




CORRESPONDENCE

Sensory-specific predictive models in the human anterior insula [version 1; referees: 2 approved]

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Abstract



Expectations affect the subjective experience of pain by increasing sensitivity to noxious events, an effect underlain by brain regions such as the insula. However, it has been debated whether these neural processes operate on pain-specific information or on more general signals encoding expectation of unpleasant events. To dissociate these possibilities, two independent studies (Sharvit *et al.*, 2018, *Pain*; Fazeli and Büchel, 2018, *J. Neurosci*) implemented a cross-modal expectancy paradigm, testing whether responses to pain could also be modulated by the expectation of similarly unpleasant, but painless, events. Despite their differences, the two studies report remarkably convergent (and in some cases complementary) findings. First, the middle-anterior insula response to noxious stimuli is modulated only by expectancy of pain but not of painless adverse events, suggesting coding of pain-specific information. Second, sub-portions of the middle-anterior insula mediate different aspects of pain predictive coding, related to expectancy and prediction error. Third, complementary expectancy effects are also observed for other negative experiences (i.e., disgust), suggesting that the insular cortex holds prospective models of a wide range of events concerning their sensory-specific features. Taken together, these studies have strong theoretical implications on the functional properties of the insular cortex.



Keywords

Pain, Expectancy, Nocebo, Bayesian Coding, Unpleasantness

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Any reports and responses or comments on the article can be found at the end of the article.

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One of the most striking breakthroughs in pain research has been the discovery of expectancy modulations, according to which subjective experiences do not only reflect nociceptive input but also individuals' previous knowledge and beliefs¹. Expectancy modulations are noteworthy for their clinical implications, as convincing individuals of the effectiveness of an analgesic might induce a strong pain relief (placebo effect), sometimes comparable to the effects of active agents². Furthermore, expectancy effects have sparked a major theoretical debate, with influential models suggesting that pain symptoms might be better explained through a Bayesian framework, where the brain estimates the (posterior) probability of body damage, based on the integration of sensory inputs and prior representations³⁻⁶.

Many studies investigated the neural structures underlying expectancy modulations of pain, pointing to an extensive network including, among other regions, the insular cortex^{1,7-10}. In particular, whereas the posterior portion of the insula is known to receive thalamic nociceptive projections¹¹⁻¹³ and thought to process bottom-up components of the painful experience⁸, the middle-anterior portions may integrate such bottom-up signals with prior expectations^{7,8}, and generate prediction-error signals, serving to update the representation of future events⁸. However, the insular cortex (like other interconnected regions such as the cingulate cortex) does not respond to pain specifically, but also to a wide range of aversive events¹⁴, including disgust^{15,16}, negatively-valenced pictures^{17,18}, or even unfairness^{15,19,20}. Accordingly, a part of pain-evoked activity in this region might reflect supramodal dimensions of affect or motivation, such as unpleasantness¹⁵, arousal or even salience^{21,22}. This raises the question about the nature of the predictive information encoded on the middle-anterior insula, and whether it relates to pain-specifically (“*this will hurt*”), or rather to an undistinctive negative event (“*this will be bad*”).

Addressing this issue is not a trivial matter, as it would require testing whether pain-evoked activity in the middle-anterior insula is also sensitive to the expectation of a painless event of same unpleasantness or salience. Interestingly, two recent independent studies (each unbeknownst to the other) did precisely this, reaching remarkably similar results^{23,24}. The first study from Sharvit and others²³ compared the expectancy of pain with that of a disgusting odorant of similar unpleasantness (see also Sharvit and others²⁵ for an earlier behavioral implementation of the task), whereas the second from Fazeli and Büchel²⁴ used as control pictures of aversive content. By expanding on well-known paradigms of pain expectancy^{7,8}, both studies were able to replicate evidence that the middle-anterior insula integrated bottom-up nociceptive information with signals from predictive cues, but this did not occur when cues were incongruent with the subsequent event (e.g., disgust/image cues followed by painful stimulus)^{23,24}. Such convergence between researches with important differences in sensory stimuli, task structures, and data analyses^{23,24}, provides a compelling case that expectancy modulations of pain in the insular cortex are sensory-specific, and do not generalize to a broad code of unpleasantness. This also accords with other work showing for shared and segregated

portions in insula for representations of pain, disgust, and unfairness¹⁵.

Although sharing a similar take-home message, the two cross-modal experiments by Sharvit and Fazeli differ (and in some case complement each other) concerning the information coded by the middle-anterior insula. By employing rigorous Bayesian modelling, Fazeli and Büchel²⁴ dissociated a portion in the middle and dorsal-anterior portion of the insula, responsible for integrating bottom-up signals with prior expectancies, from a portion in ventral-anterior insula, responsible for generating error signals whenever the painful stimulus greatly diverged from what was predicted by the cues (see Figure 1). This was not the case in Sharvit and others²³ who adopted a paradigm where divergences between cues and subsequent stimuli were purposefully subtle to pass unnoticed^{17,25}. It is interestingly to notice, however, that Sharvit and others²³ reported a dissociation between the middle insula, exerting a mediatory role in the way in which predictive cues influenced subjective reports (as previously found⁷), and the most anterior insula, exerting instead an opposite role of suppression. Hence, in Sharvit and others²³ activity in the anterior insula seemed to prevent individuals from being influenced by their expectations, an effect that is consistent with the notion of prediction-error modeled by Fazeli and Büchel²⁴. The two studies also differ regarding the insular sub-sections involved: Sharvit and others²³ mapped mediation and suppression effects along the middle-to-anterior axis, whereas Fazeli and Büchel²⁴ described expectancy and prediction-error effects also along the dorsal-to-ventral axis of the anterior insula (Figure 1). Future studies will need to further

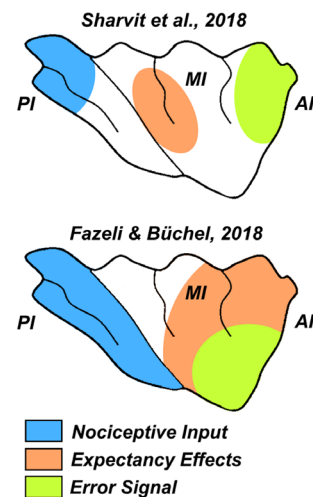


Figure 1. Schematic representation of sensory-specific expectancy processing in the insular cortex from the studies of Sharvit and others²³ and Fazeli and Büchel²⁴. Blue shades over the Posterior Insula (PI) refer to processing of pain based solely on nociceptive inputs. Orange shades over the Middle (MI) and Anterior Insula (AI), refer to processing of pain (and disgust²³) based also on prior expectations. Green shades in AI refer to regions coding prediction errors²⁴, and suppressing the effect of previous expectations²³.

clarify how different components of expectancy relate to the various insula portions.

A further, and critical, point of divergence relates to whether the insular cortex is also susceptible to sensory-specific expectancy for other events than pain. This question was addressed only by Sharvit and others²³ who described complementary effects to those observed in pain, also for the case of olfactory disgust. These results suggested that the middle-anterior insula may hold multiple predictive representations of upcoming events, which are then updated by bottom-up sensory input. Hence, although the middle-anterior insula appears sensitive to a wide range of stimuli¹⁴, it may retain sensory-specific information about each of them. Anatomical studies on primates subfields in this region²⁶, with a level of detail that exceeds that derived from neuroimaging research in humans^{27,28}. It is therefore foreseeable that different kinds of sensory events might be represented in the anterior insula through neighbouring, but distinct, neuronal

populations, which could be difficult to distinguish through radiological imaging, but nonetheless selectively dissociated through well-crafted expectancy manipulations.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Referee Report 01 March 2019

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The paper by Sharvit and colleagues is an interesting commentary paper mostly based on two studies aiming at exploring the role of the insular cortex in integrating sensory input and internal predicting models to formulate the perception of an aversive stimulus (Fazeli and Büchel (2018¹) and Sharvit *et al.* (2018²)). Sharvit and co-workers also wrote one of the two papers on which this commentary is based.

The two original studies focused on comparing the response to painful stimuli to another negative stimulation. In one case a disgusting olfactory stimulation was used, while in the other, a set of negative-valence pictures from the IAPS database were used.

The commentary paper nicely points out the convergences of the two studies and their potential limitations. It also importantly noticed the differences in the two findings discussing their convergences and the complementary nature of the two. I have no significant concerns about the commentary paper, and I believe that this offers an interesting supplement to the original discussion of Sharvit and colleagues' work.

I only wish to point out a few comments to further develop and hopefully stimulate the discussion about the potential role of the insula in predictive coding.

1. It is known that it can be difficult to match the saliency of negative stimuli with the saliency of positive stimuli. The former are typically more arousing than the latter (Ferri *et al.* (2015³)). However, when this aspect is taken into consideration carefully, results (at least at the behavioural level) show that saliency matters more than valence (Spaccasassi *et al.* (2019⁴)). Although it is clearly the aim of the two original studies, is it possible that the insula contributes to the predictive coding of every salient stimulus? In other words, is it possible that the role of the insula is not limited to the two hypotheses "this will hurt" or "this will be bad", but may extend to "this will be arousing"?
2. Relatedly, an even more extreme hypothesis could be made. The insula might be a sort of bottle-neck for the integration of internal models with sensory stimuli. Returning to the previous example, it is possible that the insula processing is the following: "are the sensory information and the internal models on the same page? Can I integrate the two sources of information?" The middle and anterior insula might be involved in the processing of this very general aspect. Sharvit and Fazeli papers mostly work in the prediction of stimuli of different sensory modalities with a similar intensity and the same negative valence, revealing a crucial role of the middle and anterior insula in

coding prediction errors across sensory modalities. Potentially, it is possible to create a prediction incompatible with the incoming stimulus, so that it won't be integrated, within a sensory modality. For example, the prediction of a very low painful stimulus coupled with a very high level of painful stimuli may generate the same prediction error signal that leads to the non-integration of the internal/external signals when coming from different sensory modalities. Fazeli and Büchel (2018¹) already proposed this point as a limitation of their study in their discussion.

3. There is a debate that social exclusion may generate what is called “social pain”, which would have a brain footprint largely overlapping with physical pain (Eisenberger and Lieberman (2004⁵)). I am not personally a great sponsor of this “overlap theory”, the difference between the two experiences is immense perceptually so that the overlap between the two functions should be taken cautiously. Besides my personal concerns, one hypothesis is that with current experimental procedures we capture effects that are shared by all the arousing stimuli and not limited to pain (Legrain *et al.* (2011⁶)). Do the authors predict that the role of the insula in integrating expectations and sensory input would somehow work also for social pain? Alternatively, can the sensory-specific pattern of response for expectations, discussed in this commentary, help to distinguish the processing of physical pain from social pain?

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Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Yes

Is the conclusion balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cognitive neuroscience, experimental psychology and neuropsychology. One focus of my research is how body representation and multisensory integration influence the pain perception.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 01 March 2019

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In this paper, Sharvit, Vuilleumier and Corradi-Dell'Acqua draw on evidence from two recent studies (Sharvit *et al.* (2018¹) and Fazeli and Büchel (2018²)) to suggest that the middle-anterior part of the insula cortex encodes sensory-specific expectancy effects of pain while the posterior insula process nociceptive inputs. Both investigations employ within-subjects designs to examine whether the brain shows sensory-specific expectancy effects. Cues predict the intensity or unpleasantness of pain or a different modality (olfactory or aversive images), and cues about one modality are occasionally followed by the other outcome. The authors of each paper make conclusions about cross-modal versus sensory-specific effects, which are summarized in the current review with a focus on effects within the insula. The paper is well-written and covers important issues regarding whether the insula processes expectation of general unpleasantness or pain-specific expectation. This question is timely and relevant for a large body of work asking whether brain responses are specific to pain or whether responses in regions like the insula reflect domain-general processes, such as salience or unpleasantness (Legrain *et al.* (2011³)). The review is a useful addition to the literature on pain and sensory specificity. However, certain issues that should be addressed in this review to benefit future investigations on the question of expectancy effects and modality specificity.

In our opinion, the authors need to be more cautious in making conclusions regarding sensory specificity since neither study included comprehensive tests for specificity. First, they did not evaluate potentially confounding factors between pain and non-pain stimuli such as stimulus-related salience, arousal, uncertainty (the degree of learned association between cue and outcome), and threat/aversiveness. For example, a modality-specific expectancy effect in the anterior insula might be influenced by the lower level of uncertainty in the congruent conditions compared to incongruent conditions. The insula is also a core region of the salience network and affected by the salience of the stimulus (Menon and Uddin (2010⁴)) as well as threat value (Wiech *et al.* (2010⁵)) which might differ between pain and the other modality (i.e. pain has the potential to cause harm, whereas odors do not). Since these factors were not measured or controlled in either study, it should be noted that those factors might contribute to the effect of expectancy in the insula as well.

Second, Fazeli and Büchel (2018²) did not evaluate sensory-specific or sensory-general processing of expectancy in response to visual stimuli paired with either pain or visual cues. If the effect of expectancy on insula activity is truly sensory-specific and does not affect the expectancy effect on a stimulus of

another modality, the same phenomenon should be found in the non-pain modality. Finally, Sharvit *et al.* (2018¹) trained with outcome-specific cues during conditioning, and tested responses to crossed cues only in the test phase. This may have led to differences in the cross-modal cue pairs, only because those were novel in the test phase, which is also related to the issue of uncertainty mentioned above.

Finally, we think the authors should also consider that within-subjects tests of sensory specificity may lead to very different conclusions from between-subjects designs, wherein subjects would be randomly assigned to experience a single outcome modality and modalities would vary across groups. When individuals experience multiple outcomes, this engenders both value-based learning (expectations about intensity/unpleasantness) and sensory learning (expectations about outcome identity). Some regions respond similarly to both types of learning (e.g. dopaminergic neurons involved in value-based prediction error respond when outcome identity changes and value is held constant (Takahashi *et al.* (2017⁶) and Chang *et al.* (2017⁷)), whereas other brain regions respond to value irrespective of outcome identity (OFC; Padoa-Schioppa *et al.* (2008⁸)) or sensory outcome irrespective of value (lateral OFC; Boorman *et al.* (2016⁹)). In the two papers reviewed here, cues denote both outcome type (i.e. pain vs. odor/image) and outcome value (i.e. unpleasantness/intensity), which requires both types of learning. While this is theoretically interesting, the question Sharvit and co-authors focus on here is whether **value-based learning (i.e. expectancy-based modulation) is sensory specific**. A purer test of this question would be to use a between-subjects design to compare value-based processing across modalities, i.e. whether brain responses are similar when pain is preceded by pain expectancy cues and when olfactory/visual outcomes are paired with expectancy cues in those domains. When both forms of learning are combined, differences might emerge that reflect sensory learning, rather than purely testing whether value-learning is sensory-specific. The authors should acknowledge this alternative in the present review.

In addition to the two conceptual issues above, we have several minor suggestions:

1. Several terms should be defined or explained more precisely (either in a box or early in the manuscript). This includes: “sensory specificity”; the distinction between ‘unpleasant events’, ‘negative experiences’, and ‘threat’; and the relationship between Sharvit’s manipulation of ‘unpleasantness’ (Sharvit *et al.* (2018¹)) and Fazeli’s manipulation of ‘intensity’ (Fazeli and Büchel (2018²)).
2. The manuscript would benefit from more description of the two original study paradigms and how they differ (e.g. conditioning, instructions, test phases).
3. The review focuses on findings in the insula, yet both papers also found important effects outside of this region (Sharvit *et al.* (2018¹) found interesting and similar cue predictive effects in vmPFC and TPJ, and Fazeli and Büchel (Fazeli and Büchel (2018²)) showed intensity and expectancy effects in ACC in addition to the insula). Since insula has a strong relationship (functional and anatomical) with those regions in pain processing and modulation, the authors should acknowledge that other regions show similar effects and also discuss differences.

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Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Partly

Is the conclusion balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pain, Expectancy, fMRI, Placebo, Learning

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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