The Journey

1. From the Philosophical to the Concrete
2. From Generality to Particularity
3. From the Known to the Speculative
1. From the Philosophical to the Concrete

• The spatial hierarchy to match the frequency hierarchy
Human brain networks function in connectome-specific harmonic waves

Selen Atasoy¹, Isaac Donnelly² & Joel Pearson¹
Wavefunctions of the Hydrogen Atom

Energy
Analogies:

- Global Appeal: Arousal Level Training
- Hemispheric Division
- Four-quadrant Primary Protocols “Zone Defense”
- Particularity
Connectome Laplacian Eigenfunctions
The Laplacian Eigenfunctions

- Constitute a complete set: A basis set
- All Intrinsic Connectivity Networks can be constituted out of a linear combination of the basis set
1. Primary divide is hemispheric

The Hemispheric Divide is Primary in our Clinical Decision-making
3. Input-output division

- The secondary issue we face is deciding on front-back training
The combination of the hemispheric division and the input-output division gives us the four quadrants for our primary protocols.
2. Divide within each hemisphere

- This eigenfunction has large representation in the divide between the task-negative and the task-positive networks.
- The midline is the heart of the Default Mode, our task-negative network
9. High correlation with Default Mode

- Default Mode is largely constituted out of basis functions 9 and 2
3. Limbic system representation

- Right side and frontal dominance
- Strong involvement of ventro-medial Pre-Frontal Cortex (vmPFC)
Limbic (Salience) network

- Limbic system is largely constituted out of the first three basis functions
- (We know that laterality is important, even if the authors don’t)
Intrinsic Connectivity Networks
Hierarchy of Regulation

• We have migrated to the foundation of our regulatory hierarchy
  • In terms of frequency
  • In terms of spatial eigenfunctions
  • In the developmental sequence
  • In the networks
    • Our primary occupation is with the task-negative network, the Default Mode

• The next frontier is to walk back up the hierarchy
  • From the task-negative state to the task-positive state
  • Address the Salience Network that mediates between them
2. From Generality to Particularity

- Theoretical issues motivating protocol refinement
- Particularity in neural system disregulation
- The frontier of dynamic functional connectivity
Theoretical issues motivating protocol refinement

The challenge of specificity:

• In terms of target frequency
• In terms of placement

An opportunity for refinement, bifurcation:

*We treat frequency as a continuous variable*

*We can do the same for placement*
Particularity in neural system disregulation

- Refinement of the DMN training model
- Targeting the Salience Network
- Addressing the task-positive networks
Refinement of the DMN Model
Principal nodes of the DMN (2008):

- T3
- T4
- P3
- P4
- AFz
- Fpz
Connectivity within Default Mode (Buckner, 2008)
A matter of terminology:

Lateral Temporal Cortex:
- Mid-temporal region
- Superior temporal sulcus

Medial Temporal Lobe
“Intrinsic Functional Connectivity Reveals that the Default Network Is Comprised of a Midline Core and Two Distinct Subsystems”
The circuit diagram for the two subsystems:

- Retrosplenial cortex
- Parahippocampal Complex
- Posterior Inferior Parietal Lobule
Cartography of the two subsystems:
T4-P4 training is our bridge between the two
Our primary interaction with the two subsystems:
Subsidiary hub interactions with T4
The authors postulated that:

- the *Future Self* condition would preferentially activate the Medial Temporal Lobe subsystem, and the *Present Self* condition would preferentially activate the dMPFC subsystem.

**Why?**

- The future self is largely constructed on the basis of memory
- It is a relatively stable construct
- Hence, more hippocampal (limbic) involvement

The control condition was a challenge involving non-personal semantic knowledge (either future or present-oriented)
Regions within the dorsal Medial Prefrontal Cortex (dMPFC) Subsystem Are Functionally-Coherent

dMPFC = dorso-medial prefrontal cortex
TPJ = temporo-parietal junction
LTC = lateral temporal cortex
TempP = temporal pole
Regions within the Medial Temporal Lobe (MTL) Subsystem Are Functionally-Coherent

Rsp = Retrosplenial cortex
PHC = Parahippocampal cortex
HF+ = Hippocampal formation
pIPL = Posterior inferior parietal lobule
vMPFC = Ventro-medial prefrontal cortex
The core shows no such dependence:
The Regulatory Hierarchy

Within each subsystem:

Five of these nine hubs are located on the temporal lobe.
Nesting:

TempP +LTC

+TPJ

+dMPFC

TempP +LTC
Interpretation

• The authors established a central functional distinction between the two sub-networks.
• One network is engaged more with organizing the moment
• The other is oriented more to the personal context
• The “doing” self and the “being” self
Areas for potential clinical exploration:

- Training the Lateral Temporal Lobe: Temporal Pole to Temporo-parietal junction
  - Across hemispheres!
  - As refinements to T3-T4
Areas for potential investigation:

• Adjust position of pre-frontal placement for more refined control
  • Toward midline for more engagement with midline core
  • Ventral for more affective engagement
  • Dorsal for more cognitive engagement
Our primary engagement has been with the Default Mode

- The previous discussion illustrated that our existing protocols can all be motivated by reference purely to the core organization of the DMN
- All of our basic protocols directly concern themselves with the resting state rather than the engaged state
- The neurosciences have viewed the DMN mainly in a cognitive frame: What cognitive activity is associated with the DMN?
  - But the mentation associated with the resting state is not the point;
  - What matters is the role of the DMN in controlling and regulating brain activity—to which we have preferential access!
The function of the DMN

“The function of the DMN.... is still unknown.”

In:
Language in the brain at rest: new insights from resting state data and graph theoretical analysis
Angela M. Muller and Martin Meyer
Frontiers in Neuroscience, April 2014, Volume 8, Article 228

The function of the DMN is cerebral regulation in its most global aspect
Task management: The Engaged Self

• Engagement with the world is processing-intensive
• It makes sense to look at the hubs of the busiest networks:
  • Last year we looked at the “Rich Club”
  • This year, we’ll look at the hierarchy of task control

*It is observed that a unitary model of top-down control is not sustainable.*
A dual-networks architecture of top-down control

Nico U.F. Dosenbach, Damien A. Fair, Alexander L. Cohen, Bradley L. Schlaggar and Steven E. Petersen
Dual networks of top-down task control:

1. A fronto-parietal network that includes the dorso-lateral pre-frontal cortex and intra-parietal sulcus.
2. A second network, called the cingulo-opercular network, that includes the dorsal anterior cingulate/medial superior frontal cortex, anterior insula/frontal operculum, and anterior pre-frontal cortex.

Functional description of the dual networks

1. The fronto-parietal network:
   • This network emphasizes start-cue and error-related activity and may initiate and adapt control on a trial-by-trial basis.
   • This is the real-time oriented executive system

2. The cingulo-opercular network:
   • This network may control goal-directed behavior through the stable maintenance of task sets.
   • This system is oriented to the context of the action
Division into upper and lower tier:
The two networks:
Fronto-parietal network

High-lighted:
• The primary hubs of the Rich Club
• Hubs of the FPN are mainly lateralized

Is this the first time you ever saw reference to the mid-cingulate?
The Rich Club
Fronto-parietal network

• High-lighted:
• The nexus with the Default Mode Network
The human posterior parietal cortex (PPC) is divided by the intraparietal sulcus (IPS) into two parts: the superior parietal lobe (SPL) and the inferior parietal lobe (IPL).

The IPL consists of the angular gyrus (Ang) and supramarginal gyrus (Smg) and borders the superior temporal gyrus (purple) at a region referred to as the temporoparietal junction (TPJ).
The cingulo-opercular network

- Substantial involvement of the Salience Network
  - Right anterior Insula
  - Anterior Cingulate
  - Linkage to left Anterior Insula

- Linkage to the task-positive network
  - Dorsal ACC
  - Anterior thalamus
Network independence

• “... inter-network connections, as measured with rs-fcMRI, were minimal”

• “If the fronto-parietal and cingulo-opercular networks were to communicate, why did none of our large-scale analyses reveal a link between them?”
  • Dosenbach

*We are seeing functional differentiation, not independence or disconnectedness*
Dual subnetwork control of resting and engaged states

• Resting State:
  - Dorsomedial Prefrontal Subsystem
  - Medial Temporal Lobe Subsystem

• Engaged State:
  - Fronto-Parietal Network
  - Cingulo-Opercular Network
Cingulo-opercular network

• Here the Salience Network is seen in the perspective of the task-positive network, the Central Executive
• We have been looking at it in the frame of the Default Mode Network, our task-negative network

*The Salience Network leads two lives...*
Cingulo-Opercular network incorporates the Salience Network

A better perspective:
• Salience Network plays two roles:

  Default Mode Network
  Salience Network
  Task-positive Networks

The critical link here is the anterior insula
Developmental time course

Children 7-9  Adolescents 10-15  Adults

But we know that our pre-frontal placements are already effective in young children....
The clinical challenge: targeting the Salience Network

1. **Our problem:** The Insula is not readily accessible to us
   - This may be yet another rationale for re-visiting the Temporal Pole placement
2. **Perhaps the Salience Network is best addressed with (nominal) TP-AFz**
3. **We don’t yet know how the FPN should be trained**
The Cingulo-opercular network (yellow)
The larger picture

Look at the relationship between the DMN, the FPN, and the Dorsal Attention Network:

Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain

R. Nathan Spreng, Jorge Sepulcre, Gary R. Turner, W. Dale Stevens, and Daniel L. Schacter

Connectivity matrix

Fronto-Parietal Control Network

Dorsal Attention Network

Default Mode Network

Figure 2. Dendrogram of the hierarchical cluster analysis of the full correlations and corresponding color-coded correlation matrix. The upper triangle of the matrix shows full correlations, the lower triangle shows partial correlations. Colors indicate magnitude of correlation. Prefixes l = left hemisphere, r = right hemisphere. See Table 1 for abbreviations.
Observations:

• (Implied) Mutual isolation of the Default Mode and the Dorsal Attention Networks

The authors:

• “...the fronto-parietal control network was functionally interposed between the dorsal attention and default networks”

• “Spatially distinct and functionally competitive, the “default” and “dorsal attention” networks subserve internally- and externally-directed cognition, respectively”
The Puzzle

• The Dorsal Attention Network is the unimodal association area for the visual system, along with the Ventral Attention Network

• The Default Mode includes the multi-modal association areas
  • Which also just happen to be our training sites!
  • These are the recipients of the output of the sensory networks

• How then can the DMN and DAN fail to be correlated?

• Of course they are correlated also!
  • They are correlated in their baseline states
The Relationship between the Primary Sensory Networks and the DMN: Margulies

• As illuminated by connectivity analysis
Situating the default-mode network along a principal gradient of macroscale cortical organization


www.pnas.org/cgi/doi/10.1073/pnas.1608282113
Look at principal gradient (collapse the second)

“The principal gradient of connectivity... shows a spectrum between unimodal regions (dark blue) and transmodal regions (sienna), which ... peaks in regions corresponding to the DMN”
Peaks in the connectivity gradient line up with our primary training sites!
Labeling:

A1, primary auditory; ag, angular gyrus; cing, anterior cingulate cortex;
ifg, inferior frontal gyrus; infs, intermediate frontal sulcus; L, limbic;
M1, primary motor; mfg, middle frontal gyrus; mtc, middle temporal cortex;
P, parietal; Pf, prefrontal; phf, para-hippocampal formation;
pmc, posteromedial cortex; ps, principal sulcus; S1, primary somatosensory;
sfg, superior frontal gyrus; V1, primary visual; vmpfc, ventromedial prefrontal cortex.
Dynamical relationships

- Obviously there is a thread of continuity between the primary sensory areas and the multi-modal sensory processing areas of the DMN
- This holds true for the Dorsal Attention Network as well as the Ventral

*How do the roles differ between the two?*
The role of the Dorsal Attention Network

- The DAN engages in coordination with the Frontal-Parietal Network
- When the FPN activates, alpha synchrony increases between the frontal and parietal hubs
  - Alpha amplitude increases by virtue of increased synchrony
- When the DAN activates, its alpha amplitude decreases because of increased activation
- Alpha amplitudes are anti-correlated, but we have consistency

*The DAN and FPN jointly execute top-down initiatives*
Does this mean the DAN does not couple to the DMN? No!

• The correlation of the DAN with the Default Mode is greater than its correlation with the Central Executive, the FPN!
• The relationship is steady-state rather than episodic
  • So it is not picked up in some correlation studies
DAN Correlation with hubs of the DMN is greater than with Executive Network!  
(Hiltunen)
The Ventral Attention Network

• The Ventral stream of sensory processing is deemed to be “sensitive to unexpected salient stimuli and is proposed to draw attention to as yet unattended stimuli or locations”
• “...the VAT network is thought to be right-lateralized.”
  • Margulies

This all fits the vigilance model in which the right VAT, the right temporal lobe, the right insula (the Salience Network) jointly serve as our effective “pool minder” to assure our global safety
We confront two models: The cognitive model and the control system model

The Cognitive Model:
- “the “default” and “dorsal attention” networks subserve internally- and externally-directed cognition, respectively”
  - Spreng et al.

The Control System Model:
- The Default and Dorsal attention networks subserve bottom-up and top-down processing, respectively
  - Bottom-up responding is primarily reactive (mediated by VAN)
  - Top-down responding is primarily pro-active (mediated by DAN)
Defining example: The odd-ball design

- The CPT in an odd-ball design involves an anticipatory set confronting potential surprise—the odd-ball challenge
- Here the anterior insula is known to play a controlling role
- Information flow is from the Ventral Attention Network to the temporal lobe and the insula
- Then what happens?
Information outflow from anterior insula (Sridharan)
Response latency of rAI is minimal

But it is too long to the frontal regions for their involvement!

Sridharan
Recent paper illuminates issue of DAN versus VAN (albeit incidentally!)

“Individual differences in functional connectivity during naturalistic viewing conditions”

• By Tamara Vanderwal, Jeffrey Eilbott, Emily S. Finn, R. Cameron Craddock, Adam G. Turnbull, F. Xavier Castellanos
• Submitted to NeuroImage (not yet published)
Correlation in activation of Intrinsic Connectivity Networks in resting state: Note anti-correlation of DAN/VAN and DMN.
However: Observe correlation between Ventral Attention Network and Somatomotor. In the resting state.
Fast response pathway:

Ventral Attention Network
>>
Temporal Lobe
>>
Insula
>>
Motor cortex

*But where is motor planning?*
Correlation of Salience and Premotor Networks

On the basis of combined EEG and fMRI BOLD correlation analysis, the strongest correlation is between the Salience and Pre-motor networks!

-- Hiltunen
Fast response pathway:

Ventral Attention Network

Temporal Lobe

Insula

Supplementary Motor Area

Motor cortex

Odd-ball Response:
Are we truly training the resting state (in particular, the task-negative) networks?

- The same paper illuminates the issue:
  - Visual Imagery activates the VAN
Nodal involvement as function of demand

Individual Differences in Dynamic Functional Brain Connectivity Across the Human Lifespan
Davison, Turner, Schlesinger, Miller, Grafton, Bassett, Carlson
PLoS Computational Biology · November 2016
DOI: 10.1371/journal.pcbi.1005178
Rest versus passive attention
Word recognition vs. facial recognition
Hypothesis

• Observe that there is very little difference between the true resting state and the state of passive attention

*What we define as the resting state is essentially the state of passive attention...of passive vigilance*

• All the processing elements have to be on-line in this state
  • In particular, the sensory processing
  • The entire sensory processing hierarchy

• The functions we assign to the Salience Network involve the unimodal association areas—The VAN more than the DAN—and the multi-modal association areas of the DMN
Looking at network involvement as function of demand – Davison

• Observe that there is hardly any difference in network size between resting state and passive attention
• The implication is that the differentiation between resting and minimally engaged states are subtle, not macroscopic.
• The combination of Salience Network and Default Mode jointly serve the purpose of appraisal of the current state within both the historical and the immediate context
• The fronto-parietal network mediates engagement by recruiting the Dorsal Attention Network
  • Its association with the Default Mode Network is steady-state
Meehan:

- Hypothesis (following Raichle) that “intrinsic BOLD fluctuations reflect a constantly maintained state of anticipation by large-scale networks of the brain.”

_The resting state is not a state of passive perception but rather of active anticipation_

—_on the part of the brain, not necessarily the person_
Recent studies show that the spatial and temporal properties of brain functional networks change only minimally between rest and task.

- Greicius et al., 2009; Smith et al., 2009; Tagliazucchi et al., 2011)

This holds most particularly for the Salience Network
The anterior insula behaves similarly in active and resting states.

Auditory discrimination  Visual odd-ball task  Task-free resting state
All regions involved in all functional networks are continuously interacting with each other when the brain is at rest, with the same functional hierarchy that controls all brain action and cognition.

The primary networks split into subnetworks in both active and resting data in almost identical ways, e.g., into areas of slightly different function or into left vs. right subnetworks.
Mesulam, 1990

• “Pathways that carry information from sensory receptors toward motor effectors have a self-explanatory purpose. But what about the luxuriant web that interlinks limbic, paralimbic, and association areas in almost every possible permutation?”

This was written ten years before the identification of the Default Mode and Salience Networks, and before Craig’s Model of insula function.

This is the question we are now answering with ILF training
The insula is our grand arbiter

- The case has been made for the central role of the right anterior insula in mediating between passive (reactive) and active (pro-active) states
- It is the major hub for the appraisal of our internal and external state

How might one focus on insula/salience network function specifically?
The insula in the view of Robert Sapolsky

“Hmmm, extreme negative affect elicited by violations of shared behavioral norms. Let’s see... Who has any pertinent experience? I know, the insula! It does extreme negative sensory stimuli – that’s like all it does – so let’s expand its portfolio to include this moral disgust business.”

_This could hardly be more misguided!_

From the book:
The Behavior of Humans at their Best and Worst, by Robert Sapolsky.
Connectivity matrix:

Loci of high correlation:

• L-R Anterior Insula

• L-R Hippocampal Formation
Correlation of L/R anterior Insula/frontal Operculum
The prominent linkages in this analysis are largely inter-hemispheric at homotopic sites.

This may serve as an incentive to investigate other I-H placements to complement T3-T4.
Dosenbach:

• “Delay/disruption in the developmental processes of segregation and integration may play a role in disorders of control, such as autism, attention deficit hyperactivity disorder, and Tourette's syndrome.”

Control is still viewed in a narrow perspective

• “...full comprehension of how the mature system works can be powerfully illuminated by “understanding how it is constructed in development” and “how development can go awry.”

“Spontaneous fluctuations are a hallmark of neural signals.”

What is wrong with this statement?