Toward a pathophysiology of rumination: dorsal nexus resting-state functional connectivity in depression before and after serotonergic or behavioral interventions

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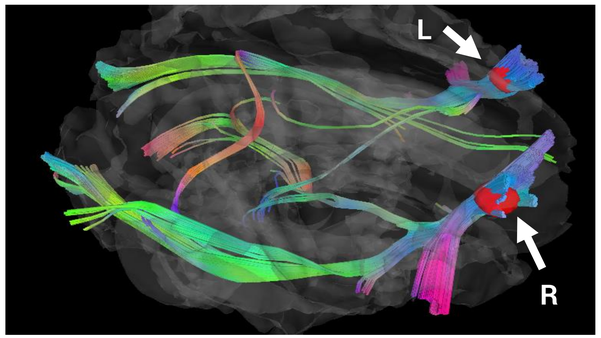
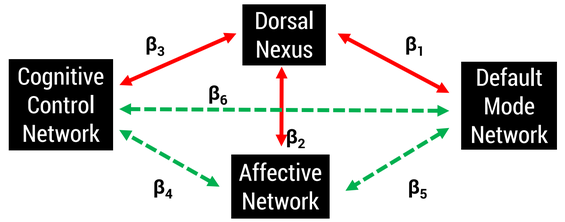


(**Fig 1**) Tractography of the dorsal nexus (white arrows) using coordinates found by Sheline et al. (2010). Dorsal nexus features anatomical connectivity to nodes of the default-mode, affective and cognitive control networks (CMU-30 DSI template).

Introduction

Rumination is characterized as the tendency to engage in repetitive, sustained and self-referential thoughts about negative topics. Rumination is a symptom of several psychiatric disorders, but is most prominent in depression. Rumination most often occurs during periods of waking rest, taking place of normal mindwandering (daydreaming). Resting-state functional connectivity measures neural activity during waking rest, and is thought to measure the overall propensity of communication between different areas of the brain.

A highly-cited study by Sheline et al. (2010) found the "dorsal nexus," a bilateral subregion of the dorsomedial prefrontal that features anomalously high connectivity with the default-mode (DMN), affective (AN) and cognitive control networks (CCN) in depressed populations. The DMN is thought to underlie internal and social modes of cognition. The AN associated with affect and psychosomatic processes. The CCN is implicated in executive functioning and goal-directed cognition. Dysfunction of these networks have been reliably found in depressed populations; the dorsal nexus may provide a unifying mechanism for this as well as the disparate cognitive, affective and somatic symptoms of depression.



Rumination = β_0 + β_1 (DN_DMN) + β_2 (DN_AN) + β_3 (DN_CCN) − β_4 (CCN_AN) − β_5 (DMN_AN) − β_6 (CCN_DMN)

(**Fig 2**) Hypothesized physiological measure of rumination using multivariate linear regression of functional connectivity strengths and rumination-related ratings scale scores.

Hypothesis

The dorsal nexus region has been implicated in the "aversive amplification" of affect, and is reliably recruited during the presentation of noxious stimuli. We hypothesize dorsal nexus hyperconnectivity to amplify affective and somatic responses during internal modes of cognition, drawing attention to and sustaining negative thought streams. We propose a pathophysiological model of rumination using multivariate linear regression of rumination-related rating scales and functional connectivity strengths (β_x) between the dorsal nexus, DMN, AN, and CCN (Fig 2), both before and after treatment with cognitive behavioral therapy or serotenergic antidepressants (SSRIs).

β_1 = Maladaptive integration of affect, somatic and executive processes during DMN-based cognition

β_2 = Aversive amplification of affective and somatic responses during DMN-based cognition

β_3 = Recruitment of attention and executive functions towards maladaptive evaluation during DMN-based cognition

β_4 = Cognitive down-regulation of affective and somatic processes

β_5 = Affective and somatic responses towards internalized cognition *not* amplified by dorsal nexus

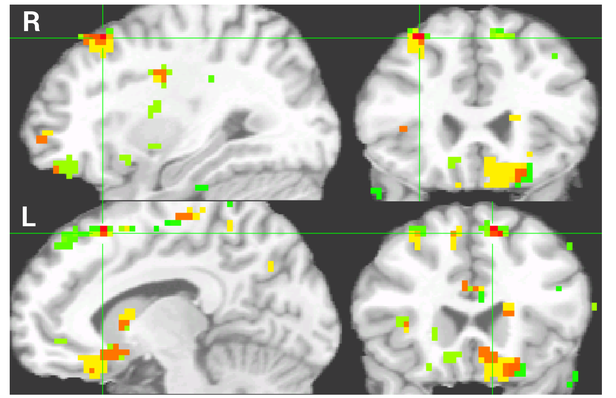
β_6 = Constructive evaluation during DMN-based cognition

Materials & Methods

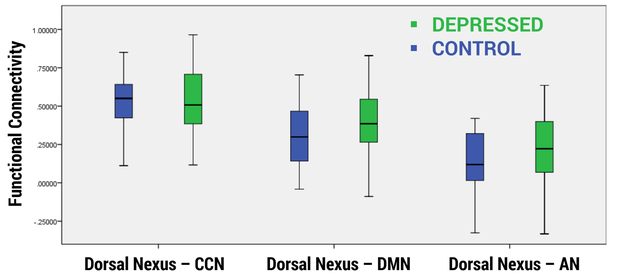
Ninety-nine right-handed adults were recruited for this study. Depressed participants (N=74) were randomly assigned either cognitive-behavioral therapy (N=54) or selective serotonin reuptake inhibitor antidepressants (N=20). The control group of healthy participants (N=25) were not treated. Resting-state functional connectivity was collected for seven minutes with fixation, before and after 6 months of treatment. fMRI data was preprocessed with two streams: one similar to Sheline et al. (2010) and another adopted from Hallquist et al. (2013). Key difference is serial vs. concurrent temporal filtering and nuisance regression. Functional connectivity was measured by structural vector autoregression. Dorsal nexus localized through conjunction of pre-treatment depressed vs. control contrasts ($p < 0.01$) using Sheline group's precuneus, subgenual cingulate, and dorsolateral prefrontal cortex seeds.

Results

Using a preprocessing stream similar to Sheline et al. (2010), a "nexus" of depression-associated increases in functional connectivity was found at [30 20 48] & [-11 17 50] through conjunction of depressed vs. control contrasts from the DMN, AN and CCN seeds (Fig 3). This "nexus" is located roughly 20mm anterior to the dorsal nexus found by the Sheline group ([-24 35 28] & [18 34 29]). However, pre/post-treatment contrasts of SSRI cohort did reveal significant ($p < 0.01$) connectivity decreases in areas much closer to Sheline's dorsal nexus, at [-14 30 30] & [18 30 24]. When using a preprocessing stream adopted from Hallquist et al. (2013), we could not find a conjunction of depression-associated decreases or treatment-associated increases in functional connectivity. *A priori* ROI analysis using Sheline's dorsal nexus coordinates did not yield statistically-significant differences in functional connectivity between the depressed and control groups (Fig 4).



(**Fig 3**) Conjunction of pre-treatment depressed vs. control contrasts from the DMN, AN and CCN seeds ($p < .01$) using original preprocessing stream. Depression-associated increases in connectivity converge at [30 20 48] & [-11 17 50]



(**Fig 4**) Pre-treatment depressed vs. control functional connectivity at Sheline dorsal nexus coordinates using a preprocessing stream adopted from Hallquist et al. (2013). Significant between-group differences were not found.

Discussion

A landmark paper by Hallquist et al. (2013) shows the deleterious impact of improper preprocessing on resting state functional connectivity. Adopting the preprocessing steps suggested by the Hallquist group, we could not find the "nexus" of depression-associated hyperconnectivity previously found using a preprocessing stream similar to that used by Sheline et al. (2010). This suggests that the "dorsal nexus" could be an artifact of nuisance regression after temporal filtering. This may be why our original preprocessing stream yielded a "nexus" roughly 20mm anterior to Sheline's. These results highlight the importance of sound preprocessing methodology in fMRI.