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The dynamic pain connectome

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Traditionally, studies of how pain and attention modulate one another involved explicit cognitive-state manipulations. However, emerging evidence suggests that spontaneous brain-wide network communication is intrinsically dynamic on multiple timescales, and attentional states are in constant fluctuation. Here, in light of studies on neural mechanisms of spontaneous attentional fluctuations and pain variability, we introduce the concept of a dynamic 'pain connectome' in the brain. We describe how recent progress in our understanding of individual differences in intrinsic attention to pain and neural network dynamics in chronic pain can facilitate development of personalized pain therapies. Furthermore, we emphasize that the dynamics of pain–attention interactions must be accounted for in the contemporary search for a 'neural signature' of the pain connectome.

The need for a new view on pain and the brain

Historical theories of pain are based primarily on nociceptive processes and do not account for interactions with cognitive and attentional processes that are inherently intertwined in the human experience [1]. Pain has a unique attention-demanding quality: it signifies immediate threat to survival and can orient us away from other environmental stimuli, ongoing thoughts, emotions, and ruminations. Given that pain is intrinsically salient (i.e., stands out relative to other stimuli), it can dramatically affect behavior. Conversely, attention-demanding tasks, stimuli, and thoughts can alter the quality and salience of pain and neural processing of nociceptive input. Thus, pain and attention mutually influence one another [2,3].

Traditionally, pain–attention interactions have been studied through explicitly manipulating a subject's attentional state. However, it is now known that neural communication across the whole brain-wide network ('connectome' [4]; see Glossary), including pain- and attention-related circuits, is intrinsically dynamic and spontaneously fluctuates on multiple timescales [4–7]. Additionally, attentional states are increasingly understood as being in constant fluctuation regardless of ongoing task demands and contents of sensory input [8–10]. Therefore, it is timely to consider pain as an intrinsically dynamic experience and process encoded by a 'pain connectome,' the spatiotemporal signature of brain network communication that represents the integration of all cognitive, affective, and sensorimotor aspects of pain. This notion is consistent with the recent characterization of the brain as a 'dynome' [11] or 'chronnectome' [12], emphasizing the role of dynamic communication within and between networks in shaping cognition and behavior. The conceptualization of a dynamic pain connectome in understanding the relation between pain and the brain is a major advance over popular, but problematic notions of a 'pain matrix' (see [13,14] for detailed critiques). Here, we describe neural networks that comprise the pain connectome and mechanisms underlying individual differences in the intrinsic dynamics of acute and chronic pain. These ideas have important clinical implications as well as consequences for recent efforts to identify a neuroimaging-based signature for pain [15].

Pain–attention interactions

Classic examples of attention modulating pain include soldiers battling in war and not noticing their extensive injuries [16], and athletes not aware of an injury while psychologically consumed during an event. Experimentally,

Glossary

A-type pain–attention interactions: an increase in cognitive performance when painful stimuli are applied during an attention-demanding task.
Antinociceptive system: the endogenous control system of the brain that functions to attenuate nociceptive responses and decrease pain.
Ascending pain system: the anatomical pathway that conveys nociceptive input from the peripheral nervous system to neurons in the spinal cord and brain.
Connectome: the full description of anatomical connections in the brain.
Default mode network (and subsystems): a set of highly interconnected brain regions, including the mPFC and PCC/precuneus (core), and at least two subsystems anchored in the medial temporal lobe and dorsomedial prefrontal cortex, respectively.
Dynamic pain connectome: the spatiotemporal signature of brain network communication that represents the integration of all aspects of pain.
Experience sampling: a paradigm in which a subject is intermittently given thought probes to assess their subjective attentional state.
Intrinsic attention to pain (IAP): the general tendency to attend to pain in the absence of any explicit manipulations or active efforts to modify the pain experience.
Multivariate pattern analysis (MVPA): an analysis of the relations among signals from different brain regions that typically involves machine-learning and pattern classification approaches to distinguish different conditions or individuals.
P-type pain–attention interactions: a decrease in cognitive performance when painful stimuli are applied during an attention-demanding task.
Pain rumination: perseverative negative thinking about pain and its possible consequences.

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Keywords: mind wandering; default mode network; salience network; antinociception; brain connectivity; dynamic functional connectivity.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2014.11.006

explicit distraction (or attention to stimuli in nonpain modalities) can decrease stimulus-evoked pain intensity in some humans [17], and can attenuate nociceptive neuronal responses in the brain [18,19]. Conversely, acute and chronic pains can impede cognitive performance for some humans [17,20,21]. Imaging studies have shown that distraction from a painful stimulus attenuates activation of the ascending pain system, including the primary and secondary somatosensory cortex (S1, S2), insula, and mid-cingulate cortex (MCC) [3,22,23]. Interestingly, Tracey *et al.* [24] showed that distraction effects on brainstem activation were associated with individual differences in perceived pain intensity change. Seminowicz *et al.* [21] and Erpelding *et al.* [21,25] showed that some individuals decrease their task reaction times due to pain ('A-type'; attention dominates), whereas others increase their reaction times ('P-type'; pain dominates). These two types of individual show differences in structure and function of pain-related brain networks, in terms of intrinsic organization and in neural responses during distraction from pain [21,25].

Conceptualizing pain as intrinsically dynamic

Studies on pain–attention interactions have provided detailed knowledge about behavioral phenomena and neural mechanisms. However, explicit manipulations have been used in almost all studies that involve pain modulation (e.g., through placebo effects, altered expectations, or instructions to actively suppress and/or enhance pain). Implicit in these designs is the assumption that there is an invariant 'baseline' neurocognitive state during which a 'normal' response to nociceptive input occurs and that this state is altered when a manipulation is introduced. However, an individual's attentional state may wax and wane spontaneously, even in the presence of unchanging nociceptive input. The high prevalence of such fluctuations, their intrinsic nature, and their importance to subjective experiences, such as pain, are exemplified by evidence from studies of spontaneous brain dynamics, the impact of pre-existing brain states on subsequent behavior and perception, and 'mind-wandering' (i.e., attention fluctuating away from the present sensory environment).

Spontaneous brain dynamics

Studies of spontaneous brain activity provide important clues about the nature of attentional fluctuations and how they might impact subjective experiences, such as pain. Such studies commonly involve a 'resting state' paradigm coupled with fMRI, where a subject is awake but is not instructed to do or think about anything in particular. In conventional analyses of resting-state fMRI data, the correlation of signal fluctuations between distinct brain regions is calculated as an index of 'functional connectivity' (FC) to reveal networks of brain regions that have highly synchronous activity [26,27]. This analysis has revealed that brain regions that tend to co-activate with one another during sensory stimulation or task performance also tend to display FC spontaneously [28,29]. Such organized patterns of spontaneous brain network communication are thought to largely reflect intrinsic physiological operations rather than ongoing fluctuations in conscious states or attention [30]. A common pattern of intrinsic network communication (unrelated to ongoing consciousness or behavior) is expressed during all task and/or cognitive states, with task-specific network changes accounting for a small proportion of FC patterns [31,32].

FC is typically evaluated as inter-regional correlations across 5–10-min scans. However, FC fluctuations can occur on shorter timescales that might reflect, in part, the dynamics of attentional states. Electrophysiological studies have shown synchronous spontaneous temporal fluctuations between brain regions on the order of seconds [33]. Simulations of human resting-state networks suggest that a 'dynamical repertoire' of brain states, constrained in part by anatomical connectivity patterns, is constantly changing on short timescales [34]. Indeed, empirical work shows that human resting-state FC can fluctuate on the order of tens of seconds [35–37] (Box 1). Dynamic fluctuations in spontaneous FC have been observed within and between brain networks, including those relevant to pain and attention [38,39]. Although some of these fluctuations may represent attentional shifts, network FC dynamically changes in anesthetized animals in a similar fashion as in the awake state [36,40], so intrinsic and/or unconscious operations must contribute. A greater dynamic range of network activity, or greater brain entropy, could in part reflect increased adaptability and/or flexibility, or efficiency [41].

Pre-existing brain states influence perception and behavior

Spontaneous brain activity that is undisturbed by stimuli or tasks can be studied through resting-state fMRI. However, in the absence of cognitive or behavioral measures,

Box 1. Dynamic functional connectivity

Resting-state FC is typically evaluated as inter-regional correlations across fMRI scans that typically last about 5–10 min, assuming temporal stationarity. A new approach of 'dynamic FC' evaluates resting-state FC fluctuations on the order of tens of seconds using a sliding time-window analysis [6]. These analyses suggest that (anti)correlations of a given pair of brain regions wax and wane over time [35–37]. There is support for an electrophysiological basis of dynamic fMRI FC [114], but the underlying neural processes remain poorly understood.

Dynamic FC studies have shown that specific transient network states recur frequently throughout scans and reproducibly across subjects [39], suggesting that spontaneous brain activity contains a 'dynamic repertoire' of states that are commonly revisited [6]. Notably, analyses of anesthetized monkeys and rats have revealed similar FC fluctuations across sliding time windows within fMRI scans [36,40], so it is unlikely that time-varying FC can be explained purely by changes in a subject's vigilance or ongoing cognition. However, because a subject's self-initiated cognitive state can be decoded with significant accuracy from whole-brain fMRI FC patterns within short time windows (e.g., 30 s) [115], dynamic FC likely reflects both intrinsic properties of brain organization unrelated to a subject's current cognitive state as well as spontaneous cognitive processes.

To integrate interindividual differences, we introduced the standard deviation of a sliding window correlation time series to represent a subject's FC variability related to pain and attention [65,116]. Clustering analyses can also be used to reveal repeating FC states, and metrics can subsequently be calculated to determine the frequency of occurrence for specific states [39]. Clinical populations, including Alzheimer's disease [117], multiple sclerosis [118], post-traumatic stress disorder [119], and schizophrenia [120], show abnormal dynamic FC.