Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience

Supplemental Information

Introduction

A Brief History of the Brain's Intrinsic Functional Connectivity

An early discovery from fMRI studies was that functionally similar neural regions showed correlated activity even when they were not actively prompted. Biswal and colleagues (1) first demonstrated this in an fMRI study of motor regions. Using the activation maps derived from a bilateral finger-tapping task, Biswal *et al.* specified a region-of-interest 'seed' in left motor cortex and queried the time courses of all other voxels during rest to identify other regions in which activity was correlated with activity in this seed region. This analysis showed that, in addition to nearby voxels, contralateral motor cortex and midline cortical regions showed timecourse correlations with the seeded left motor cortex. Thus, in this resting-state analysis, it was the *correlation* of the time courses, rather than the *magnitude* of a response, that determined network connectivity. Moreover, the functional connectivity map that resulted from this analysis was spatially similar to the map of regions that were activated by the *bilateral* finger-tapping task.

Subsequent research expanded on Biswal *et al*.'s (1) conceptualization of an implicit functional organization in the brain. In a meta-analysis of PET studies of visual processing in humans, Shulman *et al.* (2) identified regions in which metabolic activity decreased during an active task, that included the posterior cingulate cortex (PCC), bilateral parietal cortex, ventral medial prefrontal cortex (vmPFC), and medial temporal

lobe (MTL) regions. These decreases in activity, which showed remarkably little spatial variation despite a wide range of extrinsic tasks, prompted investigators to begin to study a consistent, spatially organized baseline state of metabolic functioning. Perhaps most notably, Raichle and his colleagues (3) examined metabolic demands during eyes-closed rest and described a 'default-mode' pattern of metabolic activity in the brain that included PCC, bilateral parietal cortex, and vmPFC. By using PET to examine blood flow and oxygen consumption, Raichle *et al.* were able to determine an absolute level of metabolic activity during rest, rather than a relative level of activity during the transition from rest to activity. Thus, the default mode network (DMN) identified by Raichle *et al.* reflects an ongoing metabolic demand of these regions, a physiological baseline rather than the relative baseline of blood oxygenation level-dependent (BOLD) fMRI signals (4).

Investigators have begun to examine factors that may explain the functional connectivity of the brain regions that comprise the DMN. One likely candidate is monosynaptic white-matter connectivity among these regions; another potential factor is common connectivity with a third structure. In testing these possibilities, Greicius and colleagues (5) conducted a study examining both functional and structural connectivity by using BOLD signal and diffusion tensor imaging (DTI), respectively, to visualize connectivity. To obtain seed regions for DTI, Greicius *et al*. used probabilistic independent component analysis (ICA) to analyze fMRI data. ICA decomposes the whole-brain data into independent spatiotemporal components, including the DMN (6). Using DMN regions, including the PCC, vmPFC, and MTL, as seed regions, Greicius *et al.* identified white-matter tracts that directly connected PCC to vmPFC and PCC to

MTL, but not to structures outside the DMN. Thus, the temporal correlation of activity in these regions at rest is likely due, at least in part, to tracts that link DMN regions directly.

In an important extension of formulations of macro-architectural organization of the brain, Fox and colleagues (7) posited that components of the brain's intrinsic functional organization — the DMN, described above, and the task positive network (TPN; a network of structures that increase in activation during performance of attention-demanding tasks) — have a competitive, anti-correlated relation with each other. Fox *et al.* noted that, during performance of cognitive tasks, structures comprising the TPN (dorsolateral prefrontal, lateral parietal, and anterior insular cortices) were characterized robustly by increases in activation, whereas structures comprising the DMN showed reliable decreases in activity. Importantly, Fox *et al.* documented this same negative relation between DMN and TPN during resting-state fMRI scans: fluctuations in activation in one network were associated with inverse activation fluctuations in the other network.

The DMN in MDD

Table S1. Studies Measuring Brain Resting-State Activity in Patients with MDD, Relative to Healthy Controls (8-25)

Study	Number of Subjects in Group		Characteristics of Depressed Subjects		Imaging Technique	
	Major Depressive Disorder	Comparison	% Medicated	% MDD Female Subjects	Method	Tracer
Bench *et al.* (1992)	33	23	58	36	PET	[^{18}F]FDG
Drevets *et al.* (1992)	33	23	0	54	PET	[^{18}F]FDG
Brody *et al.* (2001)	24	16	0	54	PET	[^{15}O]H_2O
Kennedy *et al.* (2001)	13	24	0	0	PET	[^{18}F]FDG
Saxena *et al.* (2001)	27	27	0	54	PET	[^{18}F]FDG
Videbech *et al.* (2001)	42	47	95	71	PET	[^{15}O]H_2O
Kimbrell *et al.* (2002)	38	37	0	66	PET	[^{18}F]FDG
Skaf *et al.* (2002)	9	12	0	44	SPECT	[^{99}mTc]ECD
Mayberg *et al.* (2005)	6	5	100	50	PET	[^{15}O]H_2O
Perico *et al.* (2005)	15	15	0	80	SPECT	[^{99}mTc]ECD
Aihara *et al.* (2007)	24	23	0	63	PET	[^{15}O]H_2O
Kohn *et al.* (2007)	33	25	0	58	SPECT	[^{99}mTc]ECD
Germain *et al.* (2007)	12	13	0	83	PET	[^{18}F]FDG
Krausz *et al.* (2007)	10	10	0	90	SPECT	[^{99}mTc]ECD
Martinot *et al.* (2011)	31	39	7	65	PET	[^{18}F]FDG
Richieri *et al.* (2011)	33	33	94	55	SPECT	[^{99}mTc]ECD
Vardi *et al.* (2011)	37	27	0	57	SPECT	[^{99}mTc]HMPAO
Nagafusa *et al.* (2012)	61	107	-	61	SPECT	[^{99}mTc]ECD

MDD, major depressive disorder; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Supplemental References

1. Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995): functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*. 34:537-541.

2. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, *et al.* (1997): Common blood flow changes across visual tasks .2. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience*. 9:648-663.

3. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*. 98:676-682.

4. Ralchle ME, Snyder AZ (2007): A default mode of brain function: A brief history of an evolving idea. *Neuroimage*. 37:1083-1090.

5. Greicius MD, Supekar K, Menon V, Dougherty RF (2009): Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*. 19:72-78.

6. Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005): Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B-Biological Sciences*. 360:1001-1013.

7. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*. 102:9673-9678.

8. Aihara M, Ida I, Yuuki N, Oshima A, Kurnano H, Takahashi K, *et al.* (2007): HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. *Psychiatry Research-Neuroimaging*. 155:245-256.

9. Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RSJ, Dolan RJ (1992): The anatomy of melancholia - focal abnormalities of cerebral blood-flow in major depression. *Psychological Medicine*. 22:607-615.

10. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR (2001): Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biological Psychiatry*. 50:171-178.

11. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992): A functional anatomical study of unipolar depression. *Journal of Neuroscience*. 12:3628-3641.

12. Germain A, Nofzinger EA, Meltzer CC, Wood A, Kupfer DJ, Moore RY, *et al.* (2007): Diurnal variation in regional brain glucose metabolism in depression. *Biological Psychiatry*. 62:438-445.

13. Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, McCann S, *et al.* (2001): Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *American Journal of Psychiatry*. 158:899-905.

14. Kimbrell TA, Ketter TA, George MS, Little JT, Benson BE, Willis MW, *et al.* (2002): Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biological Psychiatry*. 51:237-252.

15. Kohn Y, Freedman N, Lester H, Krausz Y, Chisin R, Lerer B, *et al.* (2007): Tc-99m-HMPAO SPECT study of cerebral perfusion after treatment with medication and electroconvulsive therapy in major depression. *Journal of Nuclear Medicine*. 48:1273-1278.

16. Krausz Y, Freedman N, Lester H, Barkai G, Levin T, Bocher M, et al. (2007): Brain SPECT study of common ground between hypothyroidism and depression. *International Journal of Neuropsychopharmacology*. 10:99-106.

17. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, *et al.* (2005): Deep brain stimulation for treatment-resistant depression. *Neuron*. 45:651-660.

18. Perico CAM, Skaf CR, Yamada A, Duran F, Buchpiguel CA, Castro CC, *et al.* (2005): Relationship between regional cerebral blood flow and separate symptom clusters of major depression: A single photon emission computed tomography study using statistical parametric mapping. *Neuroscience Letters*. 384:265-270.

19. Saxena S, Brody AL, Ho ML, Alborzian S, Ho MK, Maidment KM, *et al.* (2001): Cerebral metabolism in major depression and obsessive-compulsive disorder occurring separately and concurrently. *Biological Psychiatry*. 50:159-170.

20. Skaf CR, Yamada A, Garrido GEJ, Buchpiguel CA, Akamine S, Castro CC, *et al.* (2002): Psychotic symptoms in major depressive disorder are associated with reduced regional cerebral blood flow in the subgenual anterior cingulate cortex: a voxel-based single photon emission computed tomography (SPECT) study. *Journal of Affective Disorders*. 68:295-305.

21. Videbech P, Ravnkilde B, Pedersen AR, Egander A, Landbo B, Rasmussen NA, *et al.* (2001): The Danish PET/depression project: PET findings in patients with major depression. *Psychological Medicine*. 31:1147-1158.

22. Martinot M-LP, Martinot J-L, Ringuenet D, Galinowski A, Gallarda T, Bellivier F, *et al.* (2011): Baseline brain metabolism in resistant depression and response to transcranial magnetic stimulation. *Neuropsychopharmacology*. 36:2710-2719.

23. Nagafusa Y, Okamoto N, Sakamoto K, Yamashita F, Kawaguchi A, Higuchi T, *et al.* (2012): Assessment of cerebral blood flow findings using 99mTc-ECD single-photon emission computed tomography in patients diagnosed with major depressive disorder. *Journal of Affective Disorders*. 140:296-299.

24. Richieri R, Boyer L, Farisse J, Colavolpe C, Mundler O, Lancon C, *et al.* (2011): Predictive value of brain perfusion SPECT for rTMS response in pharmacoresistant depression. *European Journal of Nuclear Medicine and Molecular Imaging*. 38:1715-1722.

25. Vardi N, Freedman N, Lester H, Gomori JM, Chisin R, Lerer B, *et al.* (2011): Hyperintensities on T2-weighted images in the basal ganglia of patients with major depression: Cerebral perfusion and clinical implications. *Psychiatry Research-Neuroimaging*. 192:125-130.