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Narrative Review

The default mode of chronic pain: What does it mean and how should we frame it to our patients?

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The brain can be organized into defined networks based on the coherent activity fluctuations between certain regions at rest when no external task or stimuli are applied. In patients with chronic pain, alterations in the way these networks act and interact become apparent, especially within the default mode network (DMN) and in the way it functionally interacts with the salience network (SN). However, the implications of these cortical alterations remain speculative, and a clear framework for how we might explain the meaning of them to the patient with chronic pain is lacking. Therefore, here we provide an up-to-date theoretical model for the implications of the DMN alterations observed in the state of chronic pain, and how to integrate the key points of this model into an explanatory framework to use in the clinical meeting with chronic pain patients (e.g., during pain neuroscience education).

Keywords: *Default mode network, Salience network, Chronic pain, Pain neuroscience education, Attention, Threat appraisal.*

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1. Introduction

The essential role of the brain in the experience of pain is well established (1, 2). However, when pain persists, structural and functional changes within the brain become apparent (3), which have been associated with both the clinical pain state (4) as well as cognitive and emotional components related to the pain experience (5). Cortical changes with implications for pain may include a variety of events. However, a specific area of interest within chronic pain research has been the altered behaviour observed between within and between regions of the brain which at rest, when no external stimuli is applied, exihibit a coherent activation or deactivation, that is, resting-state networks (6). There are multiple resting-state networks (e.g., (7–9)); however, the one which may have gained the most attention in the context of chronic pain, and which has been found to display greater abnormalities in chronic pain patients compared with other resting-state networks (10,11), is the so-called default mode network (DMN). The DMN is believed to be important for interoception related to one's self, that is, self-generated thoughts (12) such as mind-wandering. Multiple models have been presented suggesting how the interaction between the DMN and other resting-state networks may shape the experience of pain, and how abnormalities in within- and cross-network communication may contribute to the state of chronic pain patients compared to pain-free, healthy individuals (13–15). However, the review has focused specifically on DMN within the context of chronic pain. Furthermore, although there are suggestions within the papers of the existing models for how we may implement the current knowledge of resting-state networks into the treatment of patients with chronic pain (13, 14), a framework for how this knowledge can be explained to the patient with chronic pain is lacking. Hence, the current work aims to present an up-to-date view of the role of the DMN in the state of chronic pain, and how it may be conceptualized to the patient with chronic pain.

1.1. An overview of the default mode network

The DMN is roughly centered around the ventral and dorsal aspect of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and adjacent precuneus, lateral parietal cortex (LPC), inferior parietal lobule (IPL), and hippocampal formation (HF) (7, 16, 17). Unlike other resting-state cortical networks, the regions within the DMN exhibit significant activation during rest in the absence of tasks or events that require externally directed, non-self-referential attention, whereas consistent deactivation is observed when external attention is required (7, 16). Since the serendipitous discovery of this cortical, resting-state network, extensive work has been performed to unravel the functional role of its distinct activation/deactivation pattern. One of the major discoveries is probably the increased engagement of the DMN during interoception related to one's self, i.e., self-generated thoughts (12), such as mind-wandering (18), as well as self-referential judgments and mental imagery related to one's present and future (19). The role of the DMN during specific self-referential cognition has also revealed the presence of at least two subnetworks within the DMN itself (19, 20). However, all subnetworks seem to converge into mPFC and PCC, which have thus been considered core hubs of the DMN (19, 20).

1.2. The default mode network in a healthy pain system

As pain is a self-oriented experience, one may assume that the presence of pain would increase the activity within the DMN. However, in healthy pain-free individuals, significant deactivation within regions of the DMN has been observed upon experimental pain stimulation (21–26), as well as a reduced within-network functional connectivity (FC) (25, 27) (i.e., correlational strength between distinct brain regions (6)). Rather, painful stimulation in healthy individuals is consistently associated with an increased activity in regions within another resting-state network centered around the anterior insula and anterior cingulate cortex (ACC) (2, 26), commonly referred to as the salience network (SN) (8, 28). The SN receives and responds to internal and external stimuli, of both positive and negative valence (29), which are deemed as personally "salient" (8, 28), with the term salient referring to the most homeostatically relevant at a given moment in time (8, 28). Together with the dorsal attention network, that is, a network involved in directed attention and working memory (9), the SN forms a larger task-positive network, which shows distinct anti-correlation with the DMN, which is rather deemed task-negative. This means that the activation within the task-positive network (including the SN) is accompanied by a proportional deactivation of the task-negative DMN (30, 31), and this relational property has also been displayed in response to experimental pain in healthy individuals (26). Thus, alongside the notion that pain is a highly salient and attention-demanding experience (32), the simultaneous deactivation of the DMN and increased activation within the SN (as a part of the bigger task-positive network) during painful events have been proposed to reflect a redirection of the person's attention to the pain, serving to promote further protective behaviors (13).

1.3. The default mode network in an unhealthy pain system

In patients with chronic pain, a great number of studies report an altered resting-state FC between regions of the DMN and SN (10, 11, 33–37), as well as between regions within the DMN itself (10, 11, 27, 34, 35, 38, 39). However, recent evidence suggests that the altered cortical patterns observed among chronic pain patients may reflect the presence of the pain itself, rather than the state of chronic pain *per se* (27, 33). Specifically, Čeko *et al.* (33) reported a significantly increased FC between the DMN and insula in patients with fibromyalgia compared with healthy controls only if the patients were experiencing pain during the brain-scanning procedure, whereas no differences were observed if the patients were pain-free during the time of the scan (33). Another study on the same topic of interest, conducted by Alshelh *et al.* (27), compared the cortical response of patients with chronic orofacial pain with that of healthy controls who were first pain-free during the brain scan, but then experienced an experimental pain induced via continuous infusion of hypertonic saline. Similar to the results by Čeko and colleagues, significant differences between patients and controls (i.e., reduced within-DMN FC) were present only when the control subjects were not experiencing pain during the scan, whereas no differences were observed when both groups experienced pain (27). Collectively, these results indeed support the notion of a pain-induced rather than chronic pain-induced altered behavior of the DMN. However, contradictory to this theoretical assumption, Alhajri *et al.* (25) recently found that both short (1 hr) and prolonged (24 hr) capsaicin-induced pain in healthy volunteers resulted in an equally reduced within DMN FC (i.e., no significant difference between the two time-points), but that only the FC pattern at the 1-hr time point was associated with pain intensity (25). Furthermore, acute modulation of the pain intensity at the 24-hr time point by the application of pain-relieving cold and pain-enhancing heat did not further alter within-DMN FC, despite significant increases and reductions in pain intensity, respectively (25). These results rather suggest that, although similar connectivity alterations may be observed in patients with chronic pain and healthy controls when controlling for the presence of pain, their functional properties may differ. Moreover, and in further support that the aberrant FC patterns observed in chronic pain patients may not solely rely on the presence of pain, differences across studies in the direction of the FC alterations are evident. Because, although the majority of studies report a reduced within-DMN FC in chronic pain patients compared to healthy controls (e.g., (10, 11, 27, 34, 38)), there are also studies reporting an increased FC (35, 39, 40), and such increases have not yet been observed in healthy individuals exposed to experimental pain (25, 27). Accordingly, of the two available studies in which the impact of clinical pain exacerbation via individually tailored, physical maneuvers was tested, one found an increased within-DMN FC (41), whereas a reduced FC was observed upon pain exacerbation in the other (35). In contrast, the cross-network FC between the DMN and SN was consistently increased upon pain exacerbation in both studies (35, 41), which suggests that there may be more to the aberrant FC observed in chronic pain patients than simply the presence of the pain itself.

Altogether, it remains controversial whether chronic pain disrupts the integrity of the DMN, or if the aberrant cortical behavior observed is reflective of a natural (homeostatic) response to pain. However, it is evident that the presence of pain, whether acute or chronic, alters the behavior of the DMN, and thus, we will in the following sections try to delineate the possible implications of such DMN alterations for the patient with chronic pain.

1.4. Attentional relocation

As described previously, the DMN has been found to work in opposition to the task-positive network (including the SN) involved in external attention (30, 31). Intriguingly, an increased FC between the insular cortex of the SN and the core regions within the DMN has repeatedly been reported in chronic pain patients when compared to healthy controls (10, 11, 33, 35–37), and the anterior insula has previously been demonstrated to serve a critical function in the relocation of attentional resources in the presence of salient events, including the suppression of DMN activation (42–44). In accordance, healthy individuals directing their attention toward a painful stimulus (i.e., a salient event) have been found to exhibit a reduced DMN activity but a significant increase in SN activation, whereas attending away from pain rather increased DMN activity and attenuated SN activation (24). However, in patients with chronic pain, there are reports of an attenuation of the typical anti-correlation between the DMN and SN (10, 34, 41), and a significant association between increased within DMN-connectivity and high levels of pain rumination (i.e., preservative negative thinking about pain (45)) have been found (40). Moreover, whereas healthy, pain-free individuals exhibit an enhanced deactivation of the DMN when exposed to painful stimuli while performing a cognitive attention-demanding task (21), patients with chronic pain rather display a reduced deactivation compared to healthy controls (46–48). Thus, one possible implication of the DMN disruptions observed in chronic pain patients may be an impaired ability to coordinate the dynamic relocation of attentional resources in the presence of salient events.

1.5. Affective appraisal of threat versus safety

Interestingly, a similar anti-correlation as observed between the DMN and task-positive network acquired during attentional relocation has also been found between region clusters of the brain related to anticipatory fear/threat and safety in healthy individuals (49). Early reports show that the pre-stimulus activation of the anterior insula within the SN can predict if the subsequent stimulation is perceived as painful or not (50, 51), and it has later been confirmed that the anterior insula is also highly involved during general anticipatory fear/threat (52, 53). This assumption holds true regardless if the fear appraisal is instructed, that is, information about the (aversive) outcome of a stimulus is provided before its delivery (52), or conditioned (53), that is, a previously neutral stimulus is paired with an aversive stimulus via repeated exposure (54).

Intriguingly, a comprehensive meta-analysis of brain imaging studies found that fear appraisal is not only signified by activation of the insula (among other regions) but also a significant deactivation of the majority of areas within the DMN (53). Later, Marstaller *et al.* (49) expanded on this intriguing finding by exploring the behavior of the brain in response to both learning, appraisal, and extinction of fear- and safety-related cues, with extinction referring to the process where a previous fear-conditioned stimulus is re-paired with a non-aversive stimulus (i.e., a safe stimulus) (54). Unsurprisingly, Marstaller and colleagues found an evident SN activation during fear appraisal, which became more pronounced as the fear appraisal was learned. However, they did also find a predominant activation of the DMN during safety appraisal, as well as a significant DMN activation upon fear extinction, which also became stronger as learning was improved (49). The findings of these studies suggest that the independent and/or interacting behavior of the DMN and SN may be involved in the appraisal of threat versus the safety of an upcoming event, which is of high relevance to the state of chronic pain as the pain itself, by definition, reflects the experience associated with actual or potential tissue damage (55).

1.5.1. The role of the medial prefrontal cortex in the appraisal of threat versus safety

It is important to note that the significant involvement of the mPFC in the threat versus safety appraisal is not coherently similar within the subregions of this cortical region. The mPFC is, as previously noted, considered a key hub within the DMN (19, 20), and interestingly, it is involved in the vast majority of studies where an aberrant within-DMN and/or DMN-SN FC has been observed (10, 11, 27, 34–36, 39–41). However, it is roughly separated into a dorsal (dmPFC) and ventral (vmPFC) region, which have been implicated to display opposing functional properties in the appraisal of fear/threat and safety (54). Accordingly, the significant conditioned threat-related deactivations and safety-related activations observed within several areas of the DMN have been found to involve the vmPFC, but not the dmPFC (49, 53). In contrast, although seemingly uninvolved in the appraisal of conditioned threat/fear (49, 53), activation of the dmPFC has been implicated in the appraisal of instructed fear/threat, alongside core regions of the SN (i.e., the anterior insula and ACC) (52). These data suggest distinct functional properties of the dorsal and ventral aspect of the mPFC with regards to threat/fear versus safety appraisal, which might explain some of the variety in within-DMN FC observed across studies in chronic pain patients (reduced FC: e.g., (10, 11, 27, 34, 38) versus increased FC: e.g., (35, 39, 40)).

Intriguingly, and specific to the context of pain, the vmPFC is consistently activated during placebo analgesia (56, 57), that is, the reduction in pain experienced in response to an inert treatment (56, 58), and an increased anticipatory activation within the vmPFC before a painful stimulus has been shown to predict the magnitude of the subsequent placebo analgesia (59). Furthermore, a study in which the participants could receive either a painful thermal stimulus or no stimulus found that the activity within the vmPFC increased significantly when the pain was expected to be avoided (i.e., safety expectations) both during the anticipatory phase and during the application of the thermode, independent of the outcome (i.e., pain versus no stimulus) (60).

Interestingly, the vmPFC has been suggested to serve as a unique hub that connects and conceptualizes incoming information and previous experience from different systems to provide an affective meaning of a given situation (61), such as safe versus potentially harmful. Hence, it is possible that the vmPFC provides a key region in the safety appraisal of potentially pain-related events, and that the aberrant mPFC FC in patients with chronic pain may reflect an increased threat appraisal and/or reduced safety appraisal, which is coherent with the overprotective nature of the chronic pain state.

1.6. An integrative model for the role of the default mode network in chronic pain

Bringing everything together, we present two possible implications for the altered within- and cross-network behavior of the DMN in chronic pain patients. First, we suggest that it may reflect an impaired coordinative ability to relocate attentional resources in the presence of pain, which is in accordance with previous models of the implications of DMN disruptions in chronic pain patients (13). Secondly, we also propose that the altered brain behavior related to the DMN may be reflective of an aberrant affective appraisal of threat versus safety during and/or prior to events which both may and may not be related to a painful outcome. As far as we are aware, a model which incorporates the appraisal of threat and safety concerning the altered DMN behavior has not been presented previously. Nevertheless, just like pain itself (32), a situation related to threat is associated with increased attention toward the threatful event (62), and as declared in previous sections, both pain and threat have been associated with increased activation within the SN (2, 26, 49–53) and significant deactivation within the DMN (21–26, 53, 60). Thus, cooperation between the DMN and SN in the dynamic interplay between threat versus safety appraisal and attentional relocation in the context of pain is not implausible. Evidently, if an event is internally appraised as an actual or potential threat to the organism, the event is deemed salient and attentional resources are relocated toward that event. In contrast, if the same event would be appraised as non-threatening (i.e., safe), it would be deemed non-salient and internal mentation (e.g., mind wandering) would be favored. Based on the body of literature presented in the previous sections, the activity within the DMN and SN may follow the same pattern, that is, the appraisal of threat and the attentional relocation toward the threatful event increase the activity within the SN and reduce DMN activation, whereas the opposing scenario rather increases DMN activity and suppresses the activity within the SN. A summary of this model of thought is displayed in Figure **1**.

Based on this conceptual model, the reduced anti-correlation observed between the DMN and SN (10, 34, 41) in patients with chronic pain, as well as the aberrant FC within the DMN (10, 11, 27, 34, 35, 38, 39) and between the DMN and SN (10, 11, 33–37) may reflect an impaired ability to adequately appraise (i.e., threat versus safety) and respond to (i.e., relocate attentional resources) salience. As pain is the bodily response to actual or potential damage to the tissue (55), in other words, the threat to the organism, the persistence of pain in chronic pain patients may thus reflect the inability to appraise what is truly an actual or potential threat to the tissue. This may in turn lead to an aberrant attentional relocation toward events that in reality may not be of importance for the maintenance of homeostasis, that is, events that are not truly salient.

1.7. Framing the implications of the default mode network to the patient with chronic pain

The above-outlined understanding of DMN in patients with chronic pain has implications for

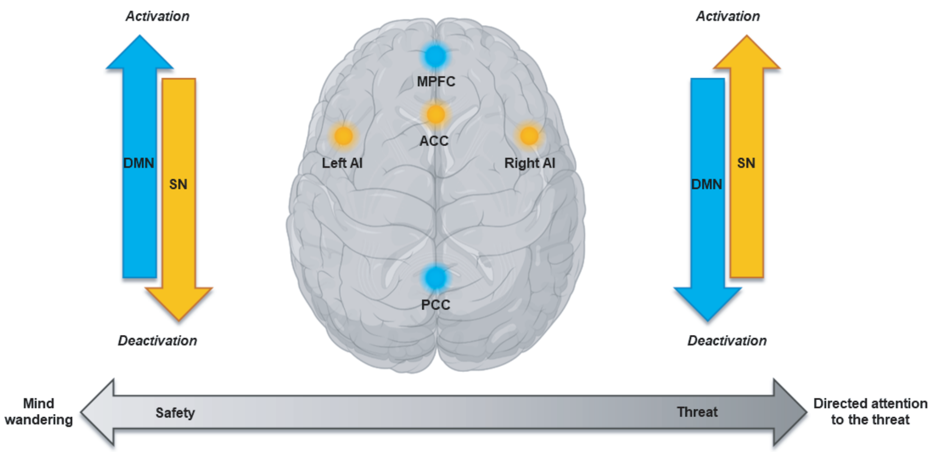

Figure 1. The key hubs of the default mode (blue) and salience (yellow) network presented from a top view of the brain and their activation/deactivation response to safety appraisal with associated mind wandering (left), and threat appraisal with associated threat-directed attention (right). DMN: default mode network; SN: salience network; MPFC: medial prefrontal cortex; ACC: anterior cingulate cortex; AI: anterior insula; PCC: posterior cingulate cortex.

assessment and treatment. Regarding assessment, clinicians can ask questions such as “Are you enjoying daydreaming as much as you used to do?” to get an idea of whether the patient’s DMN is functioning normally or not. Likewise, questioning whether patients (still) can relax and enjoy reflecting on (past) memories of happy experiences, can “shut off” from background noise at work or during public transport can generate meaningful information that can be presumed to relate to the functioning of the DMN. Likewise, questions such as “Are you able to ignore your pain by doing something else such as enjoying a movie or television show?” can give clinicians a rough idea about the balance between the DMN and SN. In case such questioning indicates aberrant DMN behavior, explaining this to the patient can decrease the frustration and stress associated with such impairments, and can even create hope for improvements. Evidently, pain neuroscience education (PNE) is recommended as a first-line treatment of chronic pain (63–66) and mixed-method research has shown that chronic pain patients find it important for their recovery to learn about how the pain system, commonly ascribed to the brain and nervous system, can become overprotective, as this explains their ongoing pain (67). Hence, an explanatory framework for the possible role of aberrant DMN behavior may provide an additional component of value to the curricula of modern PNE. Below we explain how clinicians potentially can explain aberrant DMN behavior to patients with chronic pain.

As presented within the well-established Explain Pain framework (68), the extensive communication between different regions within the brain during various contexts can be explained by using the analogy of an orchestra. Evidently, each individual musician represents an independent region within the brain, whereby all musicians (regions) serve a valuable purpose in themselves. However, together, they can form a more comprehensive contextual meaning in the form of magnificent musical pieces, and the same applies to the brain (68). Here, we suggest an expansion to this analogy to illustrate how the DMN acts and interacts within other networks (i.e., the SN) to produce certain outcomes, such as pain. By giving the example of a movie, in which different musical pieces are incorporated to provide meaning to specific scenery, the possible implication of the DMN and SN can be illustrated. Independent of the genre, the majority of movies include at least one scene in which the instrumental play becomes intensified. This may be scenes associated with danger, such as a scene when one of the main characters is being chased, and this musical work may be related to the engagement of the SN. As such, the areas within the SN can be seen as the musicians of the orchestra whose primary responsibility is to produce pieces of music that capture our attention. In contrast, the instrumental play occurring in scenes during which no critical events are taking place, that is, the types of scenes during which one may scroll through the phone without missing anything of importance to the plot of the movie is rather representative of the activity within the DMN.

In the state of chronic pain, when the balance between the DMN and SN becomes disrupted, the intense instrumental play usually presented during scenes associated with danger overruns the scenes which are otherwise calm and non-attention engaging, causing an erroneous interpretation of the meaning of these scenes. For example, this is like hearing the theme music of a horror movie in the background of a scene where a person is walking down a road. Even if nothing aversive would happen to the person walking, we would most likely interpret the situation as if the person was in potential danger, as well as remain attentionally focused on what is happening throughout the scene. In other words, a scene which is truly not associated with danger gets misinterpreted as potentially dangerous due to the erroneous context of the scene, as created by the music played in the background. Similarly, aberrant activity within the DMN and SN in the state of chronic pain may increase the likelihood of the brain to deem an event as potentially harmful, thereby also increasing the likelihood of inducing a pain response, as well as establishing an internally directed attention towards the pain.

2. Conclusion

The behavior of the DMN is altered in the presence of pain, and patients with chronic pain show alterations in FC both within the DMN itself and between the DMN and the SN. We suggest that this altered cortical behavior may reflect an impaired appraisal of threat versus safety, as well as a disrupted attentional relocation in the presence of pain, which provides an additional component of possible value to the curricula of modern PNE.

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Conflict of Interest

The authors declare that the present review was conducted in the absence of any conflict of interest.

Authors' Contribution

All authors contributed to the conceptualization and design of the present review. EJ prepared the first and final draft of the manuscript with input from IC and JN. All authors reviewed and approved the final version of the manuscript.

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