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Hippocampal morphology mediates biased memories of chronic pain

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ABSTRACT

Experiences and memories are often mismatched. While multiple studies have investigated psychological underpinnings of recall error with respect to emotional events, the neurobiological mechanisms underlying the divergence between experiences and memories remain relatively unexplored in the domain of chronic pain. Here we examined the discrepancy between experienced chronic low back pain (CBP) intensity (twice daily ratings) and remembered pain intensity (n = 48 subjects) relative to psychometric properties, hippocampus morphology, memory capabilities, and personality traits related to reward. 77% of CBP patients exaggerated remembered pain, which depended on their strongest experienced pain and their most recent mood rating. This bias persisted over nearly 1 year and was related to reward memory bias and loss aversion. Shape displacement of a specific region in the left posterior hippocampus mediated personality effects on pain memory bias, predicted pain memory bias in a validation CBP group (n = 21), and accounted for 55% of the variance of pain memory bias. In two independent groups (n = 20/group), morphology of this region was stable over time and unperturbed by the development of chronic pain. These results imply that a localized hippocampal circuit, and personality traits associated with reward processing, largely determine exaggeration of daily pain experiences in chronic pain patients.

Introduction

Everyday existence is a mixture of experiences and memories, the confluence and interaction of which guide future behaviors, and likely reflect adaptations critical for enhancing survival of the organism. Unraveling biological mechanisms regarding the relationship between experiences and the memories of those experiences is a cornerstone from which neuroscience can inform and advance psychology. Yet, the neurobiological mechanisms that determine or control such interactions remain minimally known. The emotional context (including mood and motivation) during an experience or recall significantly influences subsequent declarative and non-declarative memories (Murty et al., 2010). Moreover, memories may be enhanced to various degrees with valence and levels of arousal (Miron-Shatz et al., 2009; Murty et al., 2010; Mirandola and Toffalini, 2016), and there is also evidence that emotional valence and salience can cause memories to become unreliable or inaccurate (Murty et al., 2010; Bookbinder and Brainerd, 2016; Turnbull and Salas, 2017). Numerous studies have shown that the hippocampus is a key region for emotional memory processing, including the production of false or incorrect memories (Ramirez et al., 2013; Liu et al., 2014b; Kim et al., 2017), memory interferences (Winocur, 1985), and both its anatomical structure and associated neurophysiology are implicated in memory distortions (Ramirez et al., 2013; Liu et al., 2014b; Kim et al., 2017; Leal et al., 2017).

Here we examine the topic from the viewpoint of the daily experience of patients suffering from chronic pain, a severe pathology that remains undertreated, poorly understood and a primary source of disability worldwide (Murray and Lopez, 2013). In addition to the intrinsic difficulty in describing and quantifying pain, it has been repeatedly shown that memories for painful events are inaccurate - when asked to recall a past painful event, people tend to overestimate their pain, with the intensity usually reported more severe than actually experienced (Salovey and Smith, 1997). The magnitude and direction of the discrepancy between remembered pain and actual pain seem to depend upon many

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factors, including emotional context (Eich et al., 1985; Norvell et al., 1987; Lowe and Roberts, 1988; Smith and Safer, 1993; Algom and Lubel, 1994; Salovey and Smith, 1997; Babel, 2015), an individual's personality traits and mood (Kent, 1985; Rocha et al., 2009), and the participants' previous experience with pain (Linton and Melin, 1982; Salovey and Smith, 1997; Feine et al., 1998). The psychometric properties of acute experimental pain also account for a large proportion of the error in remembering pain. An influential study by Redelmeier and Kahneman (1996) demonstrated that patients' memories of the amount of discomfort reported after an acute minimally invasive procedure was determined primarily by the intensity of pain at both the procedure's worst and most recent episodes, a phenomenon now known as the "peak-end rule". Memory biases have also been documented in chronic pain patients, with evidence that long-term pain is remembered less accurately than acute pain (Linton and Melin, 1982; Salovey and Smith, 1997) and that people with persistent pain report intensity of previous pain less accurately than healthy people (Liu et al., 2014a). These inaccuracies in the recall of spontaneous episodes of chronic pain can become worse over time and even impact memories of treatment efficacy (Feine et al., 1998). Chronic pain populations also have higher rates of psychological co-morbidities and mood disturbances, which can in turn influence pain memories: increased depression, elevated levels of emotional distress, and sustained presence of negative moods can all result in the overestimation of recalled pain in patients with various kinds of chronic pain conditions (Jamison et al., 1989; Bryant, 1993; Sohl and Friedberg, 2008; Lefebvre and Keefe, 2013).

Despite identifying heuristic strategies and mental "short-cuts" influencing pain memory bias, its neurobiology has not been explored, and more specifically, the neural substrate responsible for memory bias in pain patients has yet to be identified. In the present study, we combined daily measures of pain and mood collected using a smartphone app, questionnaire data, and morphometry of the hippocampus to explain pain memory bias in chronic low back pain (CBP). We hypothesized that CBP patients would show a discrepancy where their recalled pain at the end of the rating period would be significantly higher than the actual pain intensity they experienced while rating and that this bias would show evidence of the peak-end rule. Although autobiographical memory processes involve numerous brain regions, given the importance of the hippocampus in memory encoding and retrieval, its role in the development of chronic pain (Mutso et al., 2012, 2014; Apkarian et al., 2016; Vachon-Presseau et al., 2016), and previous findings showing that cells in the dentate gyrus can be optogenetically manipulated to induce context-specific false memory (Ramirez et al., 2013), we chose to investigate hippocampal anatomy specifically with regards to recalled pain intensity. We hypothesized that memory biases seen in CBP would be associated with differences in the morphology of the hippocampus as well as personality characteristics. We used a discovery and validation approach to ensure generalizability of obtained results, as well as an independent dataset to study the influence of presence of pain on our results, and a follow-up investigation to test robustness of pain memories in time and relative to other kinds of memories.

Methods and materials

Participants

The data presented here are from two separate studies investigating neural mechanisms of chronic pain and its relief. The memory-based (primary) dataset was taken from the initial baseline period of a clinical trial investigating brain mechanisms and biomarkers of placebo response in chronic pain. 72 participants with chronic low back pain (CBP) who completed at least the first two visits of the trial were initially included in this analysis. In order to meet inclusion criteria, individuals must have been 18 years or older with a history of lower back pain for at least 6 months. No report or evidence of substance abuse or additional co-morbid chronic pain, neurological, or psychiatric conditions was also required; as an additional filter for psychological and neurological problems, individuals who scored $\geq$19 on the Beck Depression Inventory (BDI-1a) at Visit 1 or whose neuroimaging scans at Visit 2 indicated a current or previous neurological injury or illness (determined by a radiologist) were dropped from the study and not included in any analyses. Additionally, participants must have had a pain intensity of at least 5/10 on a VAS scale at the initial screening interview, and they were asked to stop all current pain medications for the duration of the study, beginning the day of screening.

Morphometry of the hippocampus is sensitive to age and various pathologies, including chronic pain. To investigate whether hippocampal surface deformations were a consequence of either general aging processes or of having been in long-term pain, we wanted to compare our results to people without pain and to people whose pain had only recently developed, both within a time frame that would allow for anatomical changes (which are relatively slow). Therefore, we utilized a second dataset that was taken from a completed longitudinal study identifying neural substrates of pain persistence, portions of which have been used in previous publications (Baliki et al., 2013; Hashmi et al., 2013; Petre et al., 2015; Vachon-Presseau et al., 2016). Data from 22 healthy individuals who served as control (CON) participants and 21 individuals with subacute back pain that transitioned to become chronic persisting pain (SBPp) were used in the present analysis. Each group had multiple scans collected throughout the study; for our purposes, we used data from the first baseline scan (scan 1) and the fifth scan (scan 5) that occurred approximately 1 year later. To be recruited and eligible, all patients with SBPp had to report an initial duration of pain between 4 and 16 weeks. Additionally, SBPp participants were diagnosed with back pain by a clinician and reported pain intensity of >40/100 on a visual analogue scale. Their persistence in pain was defined by the observation that their pain levels taken at each visit did not decrease by at least 20% during the study. Healthy controls must have had no current pain or history of sustained pain in the last year. As with the CBP patients in the primary analysis, both SBPp and CON participants must have had no co-morbid systemic, chronic pain, psychiatric, neurological, or substance abuse disorders (and must also have had a BDI score <19).

Participants from both datasets were recruited from general and clinical populations via community flyers and ads, as well as from physician referrals and hospital databases when applicable; demographics for all participants can be found in Table S1. The Northwestern University Institutional Review Board approved both studies, and all participants gave written informed consent prior to commencement of any research activities. A waiver of documentation of consent was provided for the follow-up analyses since they were not initially planned; those individuals who participated in the follow-up phone call (explained below) to assess memory of the study provided verbal consent prior to answering any questions.

Study design and procedure

A diagram of the study design is shown in Fig. 1a. At the initial screening visit (Visit 1), participants completed a battery of questionnaires measuring sensory and affective components of their pain experience, current and general mood states, and personality traits. These self-report measures were collected online via REDCap (Research Electronic Data Capture version 6.5.16, © Vanderbilt University) through a link sent to the participant's email addresses; if participants did not have an email address, a back-up email address created for the study was used. To avoid questionnaire fatigue, participants were encouraged to take breaks and walk around, although they were required to finish all questionnaires at the study visit. Once submitted by the participants, questionnaire answers were finalized and un-editable in the REDCap database. The remaining demographic and health history data was manually entered into REDCap at the visit by study staff.

At the end of this visit, participants were trained on how to use the electronic rating application (app) to rate their pain and mood on visual