Yvette Sheline - selected references

1 Sheline, Y. I. & Raichle, M. E. (2013). Resting state functional connectivity in preclinical Alzheimer's disease. *Biological Psychiatry, 74,* 340-347.
Notes: There has been a dramatic increase in the number of studies using resting state functional magnetic resonance imaging (rs-fMRI), a recent addition to imaging analysis techniques. The technique analyzes ongoing low-frequency fluctuations in the blood oxygen level-dependent signal. Through patterns of spatial coherence, these fluctuations can be used to identify the networks within the brain. Multiple brain networks are present simultaneously, and the relationships within and between networks are in constant dynamic flux. Resting state fMRI functional connectivity analysis is increasingly used to detect subtle brain network differences and, in the case of pathophysiology, subtle abnormalities in illnesses such as Alzheimer's disease (AD). The sequence of events leading up to dementia has been hypothesized to begin many years or decades before any clinical symptoms occur. Here we review the findings across rs-fMRI studies in the spectrum of preclinical AD to clinical AD. In addition, we discuss evidence for underlying preclinical AD mechanisms, including an important relationship between resting state functional connectivity and brain metabolism and how this results in a distinctive pattern of amyloid plaque deposition in default mode network regions Departments of Psychiatry, Radiology, and Neurology, Washington University School of Medicine, St. Louis, Missouri. Electronic address: Yvette@npg.wustl.edu

2 Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America, 107,* 11020-11025.
Notes: To better understand intrinsic brain connections in major depression, we used a neuroimaging technique that measures resting state functional connectivity using functional MRI (fMRI). Three different brain networks--the cognitive control network, default mode network, and affective network--were investigated. Compared with controls, in depressed subjects each of these three networks had increased connectivity to the same bilateral dorsal medial prefrontal cortex region, an area that we term the dorsal nexus. The dorsal nexus demonstrated dramatically increased depression-associated fMRI connectivity with large portions of each of the three networks. The discovery that these regions are linked together through the dorsal nexus provides a potential mechanism to explain how symptoms of major depression thought to arise in distinct networks--decreased ability to focus on cognitive tasks, rumination, excessive self-focus, increased vigilance, and emotional, visceral, and autonomic dysregulation--could occur concurrently and behave synergistically. It suggests that the newly identified dorsal nexus plays a critical role in depressive symptomatology, in effect "hot wiring" networks together; it further suggests that reducing increased connectivity of the dorsal nexus presents a potential therapeutic target

3 Sheline, Y. I., Pieper, C. F., Barch, D. M., Welsh-Boehmer, K., McKinstry, R. C., MacFall, J. R. et al. (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry, 67,* 277-285.
Notes: CONTEXT: Research on vascular depression has used 2 approaches to subtype late-life depression, based on executive dysfunction or white matter hyperintensity severity. OBJECTIVE: To evaluate the relationship of neuropsychological performance and white matter hyperintensity with clinical response in late-life depression. DESIGN: Two-site, prospective, nonrandomized controlled trial. SETTING: Outpatient clinics at Washington University and Duke University. PARTICIPANTS: A total of 217 subjects aged 60 years or older met DSM-IV criteria for major depression, scored 20 or more on the Montgomery-Asberg Depression Rating Scale (MADRS), and received vascular risk factor scores, neuropsychological testing, and magnetic resonance imaging; they were excluded for cognitive impairment or severe medical disorders. Fazekas rating was conducted to grade white matter hyperintensity lesions.

Intervention Twelve weeks of sertraline treatment, titrated by clinical response. Main Outcome Measure Participants' MADRS scores over time. RESULTS: Baseline neuropsychological factor scores correlated negatively with baseline Fazekas scores. A mixed model examined effects of predictor variables on MADRS scores over time. Baseline episodic memory (P = .002), language (P = .007), working memory (P = .01), processing speed (P < .001), executive function factor scores (P = .002), and categorical Fazekas ratings (P = .05) predicted MADRS scores, controlling for age, education, age of onset, and race. Controlling for baseline MADRS scores, these factors remained significant predictors of decrease in MADRS scores, except for working memory and Fazekas ratings. Thirty-three percent of subjects achieved remission (MADRS < or =7). Remitters differed from nonremitters in baseline cognitive processing speed, executive function, language, episodic memory, and vascular risk factor scores. CONCLUSIONS: Comprehensive neuropsychological function and white matter hyperintensity severity predicted MADRS scores prospectively over a 12-week treatment course with selective serotonin reuptake inhibitors in late-life depression. Baseline neuropsychological function differentiated remitters from nonremitters and predicted time to remission in a proportional hazards model. Predictor variables correlated highly with vascular risk factor severity. These data support the vascular depression hypothesis and highlight the importance of linking subtypes based on neuropsychological function and white matter integrity. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00045773

4 Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S. et al. (2010). Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biological Psychiatry, 67,* 584-587.
Notes: BACKGROUND: Important functional connections within the default mode network (DMN) are disrupted in Alzheimer's disease (AD), likely from amyloid-beta (Abeta) plaque-associated neuronal toxicity. Here, we sought to determine if pathological effects of Abeta amyloid plaques could be seen, even in the absence of a task, by examining functional connectivity in cognitively normal participants with and without preclinical amyloid deposition. METHODS: Participants with Alzheimer's disease (AD) (n = 35) were compared with 68 cognitively normal participants who were further subdivided by positron emission tomography (PET) Pittsburgh Compound-B (PIB) imaging into those without evidence of brain amyloid (PIB-) and those with brain amyloid (PIB+) deposition. RESULTS: Resting state functional magnetic resonance imaging (fMRI) demonstrated that, compared with the PIB- group, the PIB+ group differed significantly in functional connectivity of the precuneus to hippocampus, parahippocampus, anterior cingulate, dorsal cingulate, gyrus rectus, superior precuneus, and visual cortex. These differences were in the same regions and in the same direction as differences found in the AD group. CONCLUSIONS: Thus, before any manifestations of cognitive or behavioral changes, there were differences in resting state connectivity in cognitively normal subjects with brain amyloid deposition, suggesting that early manifestation of Abeta toxicity can be detected using resting state fMRI

5 Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K. et al. (2006). Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biological Psychiatry, 60,* 58-65.
BACKGROUND: A number of studies have examined clinical factors linked to worse neuropsychological performance in late life depression (LLD). To understand the influence of LLD on cognition, it is important to determine if deficits in a number of cognitive domains are relatively independent, or mediated by depression- related deficits in a basic domain such as processing speed. METHODS: Patients who met DSM-IV criteria for major depression (n = 155) were administered a comprehensive neuropsychological battery of tasks grouped into episodic memory, language, working memory, executive function, and processing speed domains. Multiple regression analyses were conducted to determine contributions of predictor variables to cognitive domains. RESULTS: Age, depression severity, education, race and vascular risk factors all made significant and independent contributions to one or more domains of cognitive function, with all five making independent contributions to processing speed. Age of onset made no independent contribution, after accounting for age and vascular risk factors. Of

the five cognitive domains investigated, changes in processing speed were found to most fully mediate the influence of predictor variables on all other cognitive domains. CONCLUSIONS: While slowed processing speed appears to be the most core cognitive deficit in LLD, it was closely followed by executive function as a core cognitive deficit. Future research is needed to help clarify mechanisms leading to LLD- related changes in processing speed, including the potential role of white matter abnormalities

6 Sheline, Y. I. (2006). Brain structural changes associated with depression. In F.G.Gilliam, A. M. Kanner, & Y. I. Sheline (Eds.), *Depression and brain dysfunction* (pp. 85-103). Abington: Taylor & Francis.