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Slow-5 dynamic functional connectivity reflects the capacity to sustain cognitive performance during pain

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A B S T R A C T

Some individuals are more distracted by pain during a cognitive task than others, representing poor pain coping. We have characterized individuals as A-type (attention dominates) or P-type (pain dominates) based on how pain interferes with task speed. The ability to optimize behavior during pain may relate to the flexibility in communication at rest between the dorsolateral prefrontal cortex (DLPFC) of the executive control network, and the anterior mid-cingulate cortex (aMCC) of the salience network (SN) – regions involved in cognitive-interference. The aMCC and aIns (SN hub) also signify pain salience; flexible communication at rest between them possibly allowing prioritizing task performance during pain. We tested the hypotheses that pain-induced changes in task performance are related to resting-state dynamic functional connectivity (dFC) between these region pairs (DLPFC-aMCC; aMCC-aIns). We found that 1) pain reduces task consistency/speed in P-type individuals, but enhances performance in A-type individuals, 2) task consistency is related to the FC dynamics within DLPFC-aMCC and aMCC-aIns pairs, 3) brain-behavior relationships are driven by dFC within the slow-5 (0.01–0.027 Hz) frequency band, and 4) dFC across the brain decreases at higher frequencies. Our findings point to neural communication dynamics at rest as being associated with prioritizing task performance over pain.

Introduction

How an individual prioritizes the importance of performing a cognitive task while dealing with pain, may be an important indicator of their ability to cope with pain while functioning across a wide range of everyday activities. When a painful stimulus is delivered to an individual who is performing a cognitively-demanding task, the outcome can be quite divergent. Intuitively, one would expect pain to impede task performance, and this is true for some people; denoted as P-type (i.e., pain dominates) individuals. However, others perform better on the task when pain is present than when it is not (A-type; attention dominates) (Erpelding and Davis, 2013; Seminowicz et al., 2004). We previously demonstrated that this divergence in behavior is related to differences in brain structure and function within areas of the dynamic pain connectome (Erpelding and Davis, 2013; Kucyi and Davis, 2015, 2016; Rogachov et al., 2016; Seminowicz et al., 2004).

Under competing demands, differences in task performance may reflect not only dissimilarities in regional brain structure and function, but also differences in the flexibility of communication between brain regions. For example, dynamic connectivity between brain regions involved with cognitive control increases from childhood to adulthood (Hutchison and Morton, 2015). Additionally, patients with traumatic brain injury and related decreased cognitive performance have reduced metastability within salience, attention, and executive control resting state networks (Hellyer et al., 2015). A core function of executive control is the ability to adaptively switch to a more optimal behavioral strategy for the task at hand in response to fluctuations in the environment (Corneil et al., 2013). A hub of the executive control network (ECN) is the dorsolateral prefrontal cortex (DLPFC) (Seeley et al., 2007), which provides signals for action and attentional selection to accomplish the goal at hand (Shenhav et al., 2013). The DLPFC communicates with the anterior mid-cingulate cortex (aMCC) – a

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region within the salience network (SN) (Seeley et al., 2007), which also plays a role in the performance of cognitive-interference tasks (Bush et al., 2000; Carter et al., 1998; Kerns et al., 2004). Therefore, we propose that flexibility in ECN-SN cross-network communication between these two hubs helps an individual adaptively prioritize task performance in the face of pain. However, the aMCC also processes pain-related information (Shackman et al., 2011), and its pre-stimulus functional connectivity (FC) with the anterior insula (aIns; another hub of the SN) can encode the threat-related bias towards pain (Wiech et al., 2010). Furthermore, greater task-induced attenuations of pain-related aIns activity occurs in A-type compared to P-type individuals (Seminowicz et al., 2004). Therefore, flexibility in communication between these two hubs of the SN may allow an individual to disengage from task-irrelevant thoughts – such as pain-perception – while maintaining attention to the task-at-hand.

An important but understudied aspect of pain interference is task performance variability, which can reflect inconsistencies in subjects' response times during a task (Kofler et al., 2013). Increased variability in task speed has been observed within individuals following traumatic brain injury (Hetherington et al., 1996) and in attention-deficit-hyperactivity disorder (Kofler et al., 2013). Thus, we additionally investigated the relationship between dynamic functional connectivity (dFC) and intra-subject changes in RT variability due to pain.

To assess brain dynamics of FC, it is critical to understand the signal frequencies that comprise resting-state fMRI data. The relationship between signal frequencies and their physiological meaning remains unclear, and FC studies do not often distinguish activity arising from multiple frequency bands. However, emerging work has shown that the relationship between dynamic signals at rest and behavior is dependent on the specific frequency of the signal. For example, abnormalities in patients with mild cognitive impairment are more pronounced within slow-5 (0.01–0.027 Hz) than within slow-4 (0.027–0.073 Hz) oscillations (Han et al., 2011). Furthermore, there are abnormalities in regional slow-5 oscillations in patients with depression, mania (Martino et al., 2016), and migraine (Hodkinson et al., 2016). Interestingly, patients with migraine can show diminished task performance (Mathur et al., 2015), and can have reduced slow-5 oscillatory power in the middle frontal gyrus (that contains the DLPFC) (Hodkinson et al., 2016). Importantly, inter-individual differences in oscillatory power within a region may underlie its FC with other brain regions (Baliki et al., 2011).

Therefore, the aim of this study was to examine the neural underpinnings underlying individual differences in how pain interferes with the ability to perform a cognitively challenging task quickly and consistently. Towards this goal, our study addressed 3 novel concepts: 1) the effect of pain on task consistency in addition to task speed, 2) the assessment of brain communication variability using the dynamic conditional correlation (DCC) method, and 3) a focus on the slow-5 frequency band. We hypothesized that pain-induced changes of task speed (A-/P-type spectrum) and consistency are related to dFC within slow-5 between the DLPFC and aMCC (key hubs of the ECN and SN respectively), as well as with dFC between the aMCC and aIns (key hubs of the SN). We predicted that individuals with more P-type behavior and greater task inconsistency due to the pain have lower dFC (i.e., less dynamic communication) at rest within slow-5 between the DLPFC and aMCC, as well as between the aMCC and aIns.

Materials and methods

Subjects

Psychophysical and neuroimaging data were acquired from 51 healthy individuals (25 male, 26 female, ages 20–31) (Kucyi et al., 2013), who provided informed written consent to procedures approved by the University Health Network Research Ethics Board. Subjects were excluded if they had contra-indications for neuroimaging, major pain within the past 6 months, using medication other than birth control, or had a history of neurological or psychiatric disorder. Two subjects were excluded from our final analyses due to technical issues with their resting-state fMRI scan.

Numerical interference task

Subjects viewed three separate boxes displayed on a computer screen, with each box containing a different number of digits. The value of the digits ranged from 1 to 9 and were identical within each box but differed across boxes. The goal of the task was to count the number of digits within each box, and report the largest number of digits contained within a single box as quickly and accurately as possible. The numerical values of the digits did not coincide with the number of digits counted in each box, and thus served as the interference to the task. Each subject underwent 8 blocks (24 trials within each block) of testing with alternating no-pain and pain-blocks, with a no-pain block being the first block. Painful transcutaneous electrical nerve stimuli (TENS) was applied to the left median nerve of the subject during each pain block, calibrated to evoke pain rated 4–5/10 (0 = no pain, 10 = most intense pain imaginable) (SI Methods). Due to learning effects in the initial blocks (Fig. S1), the last four blocks — consisting of 2 no-pain and 2 pain blocks —were used in the analysis.

Quantifying performance on the numerical-interference task

Mean and standard deviation of reaction time (RT) distributions can characterize task performance, but trials with long RTs due to normal lapses in attention skew the distributions (right-tailed) (Heathcote et al., 1991). These outliers also inflate the mean and standard deviation measures of task performance (Ratcliff, 1993). An alternative is to model the RT distribution as an ex-Gaussian function, i.e. the convolution of a Gaussian and an exponential function (Ratcliff, 1979). The parameters of the ex-Gaussian distribution include μ and σ, which characterize the mean and standard deviation respectively of the Gaussian component of the distribution, and τ characterizes the exponential component of the distribution containing the long RT outliers (Epstein et al., 2011). To derive the parameters μ, σ, and τ, we first removed inaccurate trials, followed by fitting an ex-Gaussian function using a MATLAB toolbox (Lacouture and Cousineau, 2008) onto each subject's reaction time (RT) distribution for their no-pain and pain blocks separately. As two-blocks (24 trials within each block) of each condition were included, the ex-Gaussian parameters for each condition were derived from a total possible 48 trials (before removing inaccurate trials). To determine that an ex-Gaussian function provided a better fit than a Gaussian function, a Gaussian function was also fit onto each subject's RT distributions for their no-pain and pain blocks for comparison (*SI Methods, Results*). For simplicity, we denote the ex-Gaussian parameters μ and σ as RT mean and variability respectively from this point forward. In addition to the two subjects excluded due to technical issues with their resting-state fMRI scan as mentioned previously, four additional subjects were excluded from our final analyses as two subjects had a high number of inaccurate trials, and two subjects had a $1/x$ rather than an ex-Gaussian RT distribution for their RTs, therefore making it inappropriate to calculate ex-Gaussian parameters for them.

Characterizing pain-induced changes in task performance

To assess the differences in task performance during the presence versus absence of concurrent pain, we subtracted the mean RT during no-pain blocks from that during pain blocks (pain – no pain; ΔRT_{mean}) for each subject. Thus, a negative ΔRT_{mean} denotes A-type behavior and a positive ΔRT_{mean} denotes P-type behavior (Fig. 1A, Table 1). The difference in each subject's RT variability with and without pain was also calculated (pain – no pain; $\Delta RT_{variability}$), with negative and