



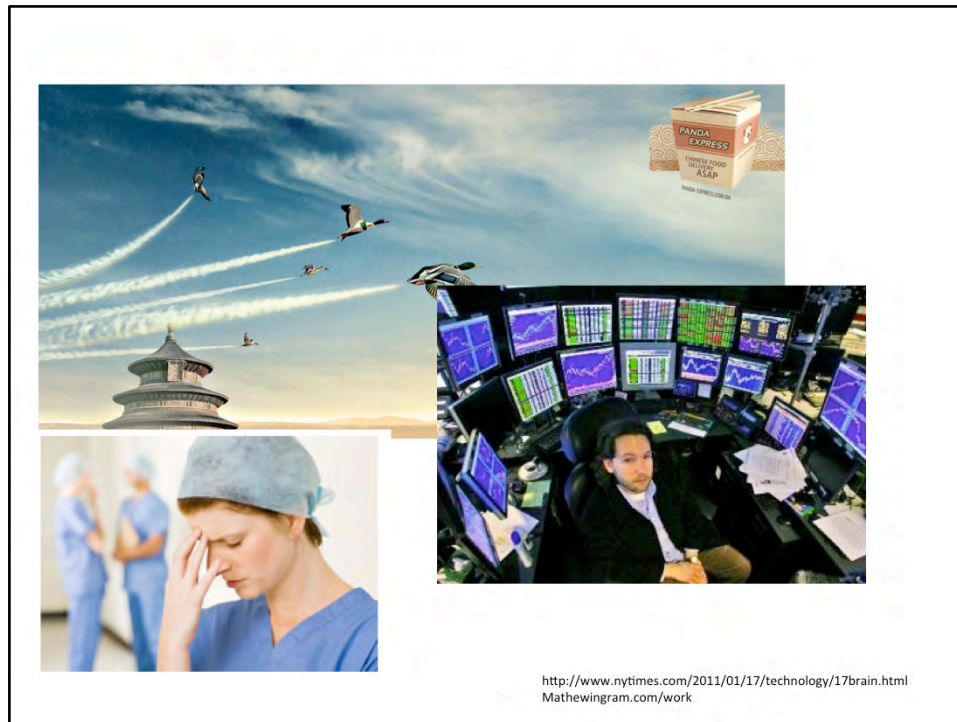
Functional Imaging of Sleep Loss

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<http://apod.nasa.gov/apod/ap001127.html>

Earth at night seen from space has changed dramatically compared to a century and a half ago. At the beginning of this decade, it was observed that about a third of adults in the US are not getting the recommended sleep duration. In East Asia where the work ethic is like that of the man running on an exercise wheel, sleep durations are typically between 1 to 2 hours less.



While there is growing expectation that services ranging from transportation to express goods delivery should be available 24/7, most of us aren't able to cope with extended and repeated sleep deprivation. In the short term this leads to errors, accidents and productivity loss. Developing a better understanding as to what cognitive domains are impaired and why motivates the functional imaging research I'm about to present.

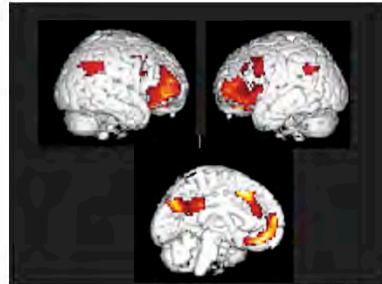
Outline

- Some relevant imaging features of sleep
- Task-related fMRI and behavioral alterations associated with sleep deprivation
 - Attention and information processing capacity
 - Negative emotional stimuli, economic decisions
 - Food stimuli
- Resting state connectivity in sleep deprived persons
- Summary and future directions

I will begin by reminding listeners about functional imaging changes observed during NREM sleep before reviewing studies involving task-related fMRI in sleep deprived persons. A quick tour of the findings concerning resting state connectivity follows and I'll conclude by speculating about future directions.

NREM Sleep results in decreased blood flow

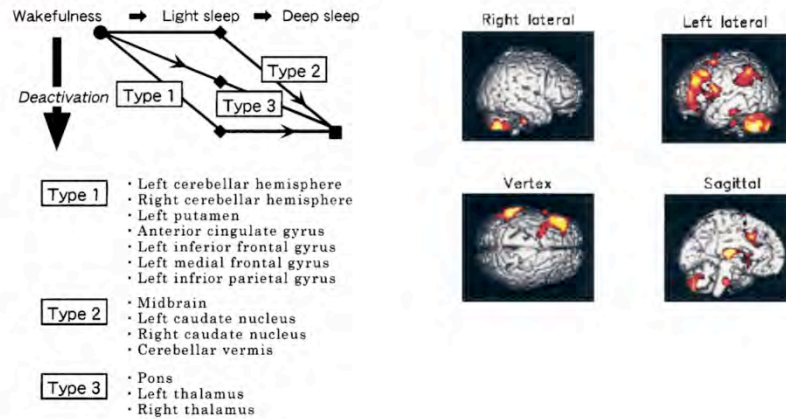
- Brainstem
- Thalamus
- Basal forebrain
- Insula
- Anterior cingulate
- Fronto-parietal association cortices



Maquet 1996,1997

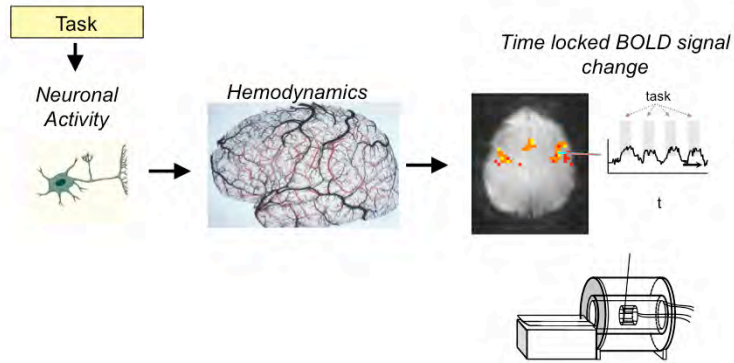
The blood flow changes accompanying the onset of NREM sleep were documented almost two decades ago through the efforts of Braun, Maquet, Kajimura and others. Multiple structures involved in maintaining arousal, sustaining attention and multimodal integration of sensory information show decreased blood flow in NREM sleep

Changes are progressive across state



Kajimura N et al.; J Neurosci 1999

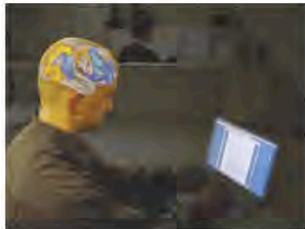
These changes reflect our withdrawal from externally oriented perception as NREM sleep deepens and are attenuated in persons with primary insomnia. We would expect that the sleep deprived brain would recapitulate some of these changes – will it? Lets see....



Task-related fMRI and behavior in sleep deprived persons

Attention:
William James c. 1890

“Focalization, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others...”



Selection

Vigilance

Processing capacity

Distractor suppression

Our exploration of the functional and allied behavioral changes associated with the sleep deprived brain begins by considering what happens with attention and perception. These processes are fundamental to other higher cognitive functions and it is no surprise that deficits in attention feature highly in a metanalysis evaluating the cognitive domains affected by sleep deprivation. It is our limited capacity to process information that requires us to be selective about what we direct attention to. Distractor inhibition and being able to sustain attention are also important aspects of attention. Consider this: How are we to remember what we did not even perceive? How would we adjust our responses to absent information?

Effects of SD on attention and perceptual processing

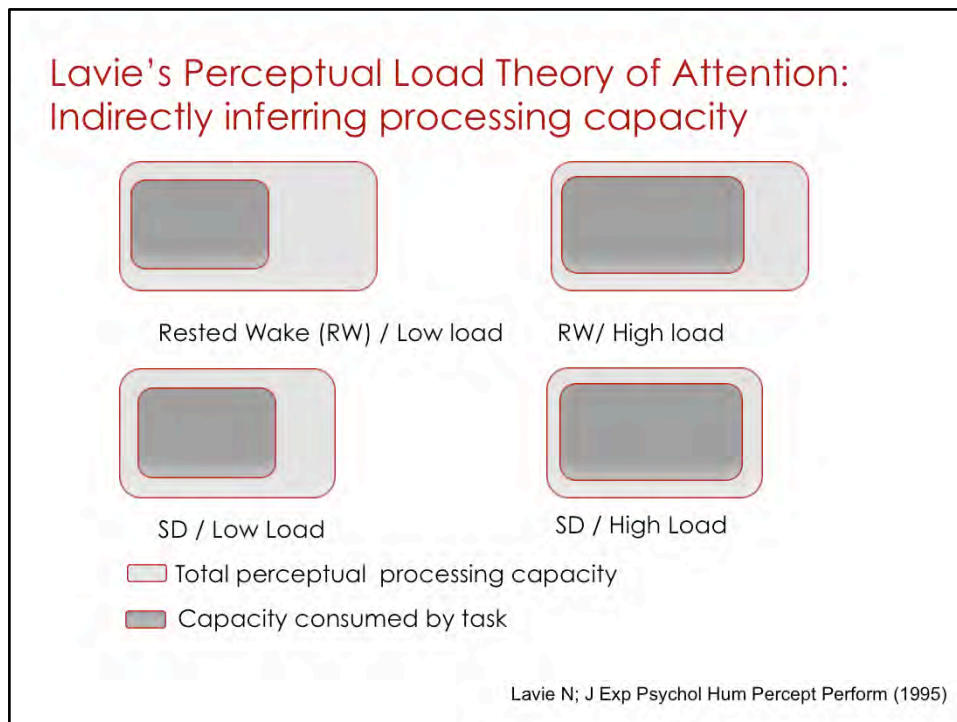
- Altered divided attention (Drummond 2001, Jackson 2011)
- ↓ selective attention (Tomasi 2008, Chee 2010 a, b; Lim 2010)
- ↓ distractor suppression (Kong 2012)
- ↓ preparatory activity before stimulus appearance is affected (Chee 2012)
- ↓ capacity to respond to rapidly presented serial images (Kong 2014)
- ↓ peripheral processing capacity (Kong 2011)
- ↓ Visual short term memory capacity (Chee 2007, Chuah 2008)
- ↑ Time-on-task effects (Asplund 2014)
- Metanalysis of attention effects (Ma 2015)

Over the last decade we and others have probed the many different facets of attention and how they contribute to reduced information processing capacity, particularly when time is limited.

I've selected a few aspects of attention and processing capacity to illustrate.



Understanding the perceptual limits of attention is relevant to a situation when one is focused on one an important central task such as monitoring the car in front of us while driving. Our ability to brake in response to an unexpected pedestrian crossing the road is dependent on having sufficient residual processing capacity to detect that person appearing at the periphery of our vision.

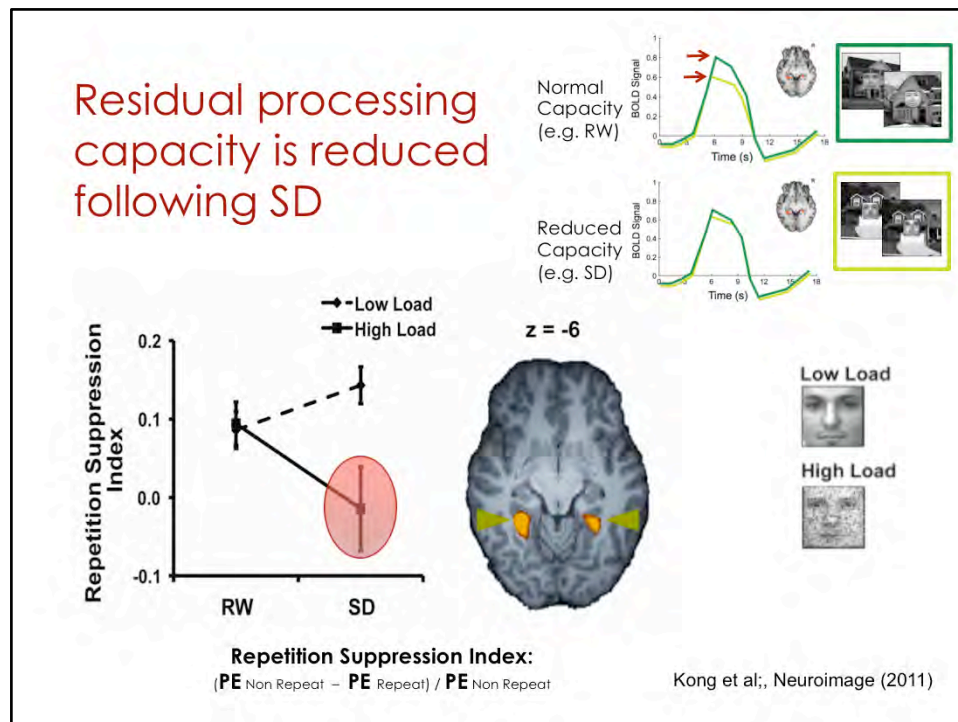


To model such a situation, let's begin by assuming that a well rested person has a finite reservoir of visual processing resources represented by this box**. According to Lavie, focusing attention on a central target will consume some of that resource. **If the target places low demands on perceptual resources, there will be residual capacity for handling task irrelevant stimuli- even if the person is not aware of this automatic busy-body brain.

**In contrast, a perceptually demanding target will take up more processing resources, leaving less for peripheral processing.

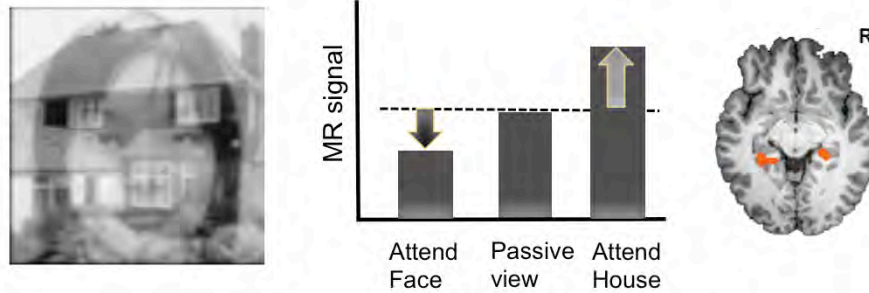
**If sleep deprivation reduces perceptual processing capacity, we can expose this by showing that the residual capacity to process task-irrelevant information is compromised, at least in the high load condition

The critical point about this framework is **that total processing capacity is indirectly inferred from the effects of manipulating central task load**



Danyang Kong, now a post doc at Stanford, helped design an experiment to show limitations in peripheral processing capacity using this paradigm. She inferred reduced processing capacity from attenuated repetition suppression to repeated compared to non-repeated incidental houses in a brain area specialized for place processing. The presence of a signal difference was used as the marker for left-over processing capacity, but the participant didn't know this. What they focused on was clearer or less clear faces that they had to detect. In the sleep deprived state, when perceptual load was higher, she found lower peripheral information processing as indexed by reduced RS.

Object selective attention: probing target enhancement & distractor suppression



Kong et al; Neuroimage 2012

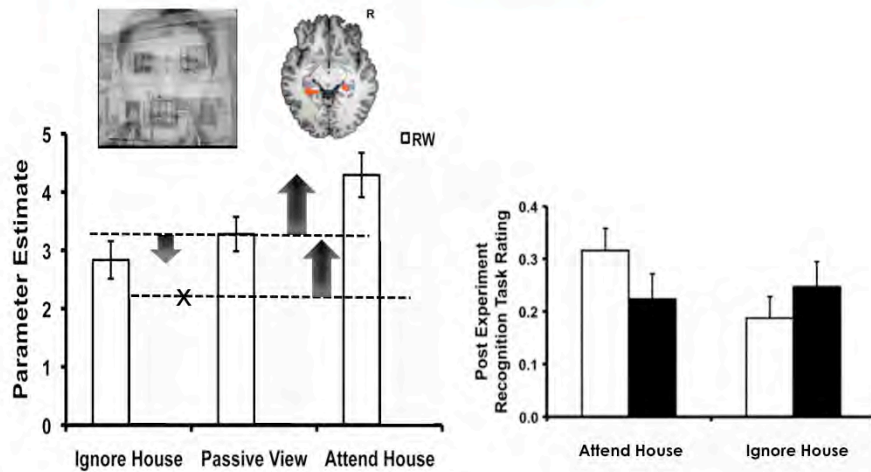
Visual clutter can delay detection and action. Remember how difficult it is to find grandma in a crowd compared to when she's the only person in an open space? In such settings, distractor suppression complements attention related enhancement to improve target detection and processing.

Here, ambiguous face house pictures elicit three different responses in the **place area** depending on how well the participant is able to follow instructions to either detect a face, a house or to passively view the ambiguous pictures

Accurate performance of this task requires attending to the object of interest and enhancing its sensory representation while concurrently suppressing the representation of the distractor object.

Distractor suppression is a known contributor to lower cognitive performance in cognitive aging, something that the sleep deprived brain is sometimes compared to.

SD: preserved target-related enhancement,
impaired distractor suppression



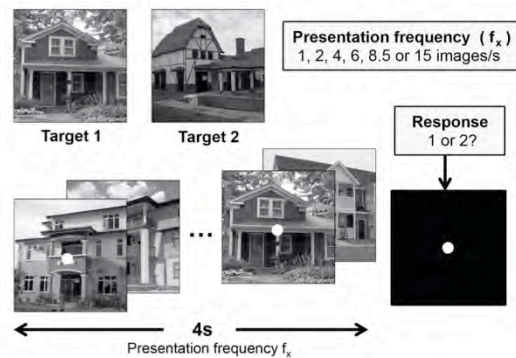
Kong et al; Neuroimage 2012

After a normal night of sleep, attention to houses enhanced sensory activation in the PPA compared to passive viewing . Conversely reduced PPA activation was observed when houses had to be ignored while picking face targets.

Critically, whereas sensory enhancement for attended houses was relatively preserved during SD, sensory suppression of irrelevant houses was impaired.

These imaging signals have behavioral counterparts when we tested recognition of house pictures at the end of each experiment. In the well rested state, there is a clear advantage to having attended to the houses. However, in the sleep deprived state, participants appear to remember houses to the same degree in both contexts, suggesting that are less selective about encoding.

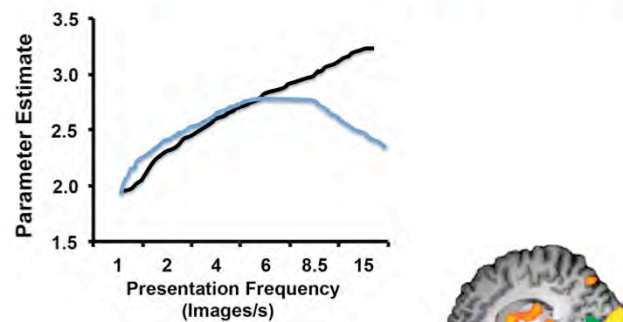
Evaluating speed of object processing – Rapid Serial Visual Processing (RSVP)



Kong et al., NeuroImage (2014)

How quickly can we churn through visually presented information? Rapid Serial Visual Presentation is an intuitive way of testing this. Participants had to identify 2 target houses in a stream of house pictures that were presented at different rates.

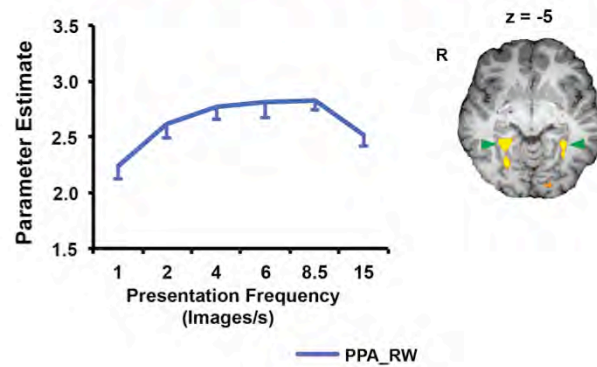
Contrasting activation profiles in early visual areas and PPA: where is the speed bottleneck?



Kong et al., NeuroImage (2014)

Brain activation within the PPA increases with presentation rate, to a point and then it falls. This reflects progressive engagement, followed by disengagement of house detection and higher visual processing. This u shaped function marks the area as a bottleneck for visual processing speed. The rate of picture presentation that is associated with the highest activation in the PPA is a proxy for processing speed

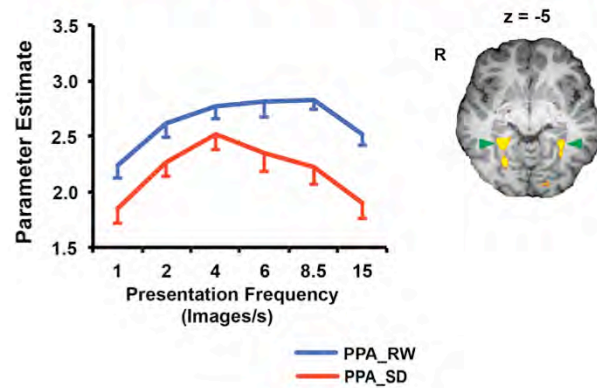
Activation in PPA peaks at ~ 7 images/s in rested wake state



Kong et al., NeuroImage (2014)

Brain activation within the PPA increases with presentation rate, to a point and then it falls. This reflects progressive engagement, followed by disengagement of house detection and higher visual processing. This u shaped function marks the area as a bottleneck for visual processing speed. The rate of picture presentation that is associated with the highest activation in the PPA is a proxy for processing speed

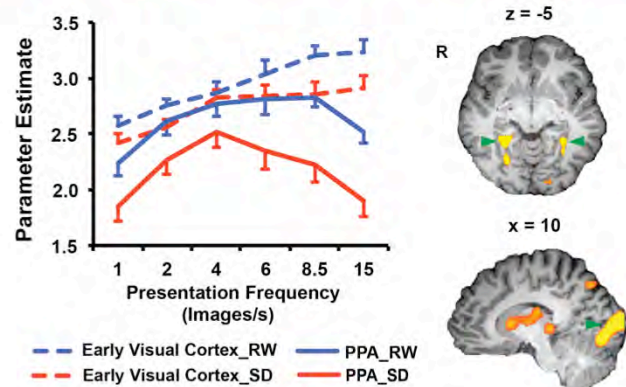
Activation peaks at ~4 images/s in SD:
Slower processing speed



Kong et al., NeuroImage (2014)

The leftward shift in the temporal tuning curve tells us that in the bottleneck of visual processing, the maximal rate of image processing is reduced

Dissociation between higher and early visual cortex responses to presentation rate



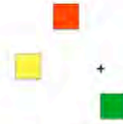
Kong et al., NeuroImage (2014)

Critically this shift in the tuning curve cannot be simply attributed to loss of engagement that might be expected when images flash by too quickly to register. One indicator of this is the continued increase in activation within early visual cortex activation with higher rates of house presentation.

Testing visual short term memory ...

■ Visual Short Term Memory

- 1 to 8 coloured squares are presented
- Respond to whether the probe square was presented earlier



■ Visual Item Load Control

- 1 to 8 coloured squares are presented
- Respond to whether or not there is a coloured square in the centre of the array

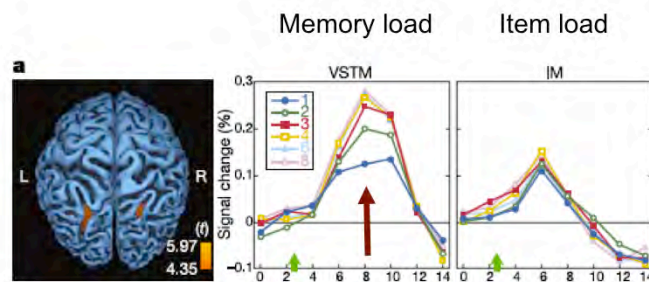
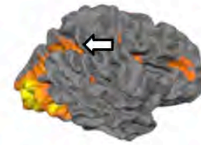


Todd & Marois: Nature (2004) Chee & Chuah: PNAS(2007); Chuah & Chee; J Neurosci (2008)

If we are not given time to reorganize our memories, most of us can only remember 3-4 simultaneously presented visual items at a time. This 'visual short term memory' capacity that is fundamental to day-to-day activities and is highly correlated with scholastic achievement. **To evaluate VSTM, an array containing between 1 to 8 colored squares is briefly shown. After an interval, subjects have to determine if the color of the probed square was present in the previous array. This task is expected to load VSTM memory more as the number of colored squares increases.

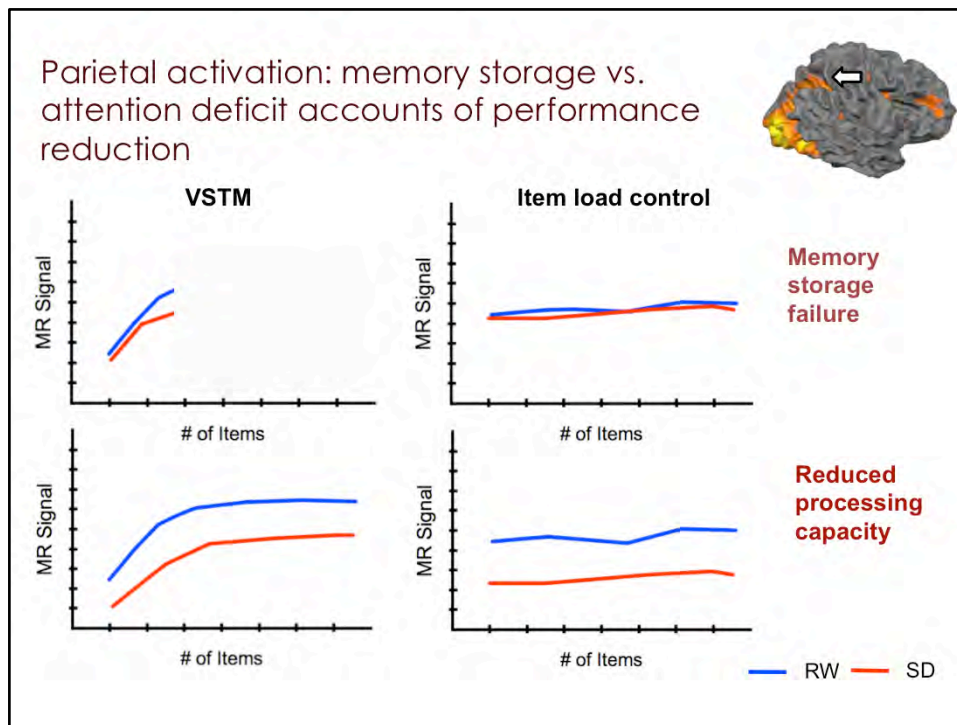
**To control for the effect of item load on visual cortex activation, between 1 to 8 colored squares are presented but instead of having to remember these, the volunteer has only to respond to whether or not a colored square was present in the centre of the array

The parietal area tracks VSTM capacity



Todd & Marois: Nature (2004)

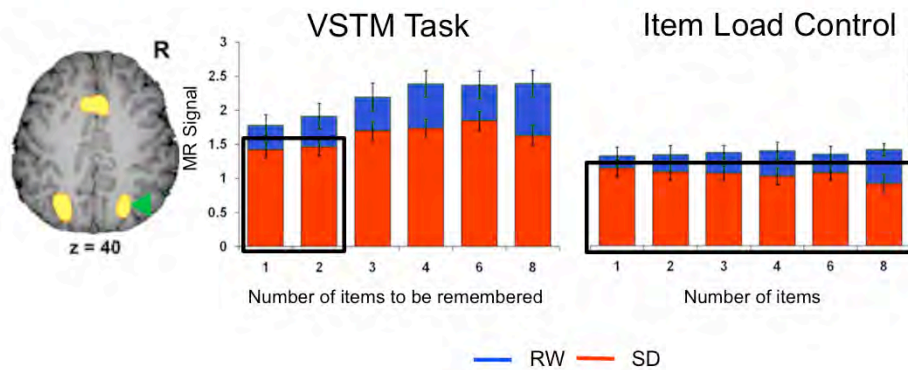
Previous research has shown that VSTM is limited to about 4 items and that activation in the superior parietal region tracks visual short term memory capacity. Activity in this putative storage region increases and then plateaus. In contrast to its response to memory load, the parietal area is indifferent to item load



If SD were to impair VSTM by inducing memory storage failure, ** the retention of only one or two test items (show) was expected to elicit signals (show) of similar magnitude in RW and SD. **However, an effect of state would be expected when more items had to be remembered.** Also we would not expect SD to affect activation in the item load control condition since memory is not taxed

Alternatively, if the problem is that when we are sleep deprived, fewer neurons or circuits are available to be recruited: we would anticipate lower activation in cognitive control areas **even when only 1 or 2 test items are presented in both the memory and item load control conditions

Sleep deprivation reduces parietal activation even when memory capacity is not taxed



Chee & Chuah: PNAS (2007); Chuah & Chee: J Neurosci (2008)

Our results supported the second line of reasoning -> that there are fewer circuits available to process information in the sleep deprived state. In both states the general form of the neural response to memory load was as expected. Activation increased as **items to be remembered** increased, and then plateaued.

The critical point is that in the memory condition under the sleep deprived condition activation is lower even only one or two items had to be remembered. **

Activation was also affected during SD in the load condition which does not tax memory.

Metanalysis of 11 studies of attention in sleep deprived persons

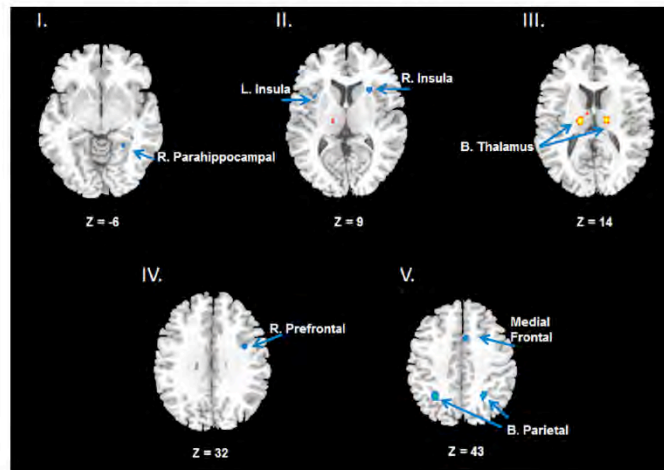
Publication	Journal	Number of Participants	Waking Hours	Type of Attention Task *
1 Chee et al., 2008 ¹⁰	J Neuroscience	17	24	Selective
2 Chee et al., 2010 ¹¹	Neuroimage	26	24	Selective
3 Chee and Tan, 2010 ¹²	Neuroimage	20	24	Selective
4 Czeisler et al., 2012 ²¹	Front Neurology	14	36	Selective
5 Drummond et al., 2001 ⁴⁹	J Sleep Research	13	35	Divided
6 Jackson et al., 2011 ⁵⁰	Brain Imaging Behav	12	27	Divided
7 Kong et al., 2011 ¹³	Neuroimage	18	24	Selective
8 Kong et al., 2012 ¹⁴	Neuroimage	22	24	Selective
9 Lim et al., 2010 ¹⁵	PlosOne	23	24	Selective
10 Mander et al., 2008 ⁵²	Brain Research	6 **	34–36	Orienting
11 Tomasi et al., 2009 ⁵³	Cerebral Cortex	14	24	Orienting

* There were no qualified studies involving only sustained attention performance. ** In Mander et al., 2008 study, there were total 7 participants, but only 6 involved in fMRI experiment.

Ma N et al.; Sleep (2015)

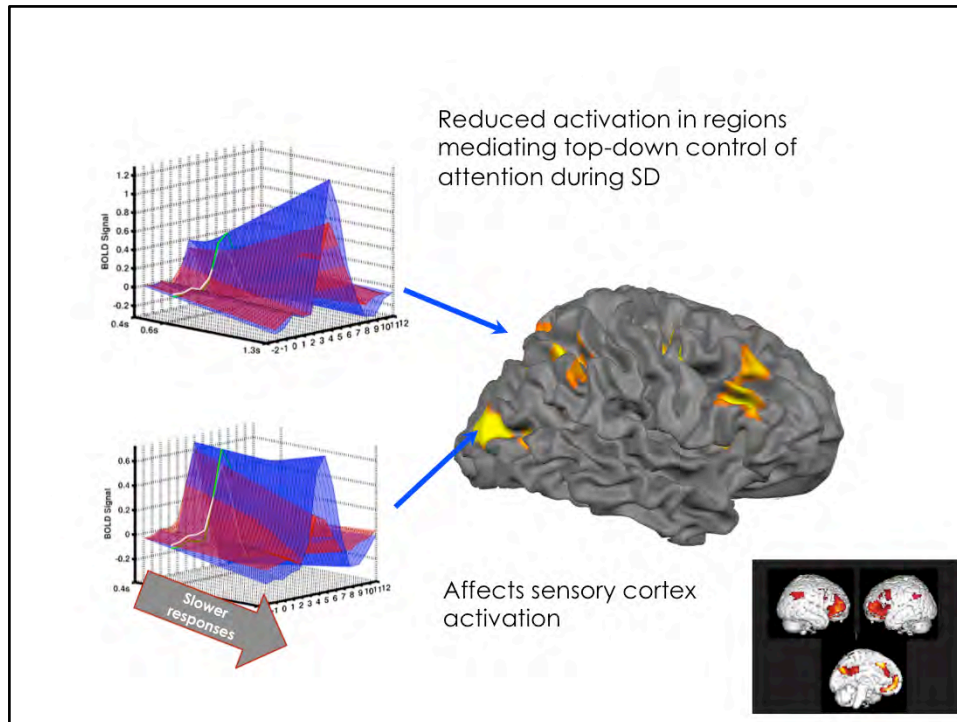
How reproducible is this finding? A recent metanalysis of 11 fMRI studies on attention in sleep deprivation, indicated that reduced fronto-parietal activation and increased thalamic activation during successful task performance are common changes across multiple studies

Metanalysis of 11 studies of attention in sleep deprived persons

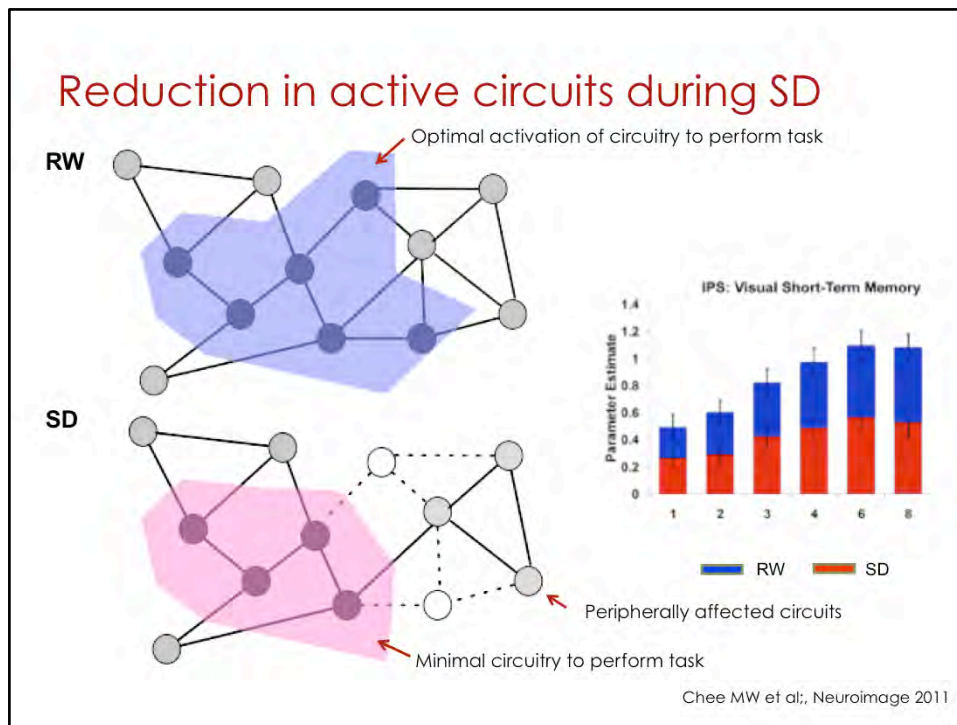


Ma N et al; Sleep (2015)

In addition, higher visual areas are affected by the loss of top-down control of attention associated with decreased fronto-parietal activation



Here is another illustration of sleep deprivation induced reductions in activation within regions mediating the top down control of attention as well as downstream effects on extrastriate visual cortex sensitive to the their modulatory influences. These fronto-parietal changes are close or similar in location to those showing reduced blood flow during sleep, leading us to posit that the fMRI changes observed in the sleep deprived state may reflect the occurrence of local sleep during task performance.

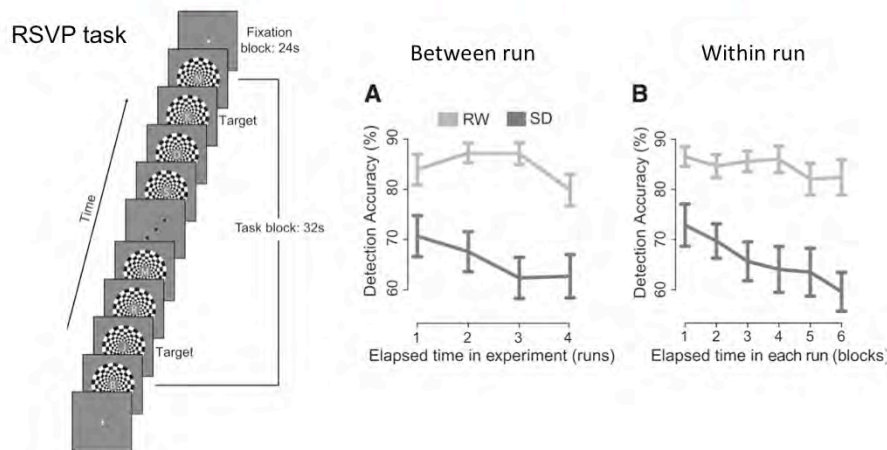


In this cartoon depicting a functional module in the brain, each node represents a cluster of neurons and each edge a connection.

In an alert person, optimal activation of circuitry to perform a task entails extra activation that reflects the gathering of 'additional but redundant information'. This information may be useful although not directly related to immediate task goals. ** For example, in the experiments evaluating VSTM capacity, correct responses elicited greater activation in the RW condition even though lesser activation seemed during SD

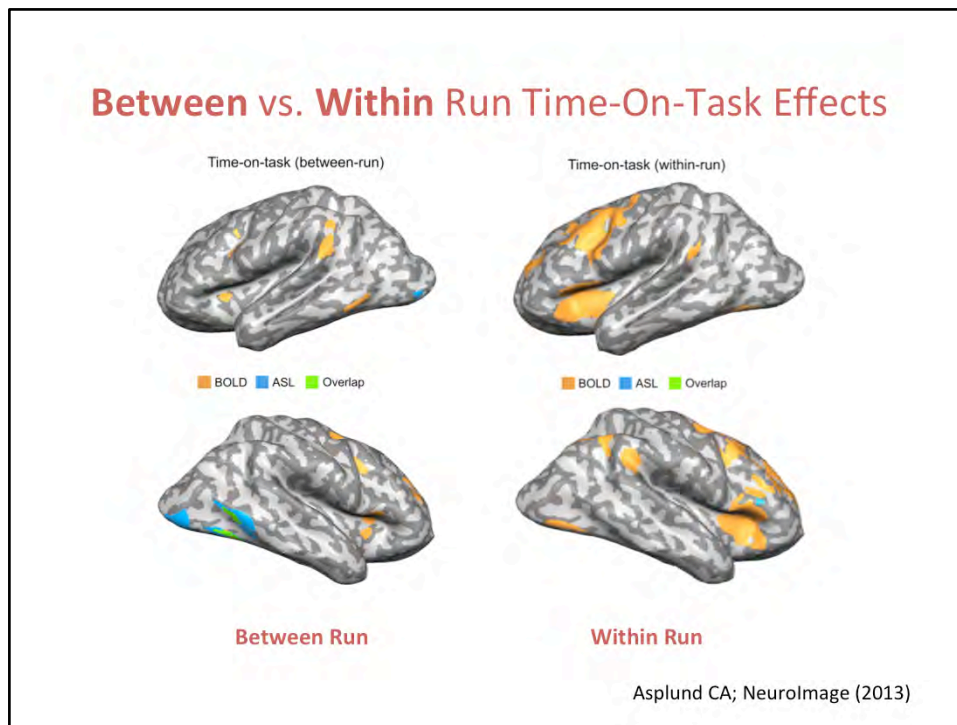
**In the sleep deprived subject neurons represented by open circles involuntarily go offline. This leaves activated a minimum circuitry necessary to perform the task. One can get by, but there is no 'safety margin' leading to overall slower and less accurate responses.

Performance accuracy shows time-on-task effects that are greater in SD



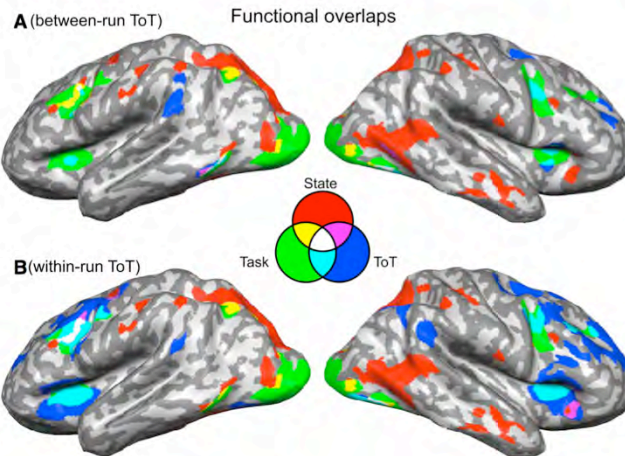
Asplund CA; Neurolmage (2013)

If local sleep occurs as a result of sustained engagement of circuits taxed by continued task performance, one might expect accentuated time on task effects in the sleep deprived state. To evaluate this possibility, Chris Asplund had participants pick out specific letters appearing in a rapid stream of them. They performed this for 6.5 minutes in each of 4 experimental runs. We found evidence for both within and between run ToT effects that were accentuated by SD. Observe how performance accuracy declines over time within each run, there being a slight reset after the 1 min pause between runs.



Interestingly, corresponding to behavioral findings, within run time on task effects were more spatially extensive than between run effects. This was clearer using BOLD rather than ASL imaging

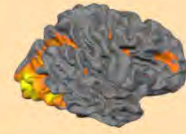
Overlap between task, state and ToT effects



Asplund CA; NeuroImage (2013)

Here, we observe impressive but incomplete overlap between the areas engaged in Task performance, those affected by state and ToT effects. This indicates that the some subareas involved in task performance are more susceptible to use dependent effects.

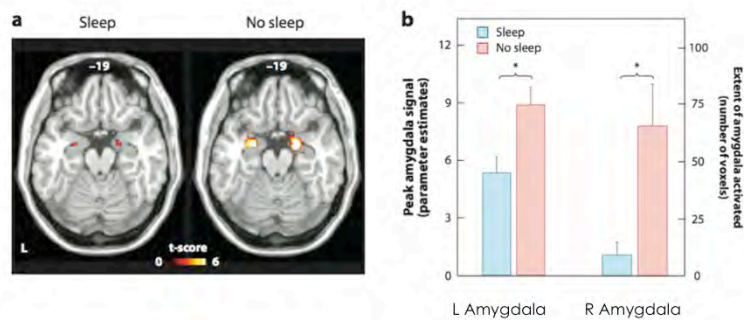
Total Sleep Deprivation:



- Reduces task-related activation of fronto-parietal areas mediating cognitive control
- Concurrently reduced top-down biasing of extrastriate (less / no effect on primary) visual cortex activation
- Behavioral consequences:
 - Reduced selectivity
 - Decreased inhibition of distractors
 - Reduced capacity to process visual information
 - Rate of visual object processing
 - Peripheral processing of irrelevant stimuli
 - Accentuated time on task effects

Before we move on, here is a brief section summary:

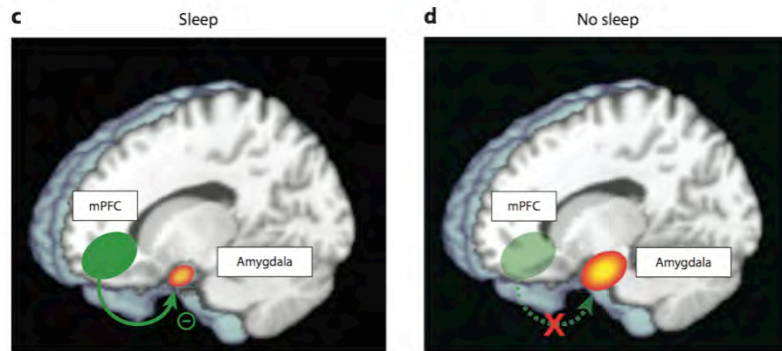
Increased amygdala activation to negative pictures after a night of TSD



Yoo SS et al.; Nat Neurosci (2007)

Being able to generate, modulate and be guided by emotions is fundamental to human life and sleep plays a vital role in this regard. Restricting sleep to five hours a night across a one-week period leads to a progressive increase in emotional disturbance in participants on the basis of questionnaire mood scales, together with diary documentation of increasing subjective emotional difficulties (Dinges et al. 1997). In an experiment conducted by Seong-Schik Yoo and Matt Walker some years ago, Half the volunteers were allowed to sleep normally and the other half sleep deprived. volunteers were then shown negative emotional pictures. Participants who underwent sleep deprivation had significantly greater amygdala activation to negative pictures

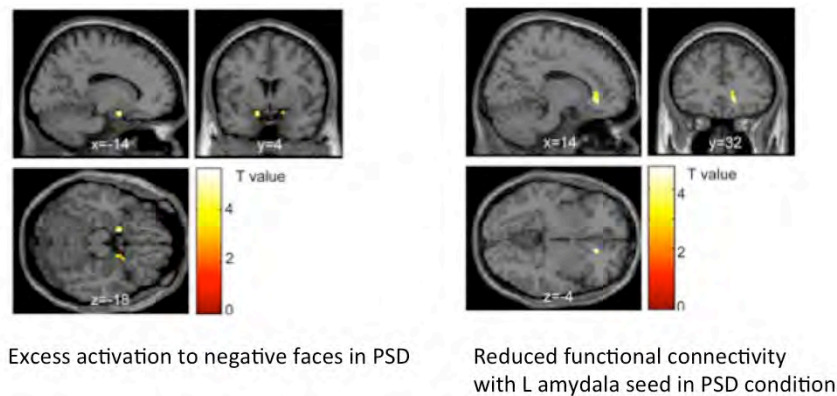
Reduced functional connectivity between amygdala and mPFC



Yoo SS et al.; Nat Neurosci (2007)

Accompanying changes in amygdala activation, was a reduction in functional connectivity between the medial orbitofrontal cortex and amygdala. This is thought to relate to a reduction in emotional regulation when participants are sleep deprived.

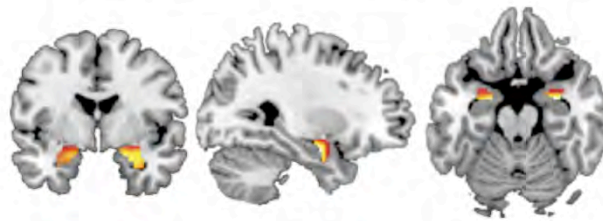
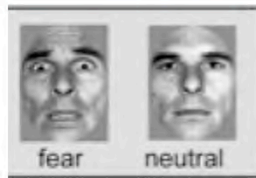
Similar patterns of amygdala activation and connectivity change after 5 nights of PSD



Motomura et al. PLoS One (2013)

A similar profile of exaggerated amygdala reactivity and reduced prefrontal connectivity occurred after five nights of 4-h sleep restriction, which is arguably a more ecologically relevant paradigm in the context of societal sleep behavior and clinical disorders. Additionally, inter-individual differences in the change in connectivity between the amygdala and mPFC caused by sleep loss correlated with increases in subjective anxiety.

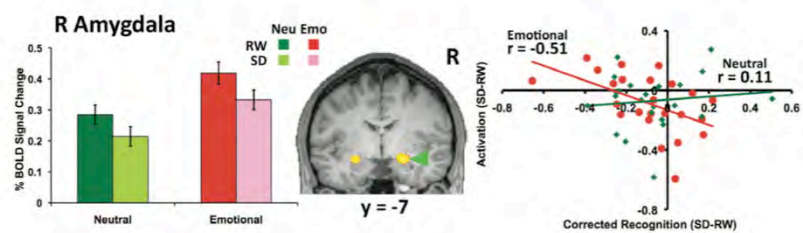
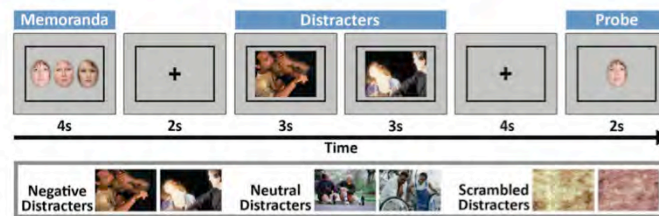
Subjective poor sleep quality also affect amygdala activation and connectivity



Prather AA, Psychosom Med (2013)

In the last of a trio of remarkably congruent experimental findings, poor sleep quality was also found to affect the affective system as shown in this experiment conducted by Prather and colleagues

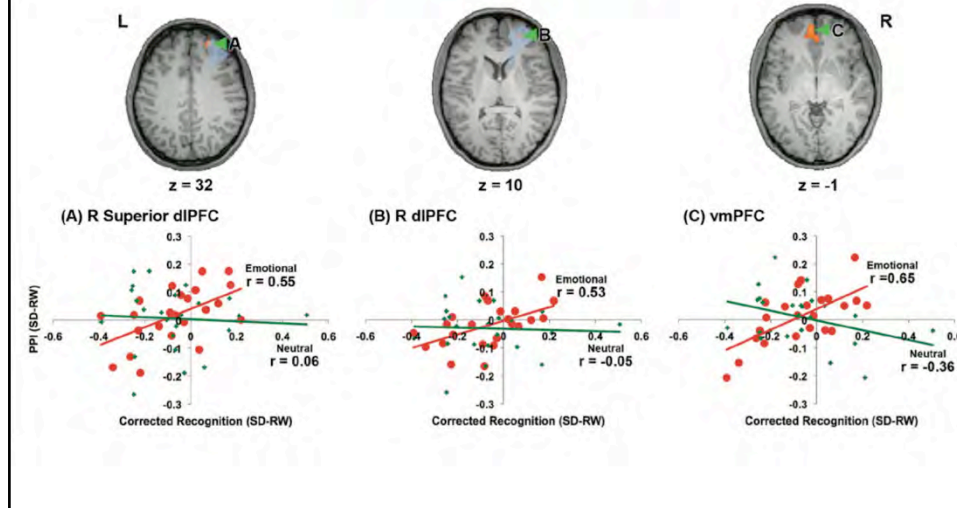
Amygdala activation to emotional distracters in SD affects working memory



Chuah L Sleep (2010)

One of the consequences of viewing emotionally salient that they capture our attention and distract us from fulfilling current task goals. This effect might be modulated by sleep deprivation. For example, Lisa Chuah had participants remember three neutral faces over an interval that was punctuated with three types of distracters. found Increased amygdala **activation** in response to negative emotional distracters, but not emotionally neutral distracters, affected corrected recognition in a working memory experiment in sleep deprived persons

Functional connectivity between amygdala and frontal regions correlates with less interference of memoranda by negative pictures



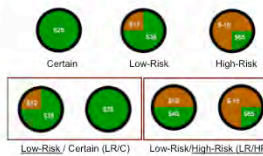
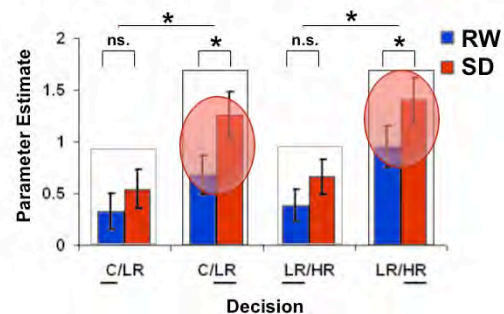
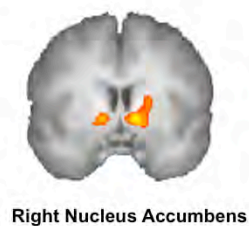
Additionally and parallel to the previous experiments, we found that emotional stimuli had a greater effect on impairing retrieval of neutral memoranda in accordance to how much amygdala frontal connectivity was disrupted. Curiously this was true of the sleep deprived state only and for emotional but not neutral distractors.

Riskier economic decisions activate the nucleus accumbens; and more in SD

- Significant main effect of risk (see also McKenna; 2007)

- C certain/LR (low risk) > C/LR
- LR/HR (High Risk) > LR/HR

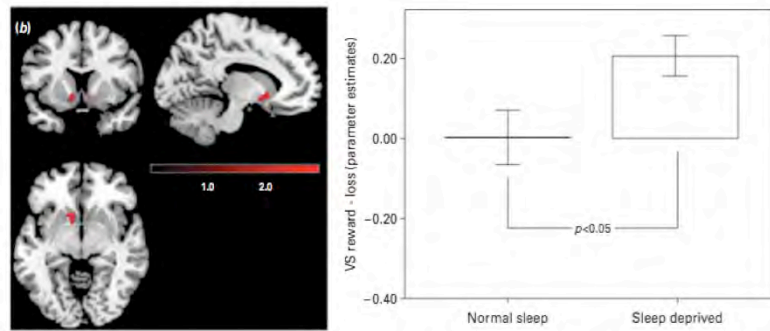
- Riskier decisions in SD elevated NA activation



Venkatraman; Sleep (2007)

Moving to another aspect of behavior that may have affective roots, we found in two experiments that SD affects the neural substrates of economic decision-making by tipping us to suboptimal economic choices. In the first experiment, Vinod Venkatraman now faculty at Temple University, had participants choose between certain and low risk and also between low risk and high risk gambles. The nu acc, part of the ventral striatum becomes more active when riskier choices are made. Critically, he found a sleep deprivation by risk interaction whereby higher risk decisions elicited relatively greater NA activation in the SD state than in the rested state. There wasn't an actual change in proportion of riskier decisions made when sleep deprived so we posited that this could mean the foreshadowing of such a behavioral shift.

Greater ventral striatal responses to win-loss trials in SD

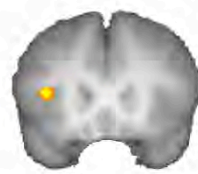


Mullin BC; Psychosom Med (2013)

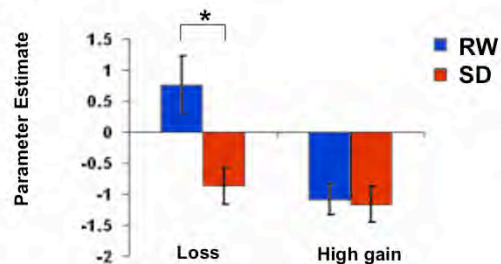
Some years later, Brian Mullin from Peter Franzen's lab had participants engage in a card-guessing game where they received positive or negative feedback on each trial. When the activation to win relative to loss trials was contrasted across state, SD participants were found to have higher VS activation, supporting the idea that acute sleep loss may result in increased sensitivity to rewarding stimuli.

SD attenuates activation in insula following losses

- Suggests reduced emotional response towards losses following sleep deprivation
- Insula related to loss averse behavior (Paulus et al., 2003; Kuhn and Knutson, 2005; Venkatraman et al., 2009)



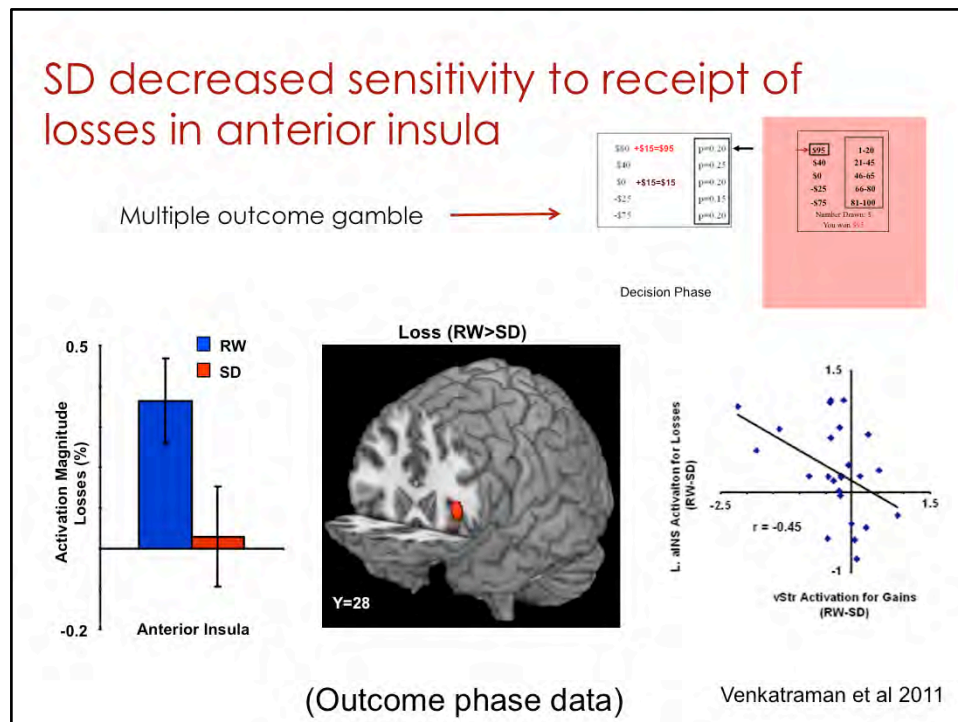
Left Anterior Insula



Venkatraman; Sleep (2007)

The anterior insula is thought to evaluate the emotional significance of a stimulus and to generate an appropriate affective response to losses.

******After a normal night of sleep, the insula showed increase activation to loss outcomes but not to high gains. After sleep deprivation this insula response to losses was attenuated.



Its always nice to see findings independently replicated and here, we see Vinod replicating earlier findings regarding the insula using a multiple outcome gambles. Interestingly, in that study he found a correlation between increased ventral striatal activation for gains and decreased anterior insula activation for losses suggesting that that these brain regions may act in concert to shift the sleep deprived person towards gain-seeking behavior while exhibiting a reduced concern for losses.

Selection of negative studies related to decision making in SD

- No change in **relative valuation of rewards** (Libedinsky 2011)
- No increase in **impulsivity** (Libedinsky 2013)
- **Intact detection of temporal distribution** of rewards (Massar submitted)
- Mixed results with Iowa Gambling Task (Killgore 2006, 2007, 2012)
- No effect on risk (Menz 2012)

Unlike the fairly clear results we have for attention and 'hot' emotions – the changes observed with economic decision making in sleep deprived persons are less clear cut and appear to be context dependent. Here are a selection of somewhat unexpected findings, given the data I just presented. For instance, one might expect the trigger happy nocturnal gambler to be more impulsive or to shift his valuation of goods. Neither happens consistently across an entire sample of participants. Food for thought.... Bringing us to the next topic – food!

Affective processing and economic decision-making summary:

- Increased amygdala activation to negative stimuli
- Amygdala-frontal connectivity alterations differ across persons; correlate with behavioral shifts
- Neural signatures for increased propensity to take higher risk and desensitization to loss under some test paradigms
- No obvious changes in impulsivity, evaluation of temporal distribution information or valuation
- State shifts not as clear-cut as with attention

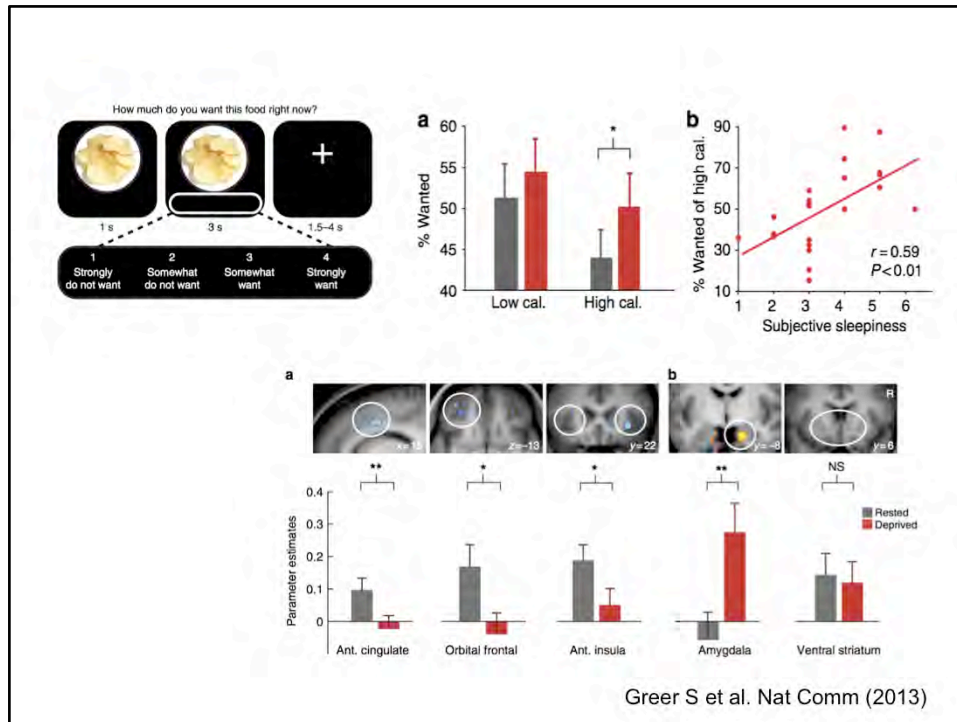
The take home messages from this work are that

Effects on appetite:



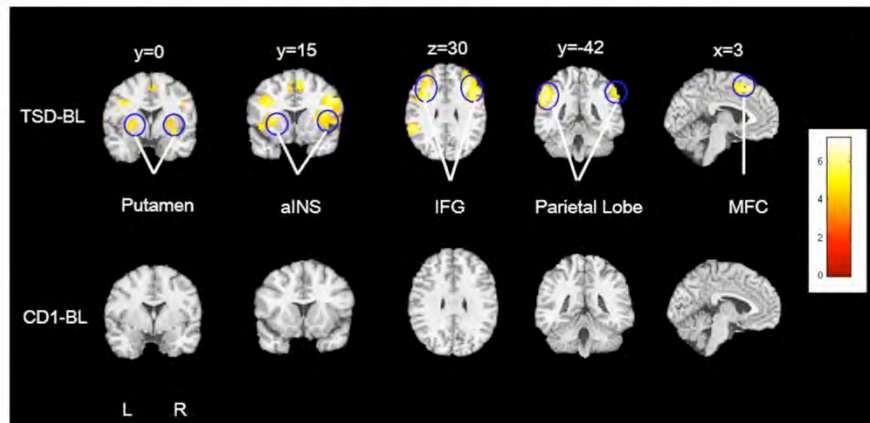
Author	TSD/PSD	Duration	N	Stimulus	Variables of interest	Imaging
Greer (2013)	TSD	1N	23	Desirability of food pictures	Sleepiness predicted desire for higher calorie foods	↓ Ant. Insula, ant cingulate, orbitofrontal, ↑ amygdala*
St. Onge(2012)	PSD	6N/ 4h/ night	30	Blocked food vs. non-food pictures	No behavioral measure	↑ Ant insula, thalamus, putamen, IFG,OFC (food>non-food) +PSD-Ctrl
Benedict (2012)	TSD	1N	12	High vs. Low Cal food pictures	↑ Self reported hunger ratings after TSD	↑ mid ACC
Fang (2015)	TSD	1N	46	Resting state - Salience network - dACC (ROI seed)	Macronutrient content in food a day after SD; ↑ fat but not carb intake	↑↑ fC in Salience network (dACC-putamen, ant insula); corrl with incr fat calorie intake

- The effects of SD on appetite / food valuation and consumptive behavior have significant impact on health. However, to date there have ben relatively few studies in this important domain.



In one of the larger studies to date, Stephanie Greer 30 participants underwent one night of TSD. In the morning, they were shown food pictures and asked to rate how strongly they desired the food. A mixture low and high calorie foods were shown. TSD induced an increased amygdala response to food and attenuated responses in insula and ACC. Participants had an elevated preference for high calorie foods although authors did not report any correlation between the caloric content of foods and the change in brain signal

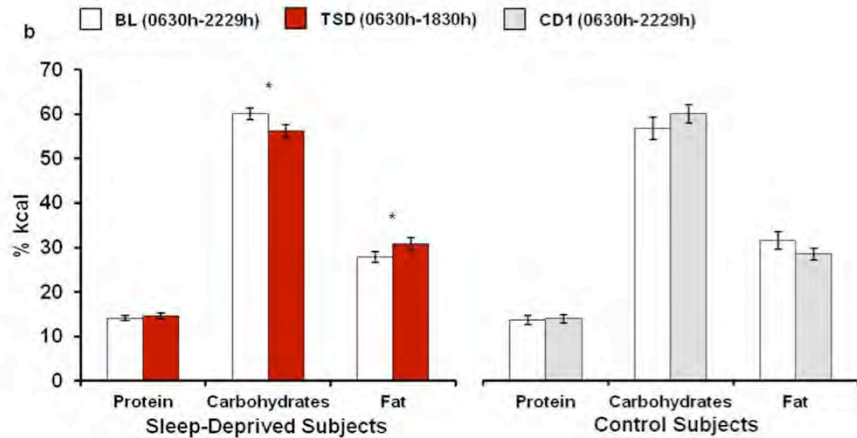
Increase in Salience Network Connectivity following SD



Fang Z et al. Scientific Reports (2015)

In Fang's study involving 31 young adults, resting state connectivity in the salience network was evaluated. This network comprises anterior insula, dACC, IFG and parietal lobes. Connectivity within these nodes was increased following TSD compared to the control night.

Increase in fat calorie intake day after TSD

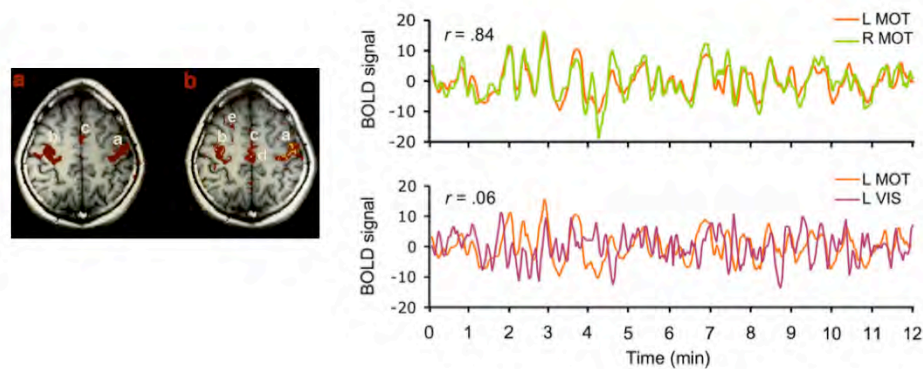


Fang Z et al. Scientific Reports (2015)

The extent to which connectivity was increased correlated with an increase in fat consumption the day after sleep deprivation. Protein and Carbohydrate consumption remain unchanged.

Resting state connectivity in SD

Intrinsic correlation of low frequency oscillations in BOLD signal



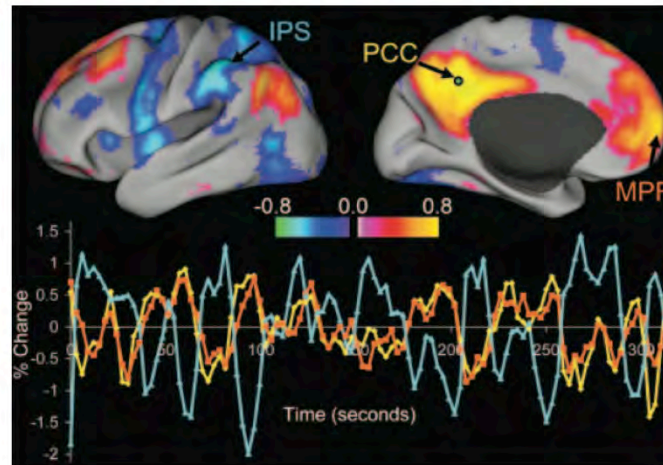
Biswal B et al; (1995), Dijk KRA (2010)

In the early 1990's it was discovered that there was spontaneous low frequency (~ 0.01 Hz) fluctuation of BOLD signal even in the absence of task performance. Non-contiguous voxels in both motor cortices showed in phase oscillations. It was later realized that voxels showing such covarying oscillations might be functionally connected.

'Resting state connectivity' has been a term used to describe this type of study. However, defining 'rest' can be tricky. It turns out that 'resting state' covarying brain oscillations can be affected by what the participant was doing prior to lying in the scanner, so the term 'task-free' fMRI connectivity has been suggested as a more neutral label for this type of study.

In a resting state experiment, a participant is told to lie still with eyes open, typically staring at a blank screen. No specific instructions are given as to what the participant should be thinking about and its likely that for most people, thought content will vary but remain autobiographical / self-referent.

Low frequency oscillations and anti-correlated functional networks



Fox et al; PNAS (2005)

A set of regions (shown here in red-yellow) that evidences prominent 'resting state connectivity' of this sort is the 'default mode network'. This network of regions participates in introspective thought while we are at rest and is 'by default' active and represent some of the most metabolically active parts of the brain at rest.

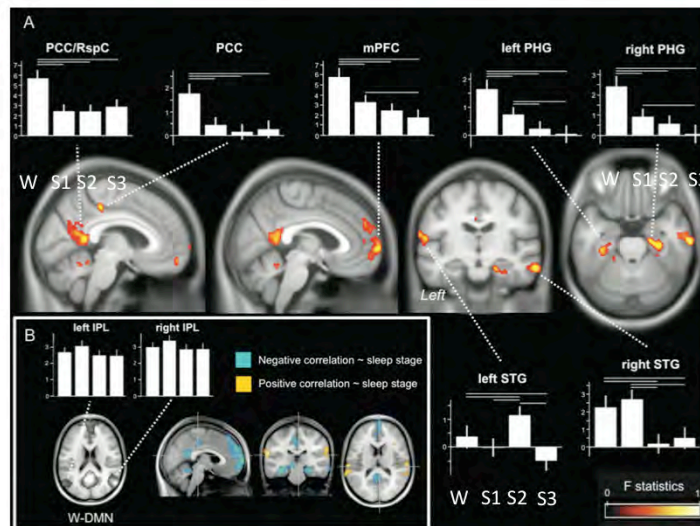
Areas involved in the maintenance of attention and cognitive control also show spontaneous, synchronous low frequency oscillation that is negatively correlated with the default mode region. Such anti-correlation breaks down in many neuropsychiatric conditions.

Resting state fMRI in SD:

Author	TSD/PSD	N	Duration / TR	Global Signal Regression	Seed	Main findings
Samaan (2010)	PSD/ 1N	14	6min TR 2s	Yes	Multiple DMN and ACN	↓ DMN correlation; ↓ anti-correlation % DMN and ACN
De Havas (2012)	TSD/ 1N	26	8min TR1.5s	Yes	Multiple DMN and ACN seeds	↓ DMN correlation; ↓ anti-correlation % DMN and CAN
Bosch (2013)	PSD/ 1N	12	8min TR 2.5s	Yes	PCC	↓ PCC and ACC; ↓ anti-correlation: PCC & DLPFC (reported as ↑ correlation)
Shao (2013)	TSD/1N	14	6.5 min TR 2s	Yes	Thalamus R/L	↓ thalamo-PHG, MTG, SFG
Yeo (2015)	TSD	68	24min RW/ 12min SD; TR 2s	Yes + No	ICA/ Template	↓ DMN correlation; ↓ anti-correlation % DMN and ACN; ↓ anticorrelation in RW predicts vulnerability to vigilance decline
Ong (2015)	TSD	24	12 min TR 2	Yes + No	ICA/ Template	Accentuated SD changes within DMN and DAN connectivity with eye-closure in SD

The attraction of resting state studies is that they can inform about many networks concurrently and provide brain health relevant information without having the participant having to perform a task or series of tasks.

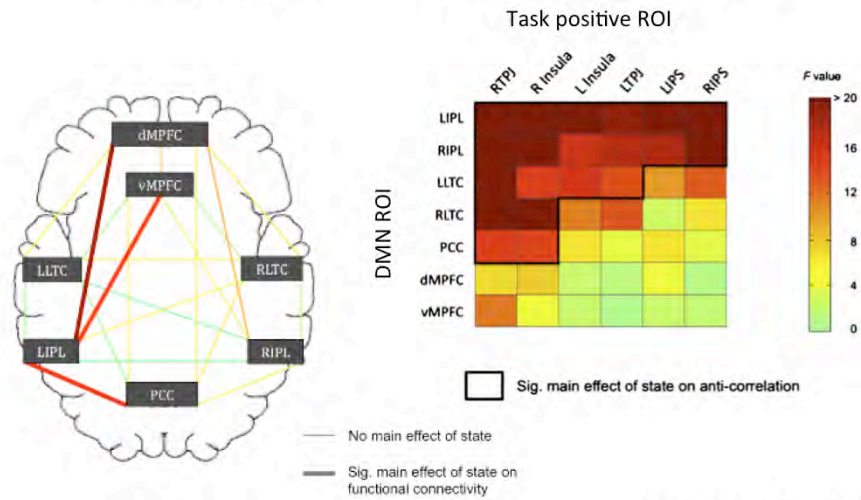
Change in DMN FC from wake to deep sleep



Sämann PG (2011); Horovitz SG (2009)

Corresponding to the seminal work by Fox and others, functional connectivity studies on sleep-deprived persons have, to date focused primarily on two resting state networks, the default mode network and the anti-correlated relationship between the task positive and default mode network. These networks are considered critical in differentiating externally oriented and internally oriented cognition respectively. Work from several laboratories found that in NREM sleep, there is progressive reduction in fC within the DMN.

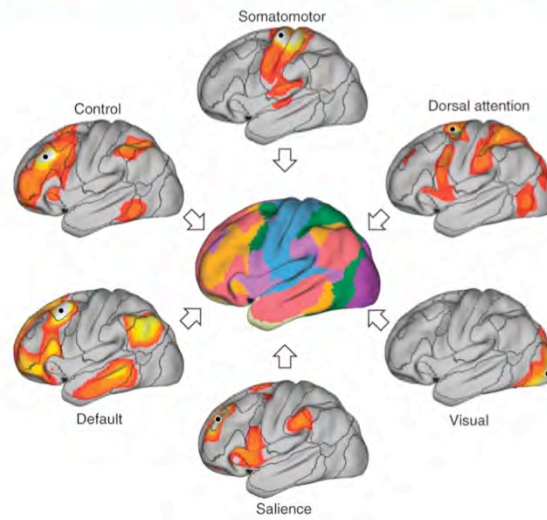
Reduced DMN connectivity and decreased anti-correlation between DMN and task-positive ROI



de Havas; NeuroImage (2012)

Sleep deprivation can be thought of as a state where one tries to stay away but periodically succumbs to sleep . Both Michael Czisch's group and ours found heterogenous reduction in DMN connectivity as well as reduced anti-correlation between the ROIs in Task positive and Default Networks

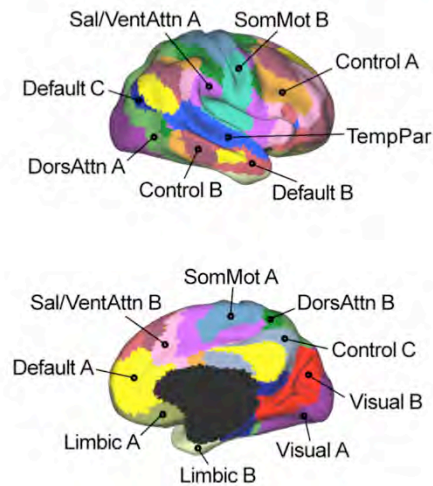
Intrinsically connected brain networks



Buckner, Krienen, Yeo (2013)

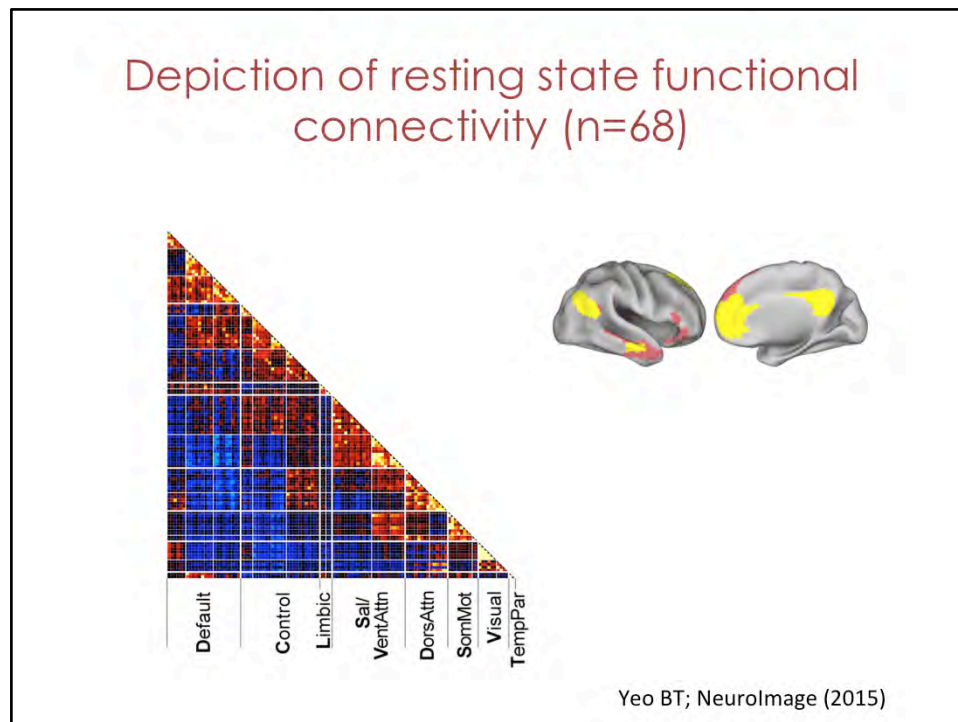
To this point, the studies reviewed used a hypothesis driven seed based approach based on informative findings from previous studies. They are somewhat myopic in their coverage of other resting state networks and fail to take advantage of the whole brain sampling afforded by task-free fMRI studies. Shown here is the automated parcellation of multiple resting state networks that is the basis for evaluation of state changes in multiple networks concurrently.

17-network resting state parcellation



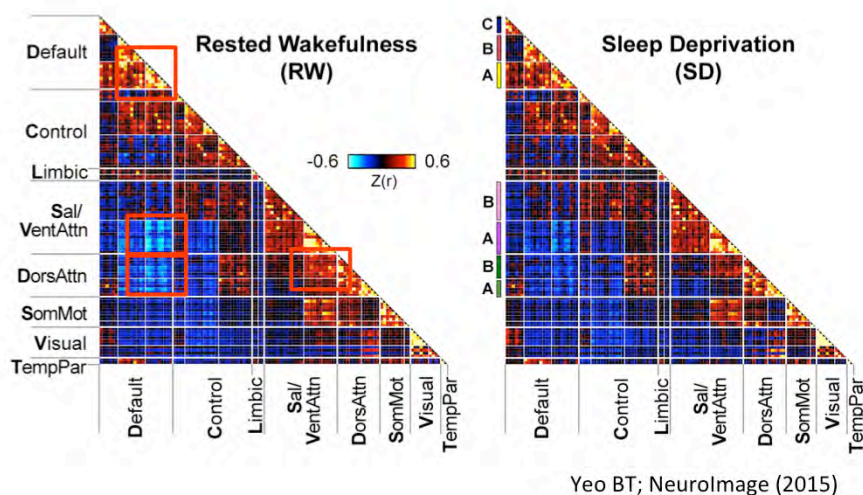
Yeo BT; J Neurophysiol (2011)

In Thomas Yeo's 17-network parcellation of the right cerebral cortex, these networks can be aggregated into 8 functional groupings for ease of discussion



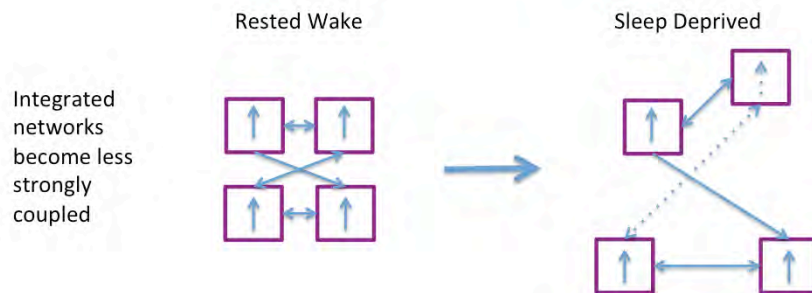
In this lower left triangular matrix, we depict how the 17 networks fit into these 8 functional groupings.
 To facilitate visualization, relevant members of the **17 networks** are color coded and **their location in the brain are shown**
 hot colors indicate positive correlation in activity between nodes
 Cool colors indicate anti-correlation between nodes.

Comparison of functional connectivity – RW vs. SD



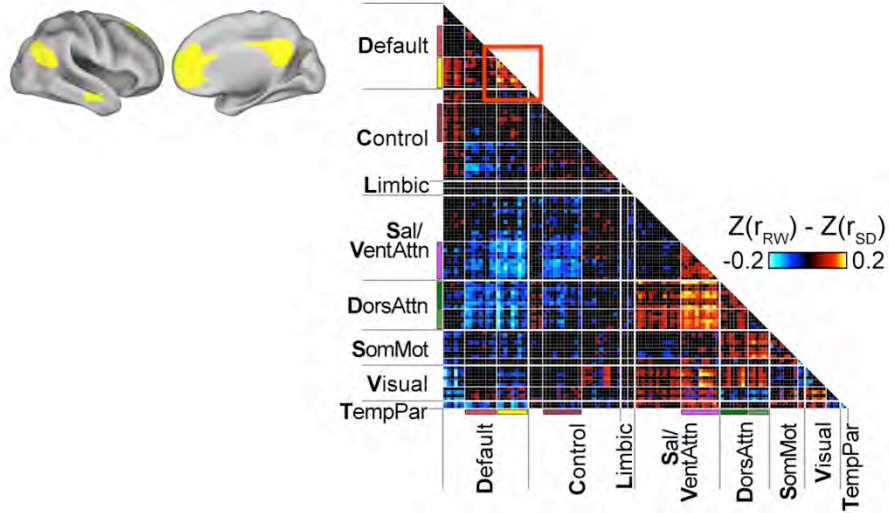
Matrices corresponding to FC in each state are depicted here.

A simplified way of interpreting state changes in functional connectivity



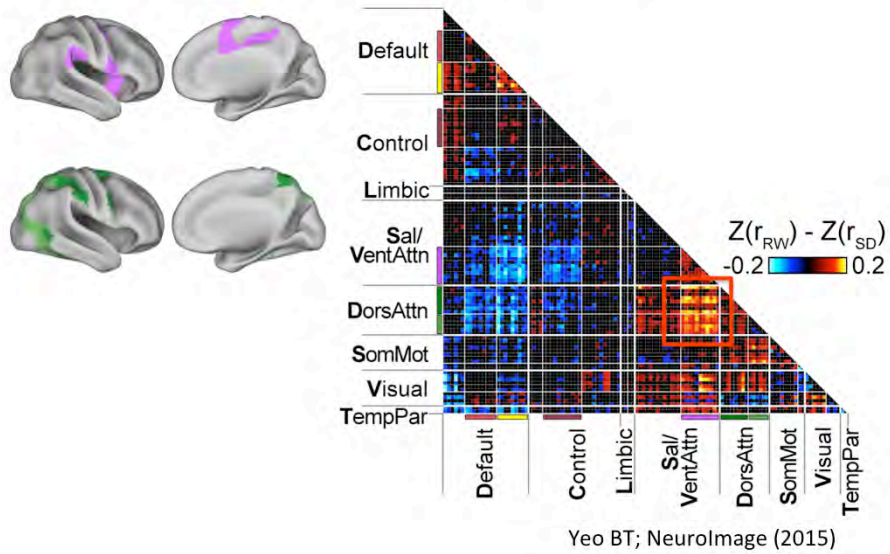
To make interpretation more tractable, we grouped state changes along a simplified theoretical framework. One set of network changes involves networks showing positively correlated activity and can be characterized as Integrated networks become less strongly coupled.

I. SD: Reduced positive correlation within Default A network



Yeo BT; NeurolImage (2015)

II. SD: Reduced positive correlation between Salience A vs. Dorsal Attention A networks



? Related to why attention control is degraded in SD?

A simplified way of interpreting state changes in functional connectivity

Rested Wake

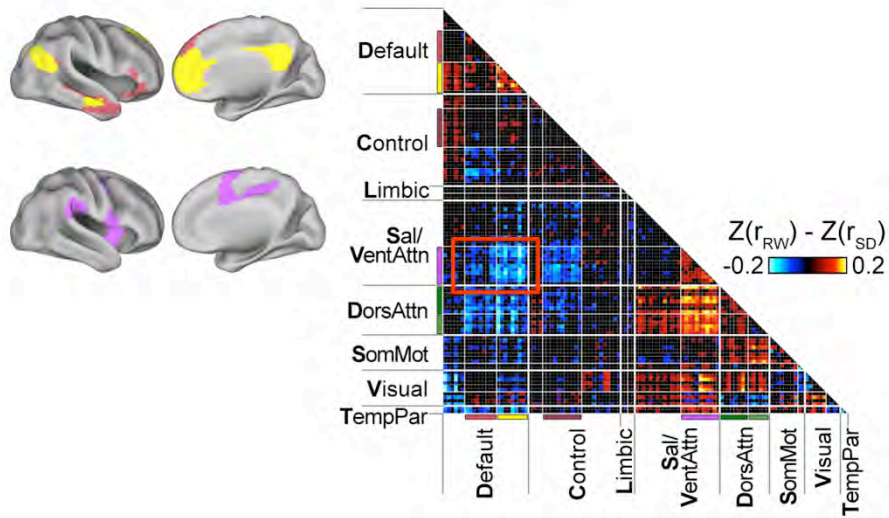
Sleep Deprived

Segregated
Networks
become less
segregated



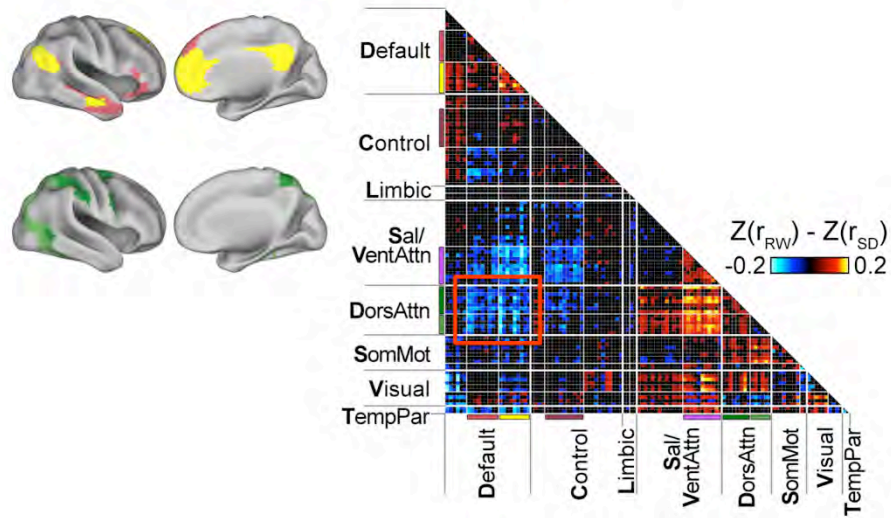
Another of network changes involves networks showing anti-correlated activity and can be characterized as segregated networks become less well segregated. When you are not day dreaming you are more focused and vice-versa

III. SD: Reduced anti-correlation between Default A&B and Salience A Networks

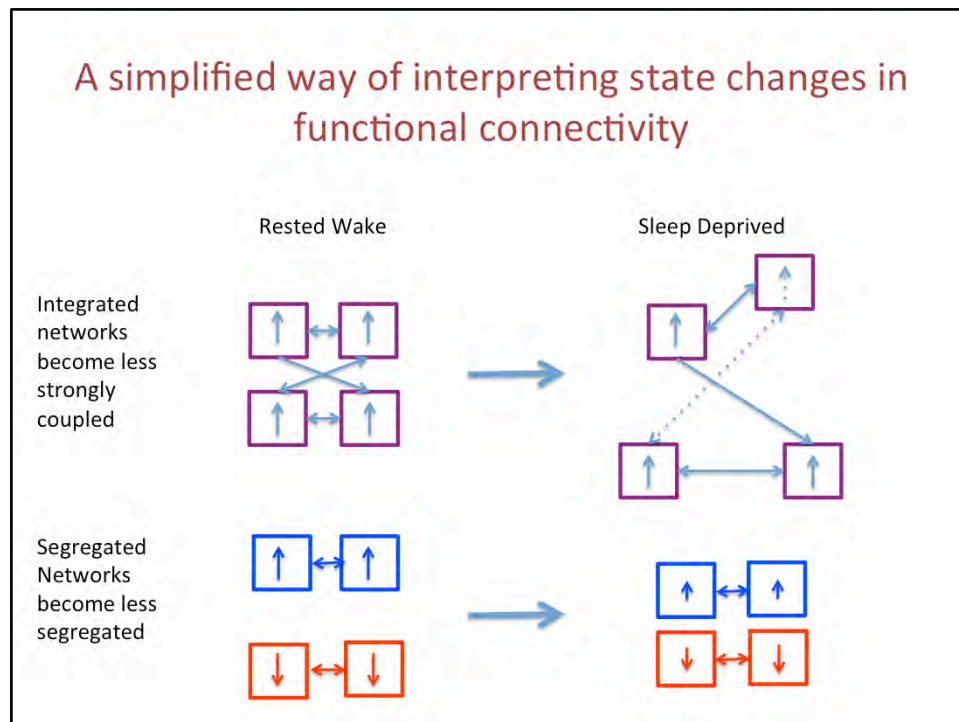


Yeo BT; NeurolImage (2015)

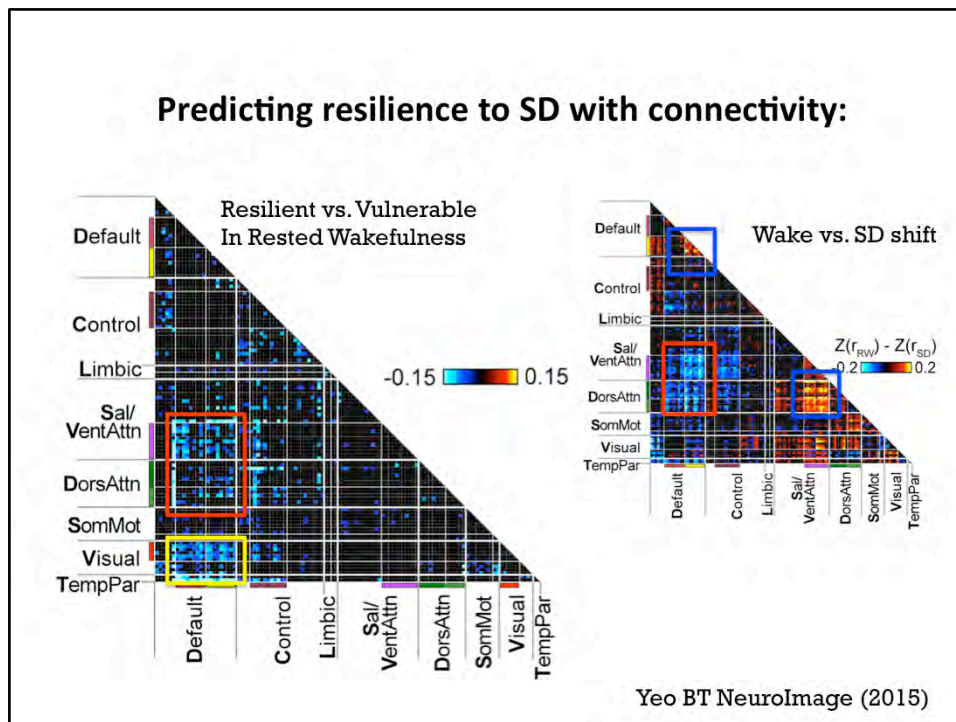
IV. SD: Reduced anti-correlation between Default A&B and Dorsal Attention A Networks



Yeo BT; NeurolImage (2015)



There thus appear to be two shifts in cortical network behavior following sleep deprivation.

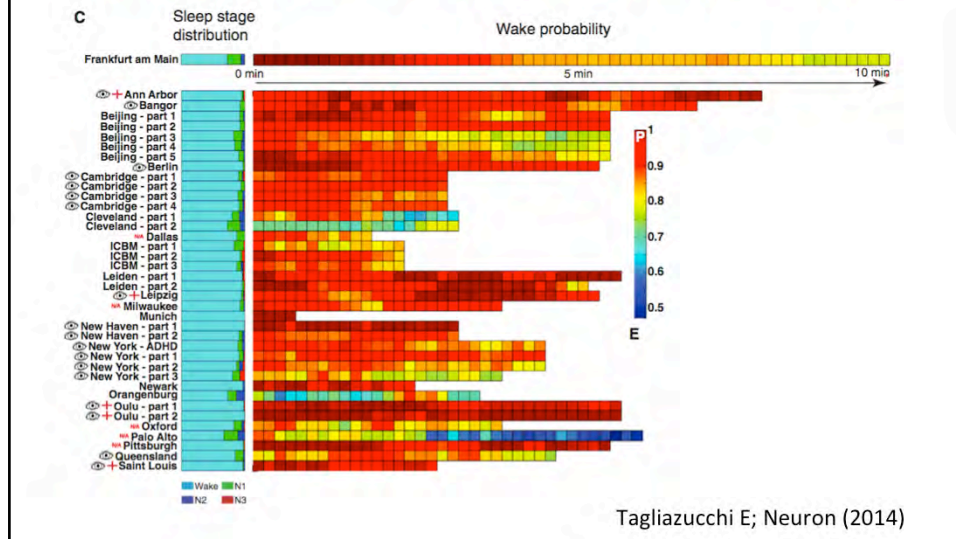


One exciting byproduct of this work has been the discovery that resting state connectivity in the rested state can inform about vulnerability to SD

The networks contributing to this prediction of resilience **all** show greater anti-correlation between one another.

They share features with networks affected by SD.

A third of long 'resting state' scans during 'wakefulness' contain sleep!



The last fMRI study highlighted is one which shows that in several 'awake' resting state fMRI studies, the longer the experiment, the more likely participants were to show MRI features of sleep. Given the network changes I've just shared with you, this suggests that if we want clearer delineation between healthy and clinical populations, we should invest in an eye-tracker or some means of tracking sleep in the scanner.

Resting state fMRI changes in SD

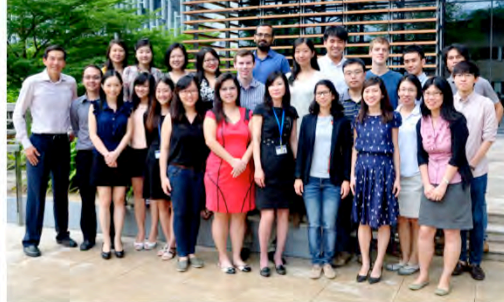
- All 'awake' resting state studies should monitor for sleep!
- ↓ connectivity within Default Mode Network (DMN)
- ↓ anti-correlation between DMN and Task-Positive Network (ACN- anticorrelated networks); = increased correlation between these
- Degree of anti-correlation in the rested state may predict vigilance changes in SD

Future directions

- Predictive marker for persons vulnerable to negative consequences of sleep deprivation
- Evaluating microstates in the sleep deprived condition
- Marker for long-term consequences of sleep loss or poor sleep quality on cognition / risk of cognitive decline or impairment
- Translation of these novel paradigms into studies involving insomnia, OSA patients

Acknowledgements

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<http://www.cogneuro-lab.org>

Presentation available from website

