Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks

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Human minds often wander away from their immediate sensory environment. It remains unknown whether such mind wandering is unsystematic or whether it lawfully relates to an individual’s tendency to attend to salient stimuli such as pain and their associated brain structure/function. Studies of pain–cognition interactions typically examine explicit manipulation of attention rather than spontaneous mind wandering. Here we sought to better represent natural fluctuations in pain in daily life, so we assessed behavioral and neural aspects of spontaneous disengagement of attention from pain. We found that an individual’s tendency to attend to pain related to the disruptive effect of pain on his or her cognitive task performance. Next, we linked behavioral findings to neural networks with strikingly convergent evidence from functional magnetic resonance imaging during pain coupled with thought probes of mind wandering, dynamic resting state activity fluctuations, and diffusion MRI. We found that (i) pain-induced default mode network (DMN) deactivations were attenuated during mind wandering away from pain; (ii) functional connectivity fluctuations between the DMN and periaqueductal gray (PAG) dynamically tracked spontaneous attention away from pain; and (iii) across individuals, stronger PAG–DMN structural connectivity and more dynamic resting state PAG–DMN functional connectivity were associated with the tendency to mind wander away from pain. These data demonstrate that individual tendencies to mind wander away from pain, in the absence of explicit manipulation, are subsumed by functional and structural connectivity within and between default mode and antinociceptive descending modulation networks.

Significance

The mind easily wanders away from mundane tasks, but pain is presumed to automatically capture attention. We demonstrate that individuals differ in how often their minds spontaneously wander away from pain and that these differences are associated with the disruptive effect of pain on cognitive performance. Brain–behavior relationships underscore these individual differences. When people’s minds wander away from pain, there are increased activations of the default mode network (DMN) and strong interactions between the DMN and periaqueductal gray (PAG), an opiate-rich region mediating pain suppression. Individuals with greater tendencies to mind wander from pain have stronger anatomical links and dynamic functional communication between PAG and DMN. These findings provide clinically important clues about why some individuals cannot disengage from pain.
Results

Unique Protocol to Evaluate Mind Wandering Away from Pain. Subject testing was carried out in two sessions. In session 1, subjects completed experience sampling and cognitive interference tasks including epochs of painful transcutaneous electrical nerve stimulation (TENS) of the left median nerve (Methods). In session 2, subjects completed experience sampling during fMRI, DWI, and resting state fMRI scans.

For the experience sampling task, the TENS level was maintained to consistently elicit pain intensity rated as 4–5 out of 10. Participants were instructed to avoid actively attending either toward or away from pain (SI Methods). On each trial, participants viewed a fixation cross while receiving painful TENS which was interrupted after 20 s with a thought probe in which subjects indicated whether their attention had just been “only on pain,” “mostly on pain,” “mostly on something else,” or “on only something else” (Fig. 1A). An IAP score was calculated for each subject based on the proportions of trials in the task with reports of attention to pain vs. attention to something else and could range from +2 (always attending to pain) to −2 (always attending to something else) (Methods). At the end of trials, participants were asked to rate the degree to which their reports of “something else” belonged to the categories of external sensory distractions (EDs) (e.g., auditory/visual events), task-related interferences (TRIs) (e.g., considering response to upcoming probe), or mind wandering (MW) (i.e., thoughts completely unrelated to present environment) (19).

The cognitive interference task was one we used previously (22) to characterize the degree to which individuals prioritize cognitive task performance versus pain (Fig. 2A). The difference between mean reaction time (RT) across pain vs. no-pain trials was used to quantify the effect of pain on performance as done previously (22). Subjects were classified as P type if their RTs were slower during concomitant pain compared with “no pain” trials (i.e., pain dominates) or A type if they had faster RTs during concomitant pain (i.e., attention dominates).

Behavioral Results. The IAP scores for sessions 1 and 2 ranged from, respectively, −1.1 to +1.9 (mean ± SD = 0.17 ± 0.67) and −1.3 to +1.6 (mean ± SD = 0.01 ± 0.68). Individual subjects showed marked fluctuations in their attention to pain from trial to trial (e.g., Fig. 1A) but did so with remarkably consistent frequency between the two sessions (see below). The group data indicate an almost equal split of trials in which subjects were experiencing “only or mostly something else” in the experience was “only or mostly something else” (Fig. 1B): trials were rated as “only pain” (session 1: 13.8%; session 2: 11.0%), “mostly pain” (session 1: 41.4%; session 2: 39.3%), “mostly something else” (session 1: 38.1%; session 2: 39.4%), or “only something else” (session 1: 6.7%; session 2: 10.3%) (Fig. 1B). There was a strong, significant intraclass correlation (ICC) between IAP scores during session 1 vs. session 2 (ICC = 0.83; P = 4.7 × 10⁻¹⁰ (Fig. 1D), suggesting that IAP is a trait-like quality.

Participants reported that they were confident in their abilities to accurately indicate attentional state during the task (average confidence rating ± SD out of 7 = 5.7 ± 0.82; 1 indicates not confident at all, and 7 indicates very confident). Participants rated the degree to which their reports of Something Else belonged to the categories of EDs, TRIs, and MW (Likert scale: 1 indicates never, 7 indicates always) as follows: EDs (session 1: 2.6 ± 1.63; session 2: 3.8 ± 1.61), TRIs (session 1: 3.9 ± 1.60; session 2: 3.5 ± 1.15), and MW (session 1: 4.8 ± 1.58; session 2: 4.1 ± 1.52) (Fig. 1C).

Correlations between session 1 and session 2 of the frequencies of categories that prompted Something Else reports also revealed significant positive correspondence (EDs: Spearman’s ρ = 0.44, P = 0.002; TRIs: ρ = 0.39, P = 0.005; MW: ρ = 0.61, P = 2 × 10⁻⁶) (Table S1). This suggests that the sensory/cognitive contents of attentional fluctuations away from pain were also stable within individuals. The correspondences between rating categories were as follows: EDs vs. TRIs (session 1: ρ = 0.28, P = 0.051; session 2: ρ = 0.33, P = 0.018), EDs vs. MW (session 1: ρ = −0.29, P = 0.037; session 2: ρ = −0.41, P = 0.003), and TRIs vs. MW (session 1: ρ = −0.65, P = 2.7 × 10⁻³; session 2: ρ = −0.22, P = 0.13). Therefore, participants who were high in MW generally tended to be low in TRIs and EDs.

We next tested whether individual factors impact IAP and found a modest trend toward a positive correlation between IAP and pain catastrophizing scale (PCS) scores (r = 0.30; P = 0.03; not significant after Bonferroni correction) (Fig. 1E). There was no correlation between IAP and daydreaming frequency scale (DDF) scores (r = −0.085; P = 0.55), indicating that the tendency to attend away from pain is unrelated to the tendency to daydream in general.

Finally, we tested our hypothesis that individuals who frequently reported that they attended to pain during experience sampling would be more likely to show A-type behavior (i.e., slower RTs during pain), whereas those who frequently attended away from pain would be more likely to show A-type behavior (i.e., faster RTs during pain). We found a significant positive correlation (r = 0.42, P = 0.003) between mean RT across pain...
vs. no-pain trials and IAP that supported this hypothesis and provided behavioral validation for the experience sampling task (Fig. 2B). There was no correlation between mean RT across pain vs. no-pain trials and PCS (r = 0.086; P = 0.55).

**Neural Correlates of Ongoing Fluctuations in Attention to Pain.** We next analyzed trial-to-trial brain activity fluctuations occurring during experience sampling with fMRI. When subjects reported attention to pain, activations occurred in regions previously reported as being pain- and salience-related (e.g., insula, MCC, thalamus, contralateral primary somatosensory cortex and secondary somatosensory cortex, and temporoparietal junction (TPJ)) (23–25), and deactivations occurred in nodes of the DMN (medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus, and temporooccipital junction (TOJ)) (23). Crucially, Pain compared with Something Else trials were associated with greater activation of a predominantly right-lateralized network (e.g., right TPJ/S2, right IFG, right dorsolateral prefrontal cortex, and bilateral insula), including regions that are consistent with previous definitions of the “ventral attention” and “salience” networks (26–28) (Fig. 3A; full list in Table S2). Something Else compared with Pain trials were associated with greater activation of the DMN (e.g., mPFC, PCC/precuneus, lateral parietal areas, and medial temporal lobe) and regions implicated in executive control (superior parietal lobule, superior/middle frontal gyrus, and supplementary motor area) (Fig. 3B; full list in Table S5).

Given the purported role of the DMN in MW and our observed anticorrelations of MW with EDs and TRIs, we next tested whether functional differences in the change of activation within the DMN core (mPFC and PCC/precuneus) (18) between Something Else compared with Pain trials (Δ DMN activation (Else > Pain)) related to MW or other fluctuations from pain. For EDs, TRIs, and MW, respectively, there was a significant negative correlation (r = −0.61, P = 0.0002), no significant correlation (r = −0.24, P = 0.19), and a significant positive correlation (r = 0.45, P = 0.011) with Δ DMN activation (Else > Pain) (Fig. 4). Therefore, individuals distracted because of EDs were unlikely to engage the DMN, whereas high-MW individuals were likely to engage the DMN when their attention fluctuated away from pain.

**Functional Coupling Between PAG and DMN.** We next tested whether activity in the descending pain modulatory system interacts with attention networks, potentially to suppress ascending nociceptive input during attentional fluctuations away from pain. To do this, we used psychophysiological interaction analysis (PPI) (29) to determine whether functional connectivity of the descending pain modulatory system related to attention toward vs. away from pain. We focused on the PAG because it has a high concentration of opiate-containing neurons with descending projections (30) and has functional interactions with the cingulate/prefrontal cortex implicated in cognitive modulation of pain (5, 7).

During Something Else compared with Pain trials, we found enhanced functional coupling of the PAG with DMN regions (mPFC, PCC/precuneus/retrosplenial cortex, and medial temporal lobe) and left middle frontal gyrus (Fig. S4; full list in Table S6). No regions had significantly greater PAG functional connectivity for periods associated with attention to vs. away from pain. However, PPI analysis for a PCC seed revealed several regions (angular gyrus, inferior/middle temporal gyri, lingual gyrus, and cerebellar regions) with greater functional connectivity for attention toward compared with away from pain (Fig. S2).

**Structural Connectivity Between PAG and mPFC.** White matter connections have been identified between the mPFC and PAG in humans (31, 32). Thus, our finding of increased PAG–DMN functional coupling within individuals during attentional fluctuations away from pain raises the possibility that individuals with stronger PAG–DMN anatomical connections more easily disengage attention from pain. We therefore tested the hypothesis that there is stronger structural connectivity in the mPFC–PAG pathway in individuals who tend to attend away from pain than in individuals who have greater IAP.

To evaluate structural connectivity, we first used probabilistic tractography (33) to define the pathway between the PAG and the mPFC region that was identified in our PPI analysis (Fig. 5). We then applied tract-based spatial statistics (34) to calculate mean fractional anisotropy (FA) in the mPFC–PAG white matter “skeleton” pathway. We found a significant negative correlation between mPFC–PAG tract FA and IAP score (r = −0.36, P = 0.009), supporting the hypothesis that individuals who frequently attend away from pain have stronger descending structural connections between PAG and the mPFC. Finally, we tested whether PAG connectivity to the DMN core predicted functional connectivity to the PAG. First, we defined the PAG connectivity mask using a significant negative correlation (r = −0.6, P < 0.001) between PAG activity and IAP (a measure of MW). There was a positive correlation between PAG–DMN connectivity and PAG–mPFC connectivity (Spearman’s ρ = 0.67, P = 0.007), indicating that PAG–mPFC connectivity is related to functional connectivity within the PAG–DMN network.
connections between mPFC and PAG (Fig. 5B). This link was even stronger when controlling for PCS score and sex ($r = 0.45, P = 0.001$).

**Dynamic mPFC–PAG Resting State Functional Connectivity.** We further probed the involvement of mPFC–PAG communication in IAP using static and dynamic “resting state” functional connectivity (FC) analysis. We found that IAP was not significantly associated with mPFC–PAG FC strength based on correlated signals over the course of a ~9 min resting state scan (i.e., static FC) ($r = 0.064, P = 0.655$). However, this conventional analysis of static FC does not capture dynamic FC fluctuations on shorter time scales (35) that may better reflect an individual’s capacity for flexible FC and/or spontaneous changes in vigilance/attention (36) related to the tendency to spontaneously disengage attention away from pain. We therefore applied a unique analysis of a metric to quantify the FC variability (FCV) as the SD of FC fluctuations over the course of a 254 sliding time windows (40 s each) in the resting state scan. Dynamic FC analysis revealed a significant negative correlation between mPFC–PAG FCV and IAP ($r = -0.32, P = 0.023$) (Fig. 6), suggesting that individuals with more dynamic/flexible mPFC–PAG FC spontaneously disengage attention from pain more frequently than those with stable mPFC–PAG FC. This correlation remained significant when controlling for PCS score and sex ($r = -0.31, P = 0.029$), overall mPFC–PAG FC strength ($r = -0.31, P = 0.027$), and mPFC–PAG tract FA ($r = -0.28, P = 0.047$).

**Discussion**

These data demonstrate that routine, spontaneous disengagement of attention to pain (i.e., mind wandering) occurs consistently within an individual but varies considerably across individuals in concert with the effect of pain on their individual cognitive task performance. Furthermore, we show that these behavioral and perceptual outcomes are linked with function and structure of pain- and attention-related brain networks. Crucially, we reveal a key role of the antinociceptive system in both intra-individual and inter-individual variability in spontaneous attentional fluctuations away from pain. These data support the notion that cognitive modulation of pain is an ongoing, intrinsically dynamic process that can occur without explicit manipulation.

Mind wandering has been defined as a state of “perceptual decoupling,” or disengagement of attention from perception (37). Our study describes the relationship between mind wandering and perceptual decoupling from pain. Pain is inherently salient compared with other sensory modalities, so diverting attention away from it likely requires a different or more robust mechanism than those previously identified. Our finding of increased functional connectivity between the DMN and PAG during attention away from pain could represent such a mechanism. The mPFC and retrosplenial cortex, identified here as DMN regions with enhanced PAG functional connectivity during attentional disengagement from pain, both have efferent connections to the PAG identified in monkeys (38, 39). Our finding of a negative correlation between FA in the descending mPFC–PAG pathway and IAP directly implicates this connection in perceptual decoupling of pain. The PAG sends antinociceptive signals to the rostral ventromedial medulla, which projects to the spinal cord dorsal horn to inhibit incoming nociceptive information (30). fMRI studies suggest that explicit cognitive manipulation of pain engages this pathway (4, 7, 9, 10). Furthermore, the pain-modulatory action of this pathway during placebo manipulations and attentional tasks is inhibited when opioid activity is blocked (4, 7). We therefore propose that during pain, interactions between the DMN and descending pain modulatory system fluctuate continuously, reflecting cognitive modulation that results in neural activity underlying perceptual decoupling of pain. In the absence of pain, structural and dynamic functional connectivity between the antinociceptive system and DMN may maintain an individual’s predisposition for spontaneously attending toward/away from pain.

For nonpain modalities, neural activity for perceptual decoupling has been associated with increased DMN and executive control network activation and decreased activation in sensory cortices (37). DMN activation has been linked to mind wandering/internal mentation in experience sampling studies (17, 19, 21). Our results reveal a similar role of the DMN in the context of pain. Notably, the role of the DMN in pain perception has remained under debate. Deactivations of the DMN during pain were reported in early imaging studies (40, 41), but recent studies suggest a more nuanced view in which the DMN responds non-linearly or even activates during pain (42, 43). In any pain study, attention likely fluctuates on a trial-to-trial basis variably in different individuals. Our findings indicate that DMN activity levels are virtually at baseline level when attention fluctuates away from pain. Thus, analysis of averaged responses within and/or between individuals would not adequately delineate the effect of pain on DMN activity. Our findings of trial-to-trial variability in pain-evoked DMN activity suggest that DMN activity varies...
with ongoing nociceptive input in chronic pain to determine the course of pain-related structural brain reorganization and disease prognosis. Supporting this notion are findings of aberrant DMN function in chronic pain disorders (47, 48). Of particular note, longitudinal studies point to a potential causal role of DMN–insula interactions in pain reduction in fibromyalgia (49) and of mPFC–nucleus accumbens interactions in the transition from subacute to chronic back pain (50). Long-term changes in DMN communication with other brain systems are likely mediated by attention to pain in daily life, involving fluctuations in neural activity identified here. Thus, further study of intrinsic attention to pain could provide critical insight into behavioral and neural mechanisms underlying individual differences in recovery from chronic pain.

Methods

General Procedures. Fifty-one healthy right-handed adults (26 female, 25 male; mean age ± SD = 25.02 ± 2.68) provided informed consent to procedures approved by the University Health Network Research Ethics Board. TENS was used to stimulate the median nerve of the left forearm. A stimulation level that evoked a pain rating of 4–5 out of 10 (0 indicates no pain; 10 indicates the most intense pain imaginable) was used during performing an experience sampling and a cognitive interference task on day 1 (described below). Participants returned on day 2 for neuroimaging with a 3 T GE MRI. Scans included one run of resting state fMRI followed by four runs of fMRI with the experience sampling task and DWI (SI Methods).

Experience Sampling and Cognitive Interference Tasks. During both psychophysics and imaging (fMRI) sessions, an experience sampling task was performed. The participant received instructions to minimize active efforts to attend toward or away from pain (SI Methods). Each trial consisted of painful TENS that was interrupted after 20 s with an attentional state probe displayed for 8 s, followed by a 22-s interstimulus interval (Fig. 1). Participants fixated on a white cross on a black background throughout. During the attentional state probe, the screen displayed, “At the end of this last trial, to what degree were your thoughts/feelings about pain or something else?” The participant indicated with a button press one of four possible responses (only pain, mostly pain, mostly something else, or only something else). Each run began with a 30-s fixation period followed by 10 repeated trials. After all runs in session 1, the participant rated how confident he or she were in his or her ability to accurately indicate attentional state during the task (Likert scale: 1 indicates not confident at all; 7 indicates very confident). After all runs in sessions 1 and 2, participants were asked to classify (Likert scale: 1 indicates never; 7 indicates always) the frequency with which their reports of something else related to each of three categories (18): (i) EDs, (ii) TTRs, and (iii) MW. A cognitive interference task (“number task”) was performed with and without concomitant painful TENS during the psychophysiology session (Fig. 2) as done previously (22) (SI Methods).

Behavioral Analysis. For the experience sampling task, an IAP score was calculated for each participant for sessions 1 and 2 separately, with the following formula:

\[ IAP = \left( \frac{2n_{\text{only pain}} + n_{\text{mostly pain}}}{} - \left(2n_{\text{only else}} + n_{\text{mostly else}}\right) \right) / n_{\text{total}}, \]

where \( n \) is number of trials.

The maximum and minimum scores (2 and 2) correspond to only pain and only something else reports on every trial, respectively. A two-way mixed intraclass correlation coefficient (absolute agreement) was calculated for session 1 vs. session 2 scores to evaluate the trait-like quality of IAP. The inter-session consistency of ratings for EDs, TTRs, and MW and correlations between these categories were evaluated with Spearman’s \( \rho \) because session 1 values for EDs, TTRs, and MW and session 2 values for TTRs and MW were not normally distributed (Shapiro–Wilk and Kolmogorov–Smirnov, \( P < 0.05 \)). Pearson’s correlation coefficient was calculated between IAP (session 1) and both PCS and DDF scores (results were Bonferroni-corrected for two comparisons). Cognitive interference task mean reaction times and performance accuracies

Fig. 6. Dynamic resting state functional connectivity between the PAG and mPFC relates to individual differences in IAP. (A) Single-subject example of PAG and mPFC signals during a resting state scan (Upper) and fluctuations in functional connectivity between PAG and mPFC across 40-s sliding windows (each window progressively sliding every 2 s) (Lower). (B) Group-level significant negative correlation between IAP and mPFC–PAG functional connectivity variability (SD of correlation values across sliding time windows) \((r = -0.32, P = 0.023)\).
FMRI B Software Library (FSL v5.0), MATLAB v7.12.0, fMRISTAT (51), and statistical package for the social sciences (SPSS v21.0) (IBM Corp.). Contrasts were performed using identical activation/deactivation during stimulation before pain and else reports as well as pain > else and else > pain differences (SI Methods). Group-level analysis was performed with FMRI B’s local analysis of mixed effects (FLAME) 1 + 2 (whole-brain family-wise error (FWE)-corrected Z > 2.3; cluster P < 0.05).

We performed a PPI analysis (29) with a seed region defined in the PAG as was done previously (7) (SI Methods). Contrasts were performed between two interaction parameters (PAG time course × stimulation before pain reports and PAG time course × stimulation before else reports) to identify regions with pain > else and else > pain functional connectivity (FLAME 1 + 2 thresholding: whole-brain FWE-corrected Z > 2.3; cluster P < 0.05).

Diffusion MRI Analysis. Probabilistic tractography was used to define the mPFC–PAG pathway for analysis with tract-based spatial statistics (TBSS) in all 51 participants (SI Methods). A white matter skeleton obtained from TBSS was masked with the PAG–mPFC pathway derived from probabilistic tractography. Pearson’s correlation coefficient was then calculated between mean PAG–mPFC pathway FA values and IAP (session 1) scores.

Resting State fMRI Analysis. Mean time series across voxels were calculated from preprocessed data (SI Methods) within PAG and within mPFC. Overall FC strength was calculated using Fisher-transformed correlation between PAG and mPFC mean time series. For dynamic FC analysis, both time series were split into 40-s sliding time windows, with each window shifted 2 s forward from the previous window (i.e., 1 volume [i.e., 1 TR (repetition time)]). Fisher-transformed correlations between PAG and mPFC within each of the 254 obtained windows were then computed, and FCV was calculated as the SD of these correlation values. Pearson’s correlation coefficient was then calculated for PAG–mPFC FC and FC vs. IAP (session 1) scores (data were normally distributed). To test the effect of sliding window duration on the correlation between FCV and IAP, we reid the FCV analysis using 30-, 50-, and 60-s windows and demonstrated converging results (Table S8).

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