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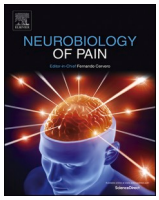

Original Research

Neuronal activation patterns during self-referential pain imagination

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ABSTRACT

In clinical assessments and pain therapy, patients are asked to imagine themselves in pain. However, the underlying neuronal processes remain poorly understood. Prior research has focused on empathy for pain or reported small sample sizes. Thus, the present study aimed to promote the neurobiological understanding of self-referential pain imagination. We hypothesised to find activation contrasts (pain vs. no pain) across pain-related areas and expected two of the most prominent predictors of chronic pain, pain sensitivity (PS) and locus of control (LoC), to be moderators.

In an fMRI study, $N = 82$ participants completed a pain imagination task, in which they were asked to imagine themselves in painful and non-painful situations presented in the form of pictures and texts. After each trial, they were instructed to give painfulness ratings. As a laboratory measure of PS, electrical pain thresholds were assessed. A questionnaire was completed to measure LoC.

Across presentation modes we found activity contrasts in previously pain-related regions, such as the prefrontal, supplementary motor, primary motor, somatosensory and posterior parietal cortices, and the cerebellum. We found positive associations of PS and external LoC with painfulness ratings, and a negative correlation between PS and internal LoC. Despite our hypotheses, neither PS nor internal LoC were significant predictors of the BOLD-signal contrasts.

Though future studies are needed to draw further conclusions, our results provide preliminary evidence of a potential neuronal imagination-perception overlap in pain.

1. Introduction

In clinical assessments, pain patients are asked to describe how they feel and what they think about when they are in pain (Jamison et al., 2022). To this end, it is almost inevitable to imagine oneself in pain. Mental imagery – internal representations formed by retrieving perceptual information from memory (Kosslyn et al., 2001) – also holds significance in pain management, as mental images can be intrusive and negative, causing distress, but can also serve as coping strategy. Mental imagery has thus been considered a therapeutic target for chronic pain, whilst research is lacking a comprehensive understanding of the underlying neurobiology (Berna et al., 2012; Berna et al., 2011; Fardo et al., 2015; Kaur et al., 2020). Improved scientific knowledge on the neuronal mechanisms behind pain imagery not only holds the potential to advance basic pain research in terms of how retrieval of painful memories impacts on current brain states but might also have implications for chronic pain prevention and therapy. For example, pain catastrophising, an important risk factor for pain chronification (Burns et al., 2015), is marked by imagining negative consequences of pain (Petrini and Arendt-Nielsen, 2020) and has been found to predict altered processing in pain-related and affective brain regions in the EEG in healthy participants (Ferdek et al., 2019). Investigation of altered patterns of brain activity and connectivity could lead to the identification of objective biomarkers serving to indicate chronification risk (Ferdek et al., 2019) and to evaluate treatment outcomes. Besides, if basic pain research can demonstrate that pain imagery shares common brain activity patterns with the actual experience of pain, there would be implications with respect to plasticity-related learning processes in the brain.

Across modalities, mental imagery has been shown to recruit brain regions similar to those activated during sensory perception (Kosslyn et al., 2001) and there is evidence that this also holds true for pain [e.g.,

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(Christian et al., 2015; Fairhurst et al., 2012; Kelly et al., 2007)]. However, while the neuronal mechanisms behind empathy for pain (i.e., imagining others in pain) have gained much attention [e.g., (Horan et al., 2016; Jackson et al., 2006; Lamm et al., 2011; Ochsner et al., 2008; Osborn and Derbyshire, 2010; Preis et al., 2013; Singer et al., 2004)], relatively little has been published on imagining oneself in pain. Studies employing hypnotic induction of pain have shown activity in pain-related regions, e.g., the anterior cingulate cortex (ACC), prefrontal cortex (PFC), thalamus and insula (Derbyshire et al., 2004; Raij et al., 2005), but have also demonstrated disparities in contrast to mere imagination of pain (Derbyshire et al., 2004). Other research has found activation of the ACC, dorsolateral PFC, inferior frontal gyrus, and precuneus when pain-related words were read (Osaka et al., 2004; Richter et al., 2010). Few fMRI studies have been conducted instructing participants to imagine they were in pain themselves (Christian et al., 2015; Decety et al., 2013; Derbyshire et al., 2004; Fairhurst et al., 2012; Hugdahl et al., 2001; Jackson et al., 2006; Kelly et al., 2007; Ogino et al., 2007), mostly reporting activation in areas priorly associated with pain perception. In an often-cited study by Jackson and colleagues (Jackson et al., 2006), participants were presented with pictures of hands and feet in either painful or non-painful situations and asked to imagine it was themselves, someone else or an artificial limb. When imagining themselves in pain, there was larger bilateral activation in the anterior insula, ACC, and posterior parietal cortex. Christian and colleagues (Christian et al., 2015) also asked participants to take on different perspectives (first person self, third person self, third person other) when imagining painful everyday situations, but did not include a non-painful condition to contrast this with. In another fMRI study, Ogino and colleagues (Ogino et al., 2007) showed participants pictures of painful events, as well as pictures evoking fear and rest. The participants were asked to imagine it was themselves in pain, fear, or at rest. Contrasting pain and rest, the authors found larger activation in the right anterior insula, the bilateral ACC, secondary somatosensory cortex, and cerebellum. More focused on the retrieval of autobiographical memories, Kelly and colleagues (Kelly et al., 2007) asked participants to recall memories of personal experiences in response to either pain-related or non-pain-related words presented in the scanner and reported larger activation in the left inferior frontal gyrus and left ACC. Finally, Fairhurst and colleagues contrasted BOLD-signal in response to actual pain experience and the later recall thereof. There was an overlap of activation in the left dorsolateral PFC, bilateral insula, the midcingulate cortex, left somatosensory cortex, bilateral motor cortex, parietal cortex, visual cortex, and cerebellum, while the right posterior insula (contralateral to the administration of the heat pain stimulus) was significantly more active during the actual pain experience. Although clearly, these previous investigations have contributed to the scientific knowledge in the field, the fMRI paradigms and respective activation contrasts are too heterogenous to draw conclusions across the studies. Besides, two of the available studies on self-referential pain imagination have investigated individuals with psychopathy (Decety et al., 2013) and amputation (Hugdahl et al., 2001), and in the others, sample sizes were exceedingly small, with an average of $N = 23$.

It was hence the aim of this study, which included a moderately large sample size, to complement previous work, to promote the basic neurobiological understanding of self-referential pain imagery, and to investigate factors predicting the activity contrasts (pain vs. no pain) that we expected to find across areas previously associated with the processing of painful stimuli, i.e., in the PFC, ACC, primary motor cortex, supplementary motor cortex, somatosensory cortex, posterior parietal cortex and precuneus, insula, basal ganglia, thalamus, amygdala, hippocampus, and cerebellum [see (Apkarian et al., 2014; Tracey and Mantyh, 2007)]. We included two variables prominently reported to influence actual pain processing as predictors of the activation contrast since we assumed they would also modulate pain imagery: Pain sensitivity, a person's proneness to react to a noxious stimulus (Ravn et al., 2012) and a risk factor for pain conditions (Coronado et al., 2015; Edwards, 2005; Granot, 2009; Tuna et al., 2018), was anticipated to predict the activation contrast positively. It was assumed that the more pain sensitive a person is, the stronger the activation of the above-mentioned areas upon confrontation with pain-related stimuli [see (Coghill et al., 2003; Spisak et al., 2020)]. Internal locus of control (LoC), defined as a person's perception of events as dependent on their own behaviour or character traits (Rotter, 1966) and a protective factor with respect to pain conditions (Heath et al., 2008; Musich et al., 2020; Zuercher-Huerlimann et al., 2019), was hypothesised to predict the activation contrast negatively. As it appears plausible to assume a role of personality in this regard, it was presumed that the lower the experience of being in control, the higher the distress upon the presentation of pain-related stimuli [see (Crisson and Keefe, 1988; Lee et al., 2022)]. Hence, internal LoC was expected to negatively predict activation contrast in the ACC, insula, amygdala, and hippocampus, which are thought to be involved in affective pain processing (Apkarian et al., 2014). If pain sensitivity and internal LoC were found to be significant predictors in the present study, future studies building on this could further investigate whether altered pain imagery could be a partial mediator in the relationship with pain chronification processes.

2. Methods

The study reported here was part of a larger research project for the investigation of psychological and neuronal mechanisms behind social behaviour and pain. The project was in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the University Hospital of Bonn (No. 014/20). It consisted of a questionnaire battery to be completed at home by the participants, a laboratory assessment as well as an MRI session; the latter taking place on a separate day. In the laboratory, the participants received detailed study information, gave informed consent, and went through quantitative sensory testing (see below, 2.2.2 Electrical pain thresholds). The MRI session consisted of structural and DTI scans as well as several fMRI paradigms, including the one presented here (see below, 2.2.3 Pain imagination task, PIT). Besides, blood samples for genetic and endocrine analyses were taken (data will be presented elsewhere). At the end of the MRI session, participants received a compensation of 80 euros and could register to receive feedback of the project's results.

2.1. Participants

Participants were recruited via word-of-mouth advertising, flyers, and local groups on social media platforms. Prior to participation, individuals interested in the research project answered a screening questionnaire via the online survey platform *Unipark* (Tivian XI GmbH, Cologne, Germany) to ensure eligibility. They were eligible for inclusion if they were between 20 and 50 years old and fulfilled the safety requirements for scientific MRI scanning (e.g., no claustrophobia, no metal implants, no seizure disorder). As it was the project's aim to investigate healthy participants, individuals could only take part if they did not take drugs or medication (except contraceptives) and had no diagnosed psychiatric disorder, tinnitus, nasopharyngeal disease, previous brain or spine surgery, kidney disease, cancer, thrombosis, stroke, or other cardiovascular disease.

Eventually, we recruited a sample of $N = 86$ participants, of which $N = 82$ (56.10 % female, 20–50 years, $M_{age} = 32.72$; $SD_{age} = 6.78$) could be included in the present study as a full data set was available. The majority of the sample held a university degree (63.41 %), graduated from high school (18.29 %) or completed a vocational training (13.42 %). Two participants completed a master craftsman training (2.44 %) and two more held a middle school degree (2.44 %).

2.2. Materials and procedure

2.2.1. LoC assessment

To assess their perceived LoC, participants were asked to complete the German version of the *IE-4* (Kovaleva et al., 2012), containing a total of four items to be answered on a 5-point Likert scale ranging from 1 = *does not apply at all* to 5 = *applies completely*. The IE-4 is comprised of two subscales, *internal LoC* ("I'm my own boss.", "If I work hard, I will succeed.") and *external LoC* ("Whether at work or in my private life: What I do is mainly determined by others.", "Fate often gets in the way of my plans."). Item scores of each subscale are averaged to form two mean scores, with higher values representing stronger internal and external LoC, respectively. Despite its four-item structure, the IE-4 has demonstrated good reliability and validity and can thus be considered an efficient instrument for the measurement of LoC (Kovaleva, 2012). The IE-4 was completed by the participants online via *Unipark* (Tivian XI GmbH, Cologne, Germany).

2.2.2. Electrical pain thresholds

As laboratory measure of pain sensitivity, pain thresholds (i.e., the lowest intensity at which a stimulus is perceived as painful) were assessed [see (Nielsen et al., 2009)]. The participants' dominant wrist was prepared with *Nuprep Skin Prep Gel* (Weaver and Company, Aurora, CO). The participants were then separated from the experimenter by a cubicle. Electric pulses of 2 ms were delivered to their wrist in a stepwise method of limits by means of the *BIOPAC MP160* system *STMISOC* module (BIOPAC Systems, Goleta, CA) through isotonic electrolyte gel electrodes (EL500; BIOPAC Systems, Goleta, CA) attached adjacent to each other. Following the protocol by Vetterlein et al. (2024), the pulse voltage was increased in steps of 2.50 V, starting at 2.50 V, to first detect the perception threshold (data not reported here). To assess the electrical pain threshold (EPT), the voltage of each pulse was then further increased. Participants were asked to indicate when they perceived a stimulus as painful. Above 30.00 V, the voltage was increased by 5.0 V. In accordance with the international regulatory standard IEC 601-2-10, the voltage was capped by the device. The electric current that had reached the participant was fed back to the software *AcqKnowledge 5.0.5* (BIOPAC Systems, Goleta, CA). The experimenter took note of the EPT in mA. Higher scores meant lower pain sensitivity.

2.2.3. Pain imagination task

In the MRI scanner, participants were instructed to imagine themselves in various situations presented in the form of pictures and texts. They were asked to imagine the given scenarios as vividly as possible, without pursuing other thoughts and without moving. They were told that after each trial they would be asked to indicate, on an 11-point Likert scale from 0 (*not painful at all*) to 10 (*strongest pain imaginable*), how painful they imagined the respective situation to be.

To increase power and avoid switching costs, a 2x2 block design was chosen with *scenario* (pain/no pain) and *presentation mode* (picture/text) as within-subject factors. There were two blocks per each of the four conditions (pain/picture, no pain/picture, pain/text, no pain/text) with a total of 80 trials (ten trials per block). The scenarios represented everyday situations and were parallelised so that 20 painful scenarios (e.g., "Imagine burning your lip on a hot beverage.") matched 20 non-painful scenarios (e.g., "Imagine drinking a hot beverage.") and so that each scenario appeared once as text and once as picture. Next to parallelisation of the wording in the text conditions, images in the picture conditions were all in 4:3 format and in most cases matched the colour, brightness, and perspective of the contrasted scenario. Where possible, two pictures of the same person in a painful and non-painful situation were chosen (e.g., same person drinking a hot beverage vs. burning their lip on the same). We applied an incomplete permutation of the blocks so that there never were two blocks of text or two blocks of pictures presented right after one another. Blocks of pain and no pain were, however, randomised, and so were the trials within each of the blocks. Between the blocks, there was a fixation cross that remained for 5,000 ms.

At the beginning of the blocks of pictures, participants saw a fixation cross, which was jittered with an interstimulus interval (ISI) of 500 ms, 1,000 ms and 1,500 ms. The picture was then presented for 5,000 ms, after which the participants used the response buttons in their left and right hand to rate the painfulness of the imagined scenario as described above. The rating disappeared upon button press or after 10,000 ms. Before each of the next trials, the fixation cross was shown anew, with the same jittered ISI. The procedure within the blocks of texts was the same, except that, similar to the protocol by Christian et al. (2015), there was a black screen of 5,000 ms after each text, and the participants were instructed to use this moment to imagine the just-read situation as vividly as possible (see Fig. 1).

2.3. Imaging acquisition and preprocessing

fMRI data were acquired using a 3T *Siemens Magnetom TIM Trio* scanner and a standard head coil (Siemens, Erlangen, Germany) with a mounted mirror faced towards a screen. We used an echo planar imaging (EPI) sequence (repetition time TR = 2500 ms, echo time TE = 30 ms, field of view FoV = 192 mm, flip angle 90°, 37 slices with a voxel size of $2 \times 2 \times 3$ mm^3) to measure changes in BOLD (blood oxygenation level-dependent) signal. The slices were recorded in ascending order in AC-PC orientation.

Preprocessing of the fMRI data was performed using *fMRIPrep 20.2.6* (Esteban et al., 2019), which is based on *Nipype 1.7.0* (Gorgolewski et al., 2018). A smoothing kernel (FWHM = $6 \times 6 \times 9$ mm) was applied using the *MATLAB*-based (Mathworks Inc., Natick, MA) software *SPM12* (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). For more details on the preprocessing procedure please refer to the *Supplementary materials*.

2.4. Statistical analyses

Where not stated otherwise, statistical analyses were performed using *SPSS Statistics version 28* (IBM, Armonk, NY). Mean scores of the IE-4 subscales were calculated. Painfulness ratings across the conditions in the PIT were averaged. Note that due to a technical error, painfulness ratings were only available for $N = 73$ participants. A repeated measures ANOVA with the within-subject factors *scenario* and *presentation mode* and the dependent variable *painfulness ratings* was run to check whether the manipulation had been successful and whether there was an interaction effect of *scenario* × *presentation mode*. Exploratively, to determine the strength of the associations between variables, Pearson correlations were calculated for the painfulness ratings of the scenarios, EPT, internal and external LoC.

First and second level analyses of the fMRI data were carried out in SPM12. At the first level, three BOLD-contrasts *pain* vs. *no pain* (across presentation modes), *picture/pain* vs. *picture/no pain,* and *text/pain* vs. *text/no pain* were calculated on an individual basis by means of the general linear model. At the second level, one-sample t-tests for the three contrasts were computed across the sample, as well as regression analyses of the resulting BOLD-contrasts using the predictors EPT, internal LoC and, for the sake of completeness, external LoC. fMRI results were considered significant at a level of FWE-(family-wise error rate)-corrected $p < 0.005$. The SPM viewing toolbox *xjView* (Cui et al., 2011) was used to determine anatomical localisations based on the *Automated Anatomical Atlas 3* (AAL3; Rolls et al., 2020). Significant BOLD-contrasts were illustrated by means of SPM12.

3. Results

3.1. Behavioural data

The repeated measures ANOVA showed a significant main effect of

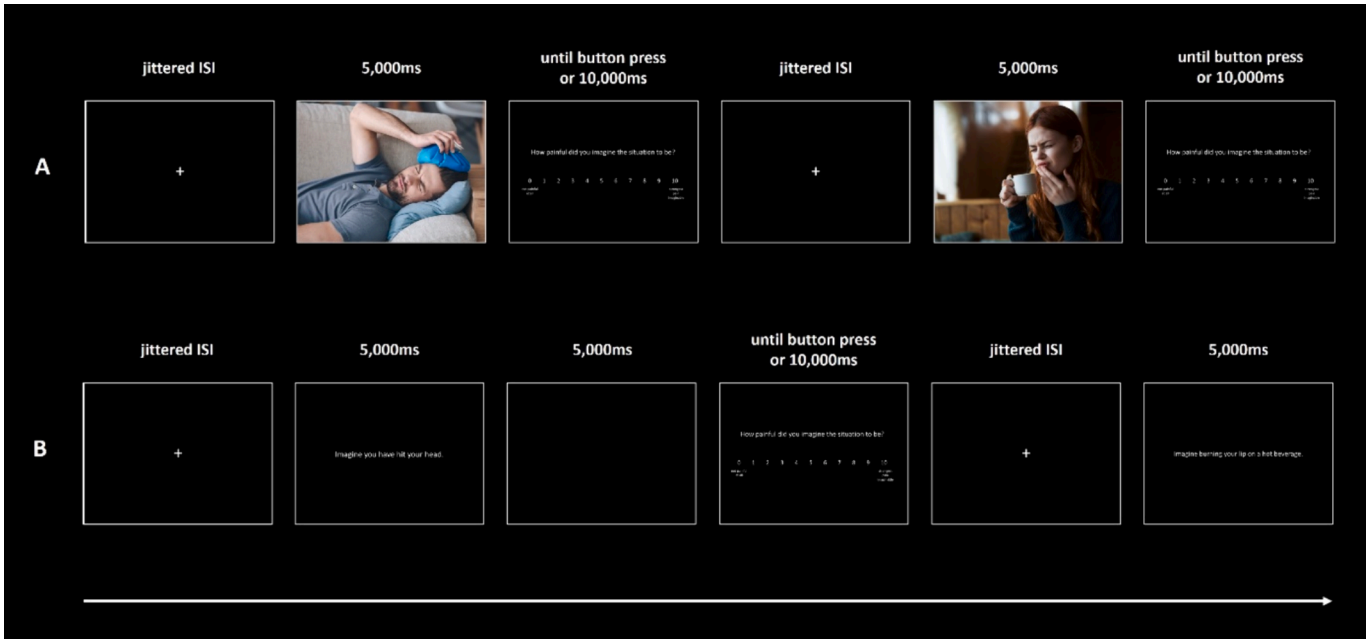

Fig. 1. Pain imagination task (fMRI paradigm). *A*: Picture/pain condition. *B*: Text/pain condition. ISI=Interstimulus interval. Scale text reads "How painful did you imagine the situation to be?" on an 11-point Likert scale from 0 = *not painful at all* to 10 = *strongest pain imaginable*. Stimuli in *B* read "Imagine having hit your head." and "Imagine burning your lip on a hot beverage". First picture l.t.r.: G-Stock Studio/shutterstock.com. Second picture l.t.r.: ShotPrime Studio/shutterstock.com.

scenario ($F_{(1, 72)} = 1385.19$, $p < 0.001$, $\eta_p^2 = 0.95$) with higher painfulness ratings in the pain conditions ($M = 6.01$; $SD = 1.10$) than in the no pain conditions ($M = 1.47$; $SD = 0.57$). There was no significant main effect of *presentation mode* ($F_{(1, 72)} = 1.34$, $p = 0.251$, $\eta_p^2 = 0.02$); pictures ($M = 3.77$; $SD = 0.83$) and texts ($M = 3.71$; $SD = 0.65$) were rated similarly across the scenarios. There was, however, a significant interaction effect of *scenario* × *presentation mode* ($F_{(1, 72)} = 29.13$, $p < 0.001$, $\eta_p^2 = 0.29$) in that texts describing painful situations were rated significantly ($t_{(72)} = -2.31$, $p = 0.024$, $d = 0.27$) more painful ($M = 6.11$; $SD = 1.10$) than pictures showing painful situations ($M = 5.91$; $SD = 1.22$), whereas pictures showing non-painful situations were rated significantly ($t_{(72)} = 5.39$, $p < 0.001$, $d = 0.63$) more painful ($M = 1.63$; $SD = 0.77$) than texts describing non-painful situations ($M = 1.31$; $SD = 0.41$; see Fig. 2).

There was a significant negative correlation between the EPT and the painfulness ratings in the pain conditions ($r = -0.29$, $p = 0.013$), which meant that the more pain sensitive the participants were, the more painful they imagined the respective situations to be. Besides, an external LoC was positively associated with painfulness ratings in the pain condition ($r = 0.30$, $p = 0.009$). Expectedly, there was a significant negative relationship between internal and external LoC ($r = -0.55$, $p < 0.001$). Besides, EPT and internal LoC were positively correlated ($r = 0.25$, $p = 0.026$). No other correlation was found significant.

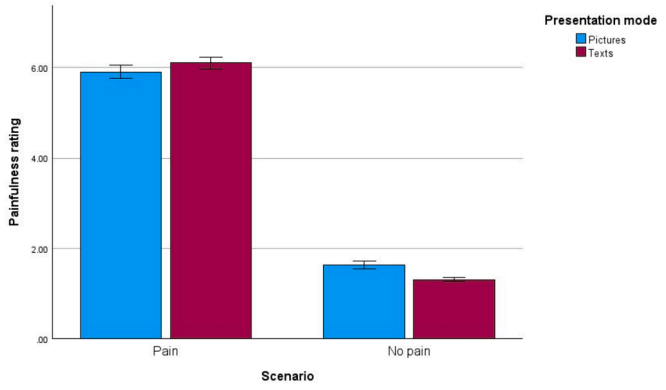

Fig. 2. Painfulness ratings (0 = *not painful at all* to 10 = *strongest pain imaginable*) in the four conditions (picture/pain, text/pain, picture/no pain, text/no pain) of the pain imagination task in the MRI scanner. Data are expressed as mean ± SE.

3.2. Imaging data

Across presentation modes, fMRI analyses identified a total of five clusters that were significantly more active when painful vs. non-painful pictures and texts were presented to the participants (see Table 1 and Fig. 3). These activation patterns included (from anterior to posterior) the left dorsolateral and medial superior frontal gyrus as well as the bilateral middle frontal gyrus (i.e., PFC), the left supplementary motor area (SMA), the right middle cingulate and paracingulate gyri, the bilateral precentral gyrus (i.e., primary motor cortex, M1), the bilateral postcentral gyrus (i.e., primary somatosensory cortex, S1), areas of the left posterior parietal cortex (PPC), such as the left inferior parietal gyrus (IPG), supramarginal gyrus and precuneus, as well as the left cerebellum. In addition, BOLD-signal contrast was found in the occipital lobes, including the bilateral calcarine fissure and surrounding cortex, the left lingual gyrus, bilateral cuneus, superior and middle occipital gyrus, and the left fusiform gyrus.

When the two presentation modes were analysed separately, comparable activation patterns were seen (see Fig. 3). When painful vs. non-painful pictures were shown to the participants, there was a larger BOLD-signal in the right PFC and M1, bilateral S1 as well as in the left inferior parietal gyrus, supramarginal gyrus, and cerebellum. Besides, there was a larger activation in other parietal as well as in occipital areas (see Table 2). When painful vs. non-painful texts were presented to the participants, activation contrasts were found in the bilateral PFC, left SMA, left middle cingulate and paracingulate gyri, right-hemispheric M1, bilateral S1, PPC, and cerebellum. Here, too, a larger BOLD-signal was also seen in occipital areas (see Table 3).

Neither EPT, nor internal LoC, nor external LoC were significant predictors of the activation contrast (pain vs. no pain), neither across presentation modes, nor in the picture or text conditions alone.

Table 1
Clusters of activation contrast pain vs. no pain.

					Peak voxel coordinates (MNI)			
Cluster no.	***p*** *(FWE)*	**R/L**	**Brain region**	***k***	***x***	***y***	***z***	***t***
1	**0.013**			**157**	**−26**	**−6**	**50**	**4.59**
		L	Superior frontal gyrus, dorsolateral	83				
		L	Precentral gyrus	47				
		L	Middle frontal gyrus	21				
2	**0.007**			**178**	**−6**	**4**	**53**	**4.68**
		L	Supplementary motor area	171				
		L	Medial superior frontal gyrus	3				
		L	Middle cingulate & paracingulate gyri	3				
3	**<0.001**			**640**	**42**	**–22**	**67**	**8.12**
		R	Precentral gyrus	368				
		R	Postcentral gyrus	240				
		R	Middle frontal gyrus	14				
4	**<0.001**			**739**	**−48**	**−30**	**50**	**6.42**
		L	Inferior parietal gyrus	340				
		L	Postcentral gyrus	389				
		L	Precentral gyrus	39				
		L	Supramarginal gyrus	21				
5	**<0.001**			**2676**	**−12**	**−76**	**−9**	**10.26**
		L	Calcarine fissure and surrounding cortex	651				
		L	Lingual gyrus	597				
		L	Cuneus	357				
		R	Cuneus	265				
		L	Lobule VI of cerebellar hemisphere	195				
		L	Superior occipital gyrus	107				
		L	Middle occipital gyrus	102				
		L	Lobule IV, V of cerebellar hemisphere	78				
		L	Precuneus	57				
		R	Middle occipital gyrus	46				
		R	Superior occipital gyrus	42				
		L	Fusiform gyrus	37				
		R	Calcarine fissure and surrounding cortex	24				
		L	Superior parietal gyrus	19				
		–	Lobule VI of vermis	12				
		R	Precuneus	2				
		–	Lobule IV, V of vermis	2				

Note. R/L=right/left brain hemisphere. *k* = number of voxels. Peak voxel coordinates are reported in MNI (Montreal Neurological Institute) standard space. General cluster information is printed in bold. A residual number of voxels per cluster could not be clearly assigned to one brain region by the viewing toolbox *xjView*. Clusters are sorted from anterior to posterior.

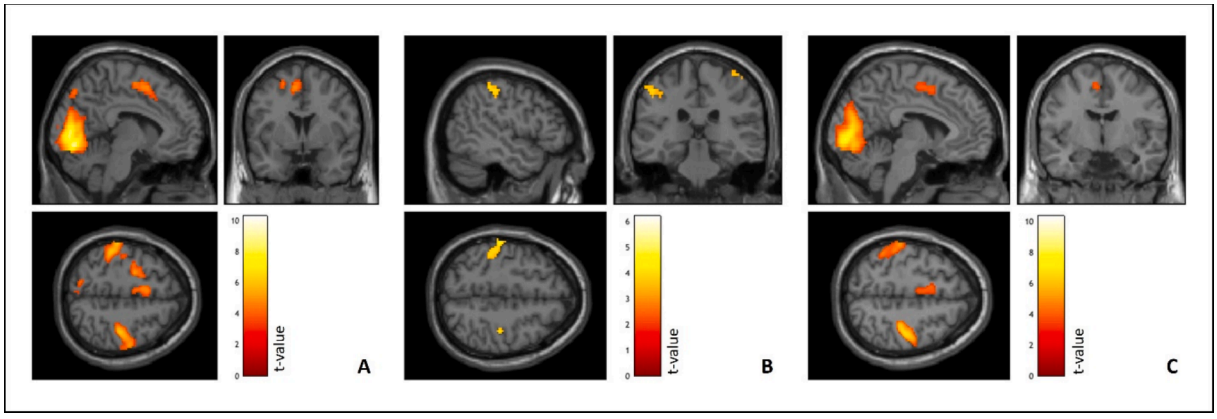

Fig. 3. BOLD-signal contrasts of (A) pain > no pain, (B) picture/pain > picture/no pain and (C) text/pain > text/no pain.

4. Discussion

The aim of this study was to promote the neurobiological understanding of self-referential pain imagination. As expected, when imagining themselves in vs. without pain, participants showed larger activity in the PFC, SMA, M1, S1, PPC, and cerebellum. There was also larger occipital activity. Despite our hypotheses, neither pain sensitivity nor LoC were significant predictors of the activation. On a behavioural

Table 2
Clusters of activation contrast picture/pain vs. picture/no pain.

					Peak voxel coordinates (MNI)			
Cluster no.	***p*** *(FWE)*	**R/L**	**Brain region**	***k***	***x***	***y***	***z***	***t***
1	**0.003**			**184**	**42**	**−24**	**67**	**5.34**
		R	Precentral gyrus	114				
		R	Postcentral gyrus	58				
		R	Middle frontal gyrus	8				
2	**0.004**			**172**	**−58**	**−20**	**44**	**4.85**
		L	Postcentral gyrus	95				
		L	Inferior parietal gyrus	55				
		L	Supramarginal gyrus	10				
3	**<0.001**			**266**	**8**	**−96**	**11**	**6.17**
		R	Cuneus	132				
		L	Cuneus	63				
		R	Superior occipital gyrus	22				
		L	Calcarine	20				
		R	Calcarine	11				
		L	Precuneus	2				
4	**<0.001**			**491**	**−12**	**−78**	**−13**	**5.63**
		L	Lingual gyrus	248				
		L	Calcarine	125				
		L	Lobule VI of cerebellar hemisphere	98				
		L	Fusiform gyrus	6				
		L	Superior occipital gyrus	3				
		L	Cuneus	2				
		L	Lobule IV, V of cerebellar hemisphere	1				
		–	Lobule VI of vermis	1				

Note. R/L=right/left brain hemisphere. k = number of voxels. Peak voxel coordinates are reported in MNI (Montreal Neurological Institute) standard space. General cluster information is printed in bold. A residual number of voxels per cluster could not be clearly assigned to one brain region by the viewing toolbox *xjView*. Clusters are sorted from anterior to posterior.

level, we found positive associations of pain sensitivity and external LoC with painfulness ratings. Lastly, our analyses revealed a negative correlation between pain sensitivity and internal LoC.

4.1. Neuronal activation patterns when imagining oneself in pain

Our findings corroborate previous research suggesting that imagining oneself in pain recruits brain areas similar to those previously associated with the actual experience (Fairhurst et al., 2012; Kelly et al., 2007; Ogino et al., 2007). A prior fMRI study also found activation in the dorsolateral PFC, SMA, midcingulate gyrus, M1, S1, IPG, precuneus, and cerebellum when participants were asked to recall a painful stimulation (Fairhurst et al., 2012). In another study where participants were shown pictures of pain-related events and asked to imagine it was themselves in pain, activation was also found in the PPC, cerebellum, and occipital cortex (Ogino et al., 2007). In an fMRI task in which participants were presented with pain-related vs. non-pain words, there was increased activation in the posterior cingulate gyrus, fusiform and lingual gyrus in the pain condition (Kelly et al., 2007). Finally, participants in another study showed stronger activation in the dorsolateral PFC, posterior cingulate gyrus, M1, inferior parietal gyrus, and precuneus, when imagining situations associated with pain-related vs. neutral words (Richter et al., 2010).

Some of these studies also found activation of the S2, thalamus, and basal ganglia [e.g., (Fairhurst et al., 2012)]. Notably, the comparability between ours and other studies is limited due to the heterogeneity of the designs and contrasts. Nonetheless, the question remains why no increased activation was found in these areas or in the insula, amygdala, and hippocampus. Potentially, activation in these areas depends on task characteristics [cf. (Tracey and Mantyh, 2007)].

Importantly, although the PFC, SMA, M1, S1, PPC, and cerebellum, in which we found activation contrasts in the present study, have been previously associated with pain processing (Tracey and Mantyh, 2007), there is extensive evidence in the recent literature suggesting that brain activation typically seen in response to painful stimuli is not specific to pain but rather represents salience-dependent activation (Su et al., 2019b). As imagining painful scenarios can be assumed to be more salient than imagining non-painful scenarios, involvement of the salience network including the fronto-insular cortex and dorsal ACC (Seeley et al., 2007) is conceivable. However, in the present study, there was no greater activation seen in these areas, suggesting a minor role of the salience network in explaining the contrasts.

It could be argued that the activation patterns seen in the present study represent imaginations of sensory vs. non-sensory experiences rather than pain-specific activation. Yet, we parallelised the scenarios in such a way that participants were instructed to, e.g., imagine burning their lip on a hot beverage or drinking a hot beverage, so that either imagination would be sensory. Nonetheless, this does not rule out the possibility that imagining painful scenarios vs. non-painful scenarios leads to an increased brain response solely based on the presumably more intense sensory experience of pain. Interestingly, a previous fMRI study applying intensity-matched painful and non-painful stimuli has demonstrated larger activity in the bilateral operculum, left SMA, and right middle and inferior frontal cortex in response to painful laser stimuli (Su et al., 2019a), the latter two areas corresponding to regions in which we found larger activation, as well. Ultimately, with respect to our design and analyses, we cannot rule out the issues just presented. However, in the past decade, brain response signatures based on multivariate pattern analysis such as the neurological pain signature (NPS) (Wager et al., 2013) and the stimulus intensity independent pain signature (SIIPS1) (Woo et al., 2017), have successfully tried to overcome these problems, discriminating between painful and non-painful sensations and representing spatial activation patterns beyond mere nociception (Su et al., 2019b). Future fMRI studies using the PIT could make use of such machine learning techniques and investigate whether, for example, the painfulness ratings during the imagination can be

Table 3
Clusters of activation contrast text/pain vs. text/no pain.

					Peak voxel coordinates (MNI)			
Cluster no.	***p*** *(FWE)*	**R/L**	**Brain region**	***k***	***x***	***y***	***z***	***t***
1	**0.046**			**119**	**−8**	**4**	**50**	**4.44**
		L	Supplementary motor area	114				
		L	Superior frontal gyrus, dorsolateral	2				
		L	Middle cingulate & paracingulate gyri	2				
2	**<0.001**			**704**	**38**	**−26**	**57**	**6.86**
		R	Precentral gyrus	442				
		R	Postcentral gyrus	232				
		R	Middle frontal gyrus	1				
3	**<0.001**			**541**	**−52**	**−30**	**47**	**5.70**
		L	Inferior parietal gyrus	392				
		L	Postcentral gyrus	121				
		L	Supramarginal gyrus	8				
4	**<0.001**			**2726**	**−12**	**−82**	**−3**	**10.29**
		L	Calcarine	718				
		L	Lingual gyrus	607				
		L	Cuneus	320				
		L	Lobule VI of cerebellar hemisphere	205				
		R	Cuneus	169				
		L	Superior occipital gyrus	161				
		R	Calcarine	111				
		L	Middle occipital gyrus	110				
		L	Lobule IV, V of cerebellar hemisphere	105				
		L	Fusiform gyrus	39				
		–	Lobule VI of vermis	18				
		L	Inferior occipital gyrus	17				
		L	Precuneus	7				
		R	Superior occipital gyrus	6				
		R	Middle occipital gyrus	1				

Note. R/L=right/left brain hemisphere. k = number of voxels. Peak voxel coordinates are reported in MNI (Montreal Neurological Institute) standard space. General cluster information is printed in bold. A residual number of voxels per cluster could not be clearly assigned to one brain region by the viewing toolbox *xjView*. Clusters are sorted from anterior to posterior.

predicted by respective pain-specific brain response signatures.

The activation cluster in occipital areas could be a result of imbalanced stimuli properties across conditions. However, these would be expected to vary more strongly between pictures, yet the cluster appeared more pronouncedly in the text contrast. Besides, previous studies have also reported occipital activation (Kelly et al., 2007; Ogino et al., 2007). It could be argued [see (Kelly et al., 2007)] that some of these regions, e.g., the primary visual cortex and fusiform gyrus, have been implicated in the generation of visual imagery (D'Esposito et al., 1997; Pearson, 2019). As the participants were asked to give painfulness ratings, their judgment of non-painful situations might have been prompt, costing little imagery effort. Due to the visual support, not much imagery resources might have been needed for the picture/pain condition either. However, in the text/pain condition, participants likely tried more strongly to imagine a comparable situation, potentially explaining the larger occipital activation.

4.2. The influence of pain sensitivity and locus of control

Although both pain sensitivity and internal LoC have been reported to exert opposing effects on pain processing [e.g, (Edwards, 2005; Musich et al., 2020), the literature on their association is scarce and focused on patient's pain outcomes [e.g., (Campbell et al., 2017; Cano-García et al., 2013; Lee et al., 2022; Stewart et al., 2018)]. In one experimental study, however, healthy participants with an external LoC did not differ in their pain perception compared to those with an internal LoC (Jokic-Begic et al., 2009). Another experimental study did find a negative correlation between internal LoC and pain ratings (Williams et al., 2004), which is in line with our behavioural results. It seems plausible that when a person experiences high self-efficacy, they also feel armed to cope with pain. Accordingly, it appears reasonable that the more pain sensitive a person is and the more externally controlled they feel, the more painful they tend to imagine situations as the ones presented in the PIT. It could also be argued that the more vigilant a person is to the pain-associated valence of a stimulus, the more prone they would be to react to a noxious stimulus.

In light of this it is difficult to interpret the null findings of pain sensitivity and LoC with respect to predicting the BOLD-signal contrasts. It could be argued that the task design lacked power, however, it is also possible that LoC influences self-referential imagination processes independent of the situation's valence. In addition, pain sensitivity and LoC might not play a role in the imagination of painful situations but in response to actual pain. A replication of the study with the addition of a perception vs. imagination and a pain vs. imagination contrast could shed more light on this issue.

4.3. Strengths and limitations

The study reported here adds to the currently modest number of fMRI studies investigating brain activity patterns underlying self-referential pain imagination. Prior research had been focused on empathy for pain [e.g., (Ochsner et al., 2008)] and existing publications examining a first-person perspective either investigated subgroups [e.g., (Decety et al., 2013)] or reported small sample sizes [e.g., (Fairhurst et al., 2012)]. Thus, a noteworthy strength of our study is its relatively large sample size with a balanced sex distribution. We paid attention to address a wider population, rendering our sample more heterogeneous

than usual, although, the generalisability is still limited due to the young average age and the WEIRD[1] issue.

The inclusion of a laboratory measure for pain sensitivity can further be seen as a particular strength of our study, although surprisingly, it was not associated with the expected activation patterns during pain imaginations. Potentially, this can be attributed to state influences differing between the laboratory and the MRI session.

Another strength of our study lies in the conceptualisation of the PIT, presenting strictly parallelised stimuli in two modes. At the same time, this poses limitations as our statistical power is likely to have been compromised due to the ostensibly divergent cognitive processes needed to complete the picture vs. text conditions. Additionally, to minimise the participants' time expenditure, the PIT only included 80 trials with two blocks per each of the four conditions, which might have also limited the power. An obvious caveat of our design is the lack of an actual pain condition. However, had we added a pain administration condition in the scope of the PIT, the interpretability of the contrast between imagined and actual pain would have been very limited, since acute pain induction, e.g., by means of electrical stimuli, would differ strongly from everyday painful situations as presented in the PIT. Other studies have overcome this by contrasting an acute pain experience with the respective recall of this experience (Fairhurst et al., 2012). Yet, this approach only allows drawing conclusions with respect to a very specific sensory experience and recall after a short period of time, which might heavily rely on working memory and to a much lesser extent on imagery processes comparable to when a person is asked to imagine themselves in pain. In the future, new paradigms accounting for all these aspects need development.

Although the manipulation in the PIT can be regarded as successful, there was a differential pattern of painfulness ratings between the presentation modes. Possibly, reading leaves more degrees of freedom to imagine a situation in an emotionally enriched manner than viewing a picture of a person which evidently is not amid an emergency. Reading could also make it easier to imagine *oneself* in the situation vs. when another person is depicted. It should, nonetheless, be kept in mind that a difference of 0.2 points on an 11-point scale might not be meaningful in everyday life. The higher painfulness ratings in the picture/no pain condition should not be overinterpreted either, since, strictly speaking, none of these situations should have been rated as painful. Maybe participants were primed by the overall context of pain.

Finally, instead of a region of interest approach, we chose a more conservative whole-brain analysis and still found activation in areas previously associated with pain processing, which strengthens the validity of our findings.

4.4. Implications

Though, importantly, the lack of an actual pain condition in our design does not allow us to draw definite conclusions, our results provide preliminary yet insufficient evidence for the idea that when individuals are asked to describe how they feel and what they think about when they are in pain, their brain enters a pain simulation mode mirroring the actual experience. If this could be corroborated in a paradigm including a contrast of actual pain vs. pain imagination, this could be viewed as neuronal evidence for the ecological validity of subjective assessments, but would also stress the importance of considering inter-individual differences in the ability to generate mental imagery [see (Monzel et al., 2023)]. Besides, if this neuronal overlap could indeed be confirmed, this might also suggest that frequent pain imaginations as seen during pain catastrophising (Petrini and Arendt-Nielsen, 2020) might repeatedly activate and shape pain pathways via plasticity-related processes such as long-term potentiation. Prospective studies should eventually be conducted to observe pain imagery-dependent alterations in patterns of brain activity and connectivity in the transition from acute to chronic pain.

Future studies building on our findings could also further strengthen the scientific basis of imagery techniques in pain therapy [e.g., (Kaur et al., 2020)], as findings of a neuronal overlap would also imply that it is possible to practise pain coping in a therapeutically supported, yet neuronally alike setting. To confirm these ideas, future research should replicate the PIT, including more trials, a perception-only, and an actual pain condition. Besides, investigations should be extended to include chronic pain patients. When more studies in the field will be available, meta-analyses across these are desirable to identify a common pain imagery pattern. Moreover, randomised-control studies investigating the effects of therapeutic imagery techniques could be conducted to disclose brain activity changes.

Future studies could also address the known variability in mental imagery abilities [see (Pearson, 2019)]. E.g., individuals with aphantasia, who show a reduction in or complete absence of mental imagery (Monzel et al., 2022), could be asked to complete the PIT. As people with aphantasia have recently been demonstrated to show deviating brain activity patterns (Monzel et al., 2024), it would be intriguing to investigate a respective pattern in the PIT. Finally, since visual imagery is hypothesised to neuronally function like "vision in reverse" (Pearson, 2019), meaning that perception is a bottom-up process while imagery is a top-down process, investigating whether pain imagination is "pain perception in reverse", remains an interesting endeavour.

4.5. Conclusion

When imagining oneself in painful situations, areas previously associated with pain processing appear more active compared to when imagining oneself in non-painful situations. Although pain sensitivity and internal LoC are negatively related, neither of them predicted the activation in our fMRI task. Future studies are required to replicate our results and to investigate whether the null findings still hold when the statistical power is increased.

Author contributions

All authors contributed to the conception of the study, discussed the results and their interpretations, revised and approved the article. MM and AV performed the statistical analyses. AV drafted the article and designed the figures.

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[1] Participants from a Western, Educated, Industrialized, Rich and Democratic society (cf. Henrich et al., 2010).

Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from the corresponding author, AV, upon reasonable request.

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Appendix A. Supplementary data

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