding its component parts

## APPLICATION OF FRAMEWORK TO COGNITIVE NEUROREHABILITATION

- For reviews and elaboration of concepts, see
  - Cicerone et al., 2006
  - Levine, Turner & Stuss, 2008
  - Stuss, 2008
  - Stuss, 2011

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## 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)

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## The Stuss Frontal Lobe Model Is Useful For Rehabilitation Purposes

- The 3 clients showed dissociable patterns broadly seen on all measures
- The Activation and Executive Cognition domains showed clear relative relationships in all cases
- Structured behavioural observations were easy, highly useful, and directed rehab planning

## OUTLINE

- Examples of the “Mystery” of the Frontal lobes
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## LESSONS

- I AM STILL LEARNING!
- AND I HAVE LEARNED MOST WHEN I HAVE OPENED  
MYSELF UP TO PATIENTS AND WHAT THEY “TELL”  
ME

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