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REVIEW

Modeling Pain Using fMRI: From Regions to Biomarkers

Marianne C. Reddan[1] · **Tor D. Wager**[1]

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Abstract Pain is a subjective and complex phenomenon. Its complexity is related to its heterogeneity: multiple component processes, including sensation, affect, and cognition, contribute to pain experience and reporting. These components are likely to be encoded in distributed brain networks that interact to create pain experience and pain-related decision-making. Therefore, to understand pain, we must identify these networks and build models of these interactions that yield testable predictions about pain-related outcomes. We have developed several such models or 'signatures' of pain, by (1) integrating activity across multiple systems, and (2) using pattern-recognition to identify processes related to pain experience. One model, the Neurologic Pain Signature, is sensitive and specific to pain in individuals, involves brain regions that receive nociceptive afferents, and shows little effect of expectation or self-regulation in tests to date. Another, the 'Stimulus Intensity-Independent Pain Signature', explains substantial additional variation in trial-to-trial pain reports. It involves many brain regions that do not show increased activity in proportion to noxious stimulus intensity, including medial and lateral prefrontal cortex, nucleus accumbens, and hippocampus. Responses in this system mediate expectancy and perceived control effects in several studies. Overall, this approach provides a pathway to understanding pain by identifying multiple systems that track different aspects of pain. Such componential models can be combined in unique ways on a subject-by-subject basis to explain an individual's pain experience.

✉ Tor D. Wager
tor.wager@colorado.edu

[1] Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO 80303, USA

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Introduction

Pain is a subjective phenomenon that is related to, but not reducible to, nociceptive signaling of actual or potential tissue damage [1]. Indeed, pain is a complex psychological manifestation of interactions among multiple component processes, including nociception (i.e., neurophysiology, sensation), cognitive appraisals (i.e., expectation, framing), and affect and valuation [2–8].

Physicians rely primarily on patient self-reports to diagnose and treat pain; however, self-report is subject to limitations in self-perception and metacognition, and may not provide insight into the cause of pain or how it should be treated [9–13]. Indeed, patients are sometimes unable to adequately describe their pain. For example, a study comparing dementia patients and controls found that facial expressions, but not verbal reports, scaled strongly with noxious stimulus intensity [14]. Furthermore, self-report conveys limited information about the sources and mechanisms of pain.

Pain experience is constructed in the brain, and can result from dysregulated brain circuits. In some cases, normally innocuous sensory signals or low levels of nociceptive input may be enhanced and transformed within the brain to create pain. Pain can exist independent of local peripheral nociceptive input; for example, phantom limb pain persists long after the amputation, even under spinal anesthesia [15, 16]. Even in cases where nociceptive input is required to maintain pain, the brain interprets that input and constructs pain experience by combining it with other signals. For example, nerve injury models of chronic pain

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involve neuroinflammation in the spinal cord, including cytokines and chemokines produced by spinal glial cells, which are thought to mediate persistent pain [17, 18]. These changes may require input from peripheral neurons [19], but once sensitization has occurred, persistent sensitization in nociceptive circuits can drive pain with normal sensory input. Sensitization can also occur in supra-spinal brain circuits in the thalamus [20] and amygdala [21]. Thus, understanding pain in a living individual will ultimately require understanding the neurophysiology of the supra-spinal brain processes that create it. Both limitations in self-report and the cerebral nature of pain construction make it desirable to develop models of how the human brain constructs pain experience.

Neuroimaging allows for a systems-level approach to the brain representation of pain [22–24], and can be used to develop predictive biomarkers for component processes related to pain [25]. A neuroimaging biomarker is a measurable pattern of brain activity predictive of some outcome, such as pain self-report. Calling a brain measure a "pain biomarker" does not imply that it is perfectly predictive or highly specific to pain, or that it is a complete model of pain. These issues are empirical ones, which require extended study of precisely defined markers across studies and laboratories. Imaging-based biomarkers have the potential to (1) complement self-report measures in multi-modal assessments [26]; (2) characterize the normative systems that give rise to pain and abnormalities in patients [25]; and (3) provide biological targets for pharmacological, psychological, and neuromodulatory interventions [27, 28]. Critically, even if behavioral measures of pain and other diagnostic criteria are available and trusted, biomarkers can help establish an understanding of the neurological basis for the symptoms. Showing that a brain measure strongly tracks symptoms strengthens evidence that brain features are disease-relevant. This review discusses how the biomarker approach to pain neuroimaging differs from standard brain mapping methods, and reviews progress to date in using this new approach to understand and assess pain. (For free Matlab-based software tools for creating predictive models with neuroimaging data, visit our code repositories: https://github.com/canlab).

Pain Neuroimaging: Traditional and New Approaches

Pain neuroimaging has, until recently, been dominated by studies mapping the effects of noxious stimulation and pain modulation [29]. Focus has primarily been on the 'pain matrix', a general set of brain regions responsive to noxious stimuli that includes the thalamus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), insula (Ins), amygdala, primary and secondary somatosensory cortices (S1 and S2), and the periaqueductal gray (PAG) [4, 30, 31]. Activation in these regions is associated with reports of increases in pain [32]. Human electrophysiological studies and animal models further corroborate the involvement of these brain regions in nociception [33–35].

One problem with standard neuroimaging approaches is that the pain matrix is a general concept, not a precise theory: it can be activated by touch [36], cognitive demand [37], and to some degree, it can be activated even in those who lack nociceptive input [38]. Therefore, activation in the 'pain matrix' during noxious stimulation is not necessarily specific to pain [39, 40].

A second problem is that many other brain regions play important roles in shaping various aspects of pain experience and behavior. Descending modulatory pain systems interact with nociceptive signaling in complex ways (Fig. 1) that vary across individuals and contexts [41–44]. For example, pathways involving connections between the PFC and nucleus accumbens (NAc) shape pain behavior in important ways [45, 46]—but *which* aspects of pain behavior remains less clear. These pathways may interact with primary nociception [47] in some cases, but influence motivation and avoidance independent of nociception in others [48–50]. This modulatory system is

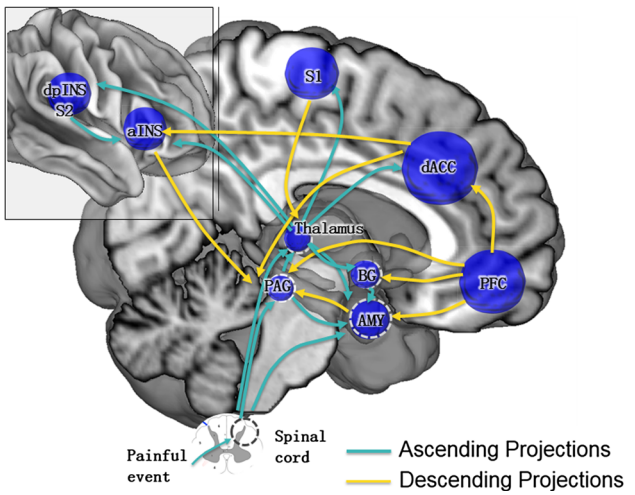

Fig. 1 The "Pain Matrix" and its Descending Modulation. Simplified overview of the brain targets of the ascending (green) and descending (yellow) modulatory pathways for pain. The "pain matrix" is comprised of the thalamus, anterior cingulate cortex (ACC), the anterior and dorsal posterior insula (aINS and dpINS), primary and secondary somatosensory cortices (S1 and S2) and the periaqueductal gray (PAG), and is often extended to include prefrontal cortices (PFC), as well as the basal ganglia (BG) and amygdala (AMY). Neuroimaging approaches to the study of these pathways must account for the complex interactions between these regions and the multiple roles any one region may play in pain perception.

further complicated by evidence that the PFC may be involved in both pain regulation [51] and pain catastrophizing [52, 53], suggesting a direct role in pain avoidance. Modeling of brain connectivity between the ventromedial PFC and PAG during pain avoidance learning also points to a critical role in avoidance beyond nociception [54]. The relationship between PFC and the NAc is just one example of a component process involved in the pain experience which remains to be understood. Indeed, the entire network of interacting components is likely to be far more complex, involving additional brain regions [55, 56], epigenetic changes [57], and glial signaling [58].

Individual studies using standard brain mapping approaches are limited in their ability to explain how neural processes interact to instantiate pain experience. Such studies yield only a collection of independent effects, rather than an integrated model of how pain is generated. Furthermore, hypotheses about where activity should be located are often vague, allowing for subjective interpretation and imprecise characterization of which regions are activated and what they may mean for pain. Thus, standard brain maps are not models of pain, and are not suitable for use as biomarkers.

Neurophysiological models of pain can be specified in ways that go far beyond general concepts like the "pain matrix", to provide quantitative, precise, testable theories about the neural representation of pain. One ingredient of such models is multi-voxel pattern analysis [59, 60]. A second is machine learning, a tool-set for creating systems that learn to make predictions by observing examples [61, 62]. These approaches can be combined into *predictive models* that integrate all available brain information into a coherent description of brain features necessary and sufficient to predict pain intensity and related outcomes [25]. When they include brain activity distributed across networks, such models treat pain as the result of interactions amongst multiple component processes and/or systems (Fig. 2A).

Several years ago, we developed a pain model called the Neurologic Pain Signature (NPS) [63]. The NPS was trained to predict participant pain ratings of four levels of thermal stimulation, ranging from warmth to painful heat. Pain reports were made under 'ideal' experimental conditions: Participants experienced randomized sequences of varying intensities, and used rating scales designed to minimize 'demand characteristics', the tendency for participants to shape their responses in order to meet experimenter expectations, and several other forms of cognitive bias [64].

The brain regions that contribute most reliably to the NPS overlap with regions in the 'pain matrix'. Significant positive NPS weights, indicating more predicted pain with greater activity, are found in the ACC, Ins, S2, and thalamus. Significant negative NPS weights, indicating less predicted pain with greater activity, are found in structures frequently deactivated by pain, such as the ventromedial PFC and precuneus (Fig. 2C). However, unlike the pain matrix, the NPS is a predictive pattern of activity, making it a single, integrative model of evoked pain. In tests to date, the NPS successfully predicts pain evoked by noxious events, with 90%–100% accuracy as long as the stimulation is clearly judged as painful [64]. This accuracy level has been replicated across multiple studies (Fig. 2D) [41, 50, 65–67].

Still, the questions remain: Is the NPS predicting *pain*, the complex psychological experience, or is it predicting a single component process that contributes to pain? Is it able to dissociate physical pain from other aversive experiences? We use the NPS and related models to illustrate the difference between standard maps and models like this one, and review what we know about the NPS so far.

Benefits of Multivariate Predictive Modeling

There are several concrete benefits of predictive models, which separate them from standard brain maps, including: (1) quantifiable metrics of representational similarity, allowing brain measures related to different outcomes (e.g., pain and negative emotion) to be compared; (2) increased sensitivity and specificity for pain and other outcomes; and (3) unbiased assessments of effect size [68].

1. *Similarity of Brain Representations.* Predictive models identify precisely specified patterns of activity, unlike standard region-based inferences, which usually involve interpreting averages over hundreds to thousands of voxels located approximately in a named brain region (e.g., 'activity in the anterior mid-cingulate'). This is advantageous because the patterns may capture subtle patterns of local functional variation that we do not yet have names for. In addition, comparing these precisely specified patterns and their output—weighted averages of activity across voxels, using the patterns as weights—provides a way of assessing *how* similar different pain-related processes are to one another. For example, experiencing somatic pain and watching someone else experience pain ('vicarious pain') produce overlapping activations: The dACC and aINS are strongly activated during both processes [65]. However, inspection of the patterns of activity within these regions reveals that activities predicting each respective process are uncorrelated. Furthermore, the pattern responses—the weighted average activity in the pattern—are separately modifiable, meaning that noxious stimuli influence only the somatic pain-related pattern, and watching others in pain influences only the vicarious pain-related pattern. This provides evidence that the brain representations underlying the two experiences are unique and dissociable.

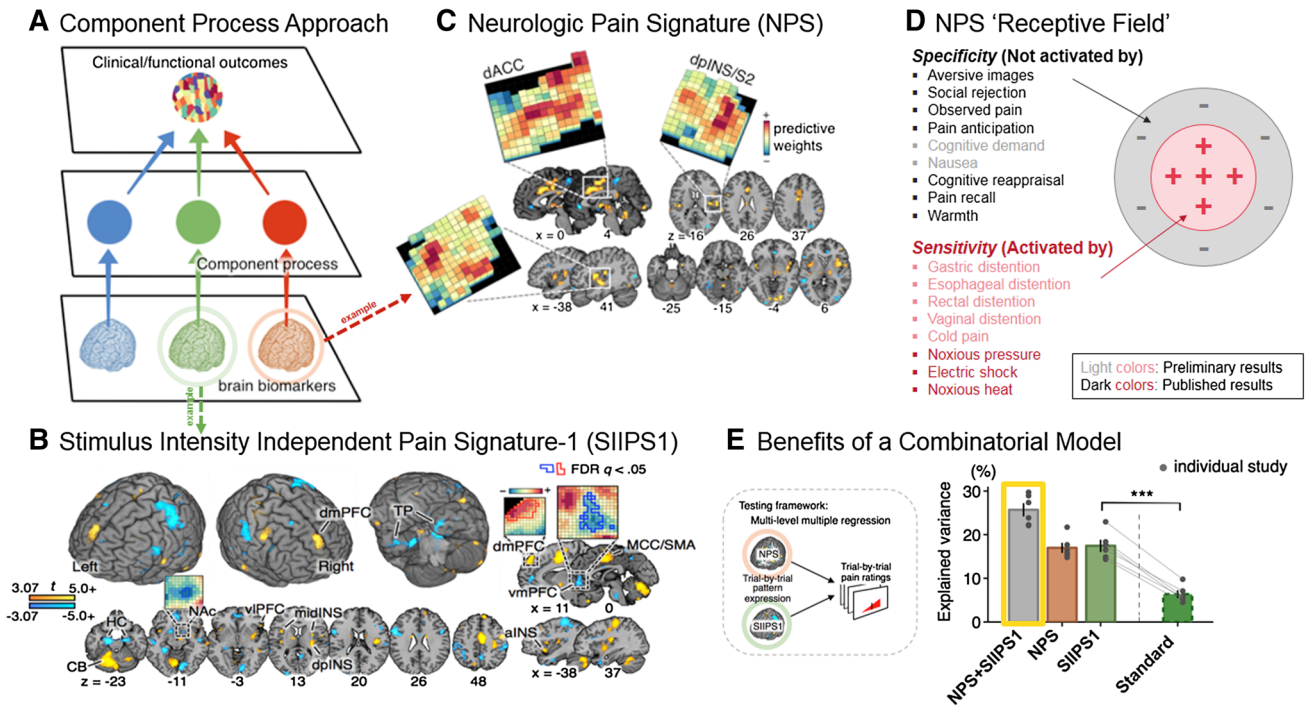

Fig. 2 Neuroimaging-based pain models can be combined to predict an individual's pain experience. **A** Component Process Approach. Patterns of activity across brain images are mapped to basic component processes, such as attention, affect, and nociception. Rather than constructing one biomarker per outcome, component models provide a set of processes that are combined in different ways to explain a pain experience. This is analogous to color, which has three components (red, green, and blue) that can be combined in different ways to form a virtually infinite number of colors (Image modified and reproduced from Woo *et al.*, 2017 [25]). **B** Stimulus Intensity Independent Pain Signature (SIIPS1). SIIPS1 is a signature for the cerebral contributions to pain rating independent of stimulus intensity and NPS response. It is an example of a component process contributing to pain. For display purposes the map is thresholded at q <0.05 false discovery rate; unthresholded patterns in selected regions are visualized in the insets. (Woo *et al.*, 2017 [67]). **C** Neurologic Pain Signature (NPS). The NPS is a signature for acute somatic pain, another component process contributing to pain. For display purposes the map is thresholded at q <0.05 false discovery rate; unthresholded patterns in selected regions are visualized in the insets (Wager *et al.*, 2013 [63]). **D** NPS 'receptive field'. A visualization of which conditions activate (sensitivity, in red) or do not activate (specificity, in gray) the NPS (Image reproduced from Woo *et al.*, 2017 [67]). **E** Left panel. Contributions of the NPS and the SIIPS1 to pain were estimated using a multilevel general linear model. The trial-by-trial responses of the NPS and the SIIPS1 were independent variables, and the trial-by-trial pain report was the outcome variable. Right panel. Bar plot of mean explained variance across 6 pain studies. 'NPS+SIIPS1' indicates total variance explained by the NPS and the SIIPS1. 'NPS' and 'SIIPS1' indicate variance explained by the NPS and SIIPS1 separately. 'Standard' indicates variance explained by the standard brain map of pain. Gray lines between 'SIIPS1' and 'Standard' connect the same study, demonstrating that the standard approach consistently explains less variance in pain ratings than the integrative pain models. ***P <0.001, one-sample t-test, which treats study as a random effect. (Image reproduced from Woo *et al.*, 2017 [67]).

Indeed, with pattern analysis we can quantify the degree of similarity with a level of precision unavailable to standard imaging analysis. When comparing the degree of shared representation, Krishnan *et al.* (2016) [65] found that the NPS explains ~90× more variance in somatic pain ratings than vicarious pain ratings, further supporting that there is very little shared representation between the processes. Finally, this study provided evidence that multi-system patterns are much more predictive of pain than local patterns within single regions. The best single regions explained an average of 4% of the variance in pain ratings, whereas the multi-system NPS explained 29.2%, 7.3× more. Together, these findings indicate that (1) pattern analysis allows finer assessments of representational similarity, and (2) local patterns alone are insufficient to accurately capture pain experience with fMRI.

2. *Sensitivity and Specificity for Pain.* Compared to the standard approach, pain models have increased sensitivity and specificity for pain outcomes. Sensitivity is the 'hit rate', the proportion of cases in which a measure returns a positive result when pain is present. Specificity is the proportion of cases in which the measure returns a negative result when pain is not present. Specificity must be evaluated relative to particular comparison conditions. For example, a brain measure may have high specificity for pain relative to rest, but low specificity relative to non-painful touch.

Most brain images show results from null-hypothesis tests, and are not precisely specified models that allow

assessment of sensitivity and specificity. They leave open the question of why activation is occurring—and, if brain activity patterns are compared across two or more conditions, what processes are driving the overlap. For example, if two pain-related processes both activate the same brain region, looking at the degree of overlap cannot tell us if this overlap is due to pain-specific processes, such as nociception, or other more general processes, such as negative affect, attention, or arousal [69, 70]. A model trained to predict perceived unpleasantness, however, can be assessed for sensitivity and specificity. Overlapping activation in measures that are predictive of behavior (e.g., those that predict pain unpleasantness), and those that are sensitive and specific for particular behaviors or outcomes, provide more meaningful inferences about shared representation.

Some measures, like the NPS measure discussed above, are trained and validated to make predictions in out-of-sample individuals—that is, the measure is based on a population model that generalizes across individuals. With such models, sensitivity, specificity, and generalizability can be quantified across diverse samples, populations, research groups, and varieties of pain. This is advantageous from the point of view of assessing specificity, as there are a large number of other conditions that may be confusable for pain (e.g., emotions, social 'pain', air puffs, itch, and aversive sounds), and it is not feasible to test all of them in a single study. It is also likely to be crucial for translational applications, which need models to be applicable across a diverse population that varies in age, gender, culture, and other demographics. The set of conditions to which a measure responds positively (i.e., those to which its sensitivity generalizes) and negatively (i.e., those against which it is specific) defines its 'psychological tuning curve' or 'psychological receptive field' [25, 70]. The tuning curve for the NPS thus far is shown in Fig. 2D, based on out-of-sample testing (with no changes in the NPS measure) in several studies [25]. In general, it shows remarkable specificity to evoked somatic pain and generalizability across multiple types of evoked pain. This does not mean that it is specific relative to every conceivable alternative condition, or that a significant NPS response can always be taken as an indicator for pain. We have observed significant variations with the NPS in the negative-response or near-zero response ranges, suggesting that inferring pain requires a significant positive response of sufficient magnitude (i.e., above some pre-specified criterion threshold) in the test condition [63].

3. *Unbiased Estimates of Effect* Size. Effect size is a unit-free measure of the strength of an effect independent of sample size. If an effect size is large enough, a finding may have clinical importance [28, 71]. Standard brain mapping analyses do not optimize relationships between brain activity and the outcome of interest, thus they yield modest effect sizes [72]. In addition, effect size estimates from standard brain maps are often optimistically biased [68, 73]. This is because the standard approach induces a selection bias: Thousands of independent tests are conducted, but only the subset of statistically significant effects are reported. Multivariate predictive models integrate all voxels into a single test, and test the model on out-of-sample data with independent sources of error, eliminating bias. However, it is crucial that the test datasets are independent of the training data.

Multivariate predictive models are also designed to maximize effect sizes, by optimizing patterns and other model parameters to explain maximal variance in the outcome(s). For example, Woo *et al.* [67] developed a multivariate predictive model of pain called the stimulus intensity independent pain signature-1 (SIIPS1; Fig. 2B), so named because it was designed to capture fluctuations in pain independent of noxious stimulus intensity and NPS responses. Across six studies, they compared the variance explained (R^2) in pain reports by two models: (1) the standard approach, which averages over separate regressions in individual voxels; and (2) the predictive model approach, here the multivariate SIIPS1 model. The first explained only 6.4% of the variance in pain ratings, whereas the SIIPS1 explained 17.4% (Fig. 2E). The SIIPS1 model yielded an effect size more than twice the size of the standard map, even when predictions were averaged across voxels to reduce noise. These percentages are relatively modest when explaining pain experience at a single moment in time. The model explains even greater variance when groups of trials are averaged within a person. For example, the SIIPS1 can discriminate between conditions that elicit modest differences in pain (1 standard deviation) with 90% or greater accuracy when averaging across 7–8 trials per condition, or combined with the NPS, in 3–4 trials per condition [67, 74].

In summary, brain-based models of pain (1) utilize fine-grained pattern information and treat pain as a distributed process by integrating activity across whole brain networks, (2) have increased sensitivity and specificity for individual components of pain, and (3) yield unbiased estimates of effect size with greater clinical impact.

The Application of Pain Models in Neuroimaging

Pain models that capture patterned fMRI activity within and across brain regions can move us forward towards understanding the neurological bases of pain. Open questions include: (1) which components of pain are affected by which types of somatic, psychological, and pharmacological manipulations; (2) how these effects differ across individuals and populations; and (3) which brain processes reflect which aspects of pain.

Models like the NPS and SIIPS1, discussed above, provide an extensible foundation from which we may develop a more complex and nuanced understanding of these issues. They make testable predictions that can be evaluated across studies, research groups, and contexts—and provide quantitative benchmarks against which to evaluate future models. Neither the NPS nor the SIIPS1 is a signature of "Pain" with a capital *P*. We view them as pain-related measures that reflect a subset of the complex physical and psychosocial ingredients that make up reported pain experience. Here, we review some 'knowns' and some 'known unknowns' based on tests of the NPS so far.

Generalizability. The NPS, although designed to detect pain related to temperature, does accurately detect other forms of acute physical pain, including visceral distention [25], mechanical pressure [65], and electric shock [66]. It also reflects pain modulation by opioids and serotonergic drugs [63]. The NPS does not respond to aversive experiences that do not involve a physical insult, such as the viewing negatively arousing images [75], experiencing social rejection [76], observing another person in pain [65], anticipating pain [63, 77], or the modulation of pain by some forms of placebo and cognitive regulation [50]. These findings indicate that the NPS is sensitive and specific to a neurophysiological component of pain, but it is not sensitive to cognitive components of pain. Furthermore, the NPS, when combined with SIIPS1, can accurately discriminate fibromyalgia patients from pain-free controls [78]. This indicates that the NPS is not the only pain signature; it is one of a large set of potential models that can capture complementary aspects of pain. Identifying the NPS is a step towards identifying other components that are either related to or independent of the NPS.

As illustrated, neuroimaging models of pain, developed using pattern analysis machine learning, can be combined and leveraged to ultimately construct complete models of individual pain experiences. Such models are advantageous because they are precisely defined, applicable to individual persons, and neuroscientifically interpretable [25, 79]. This approach augments self-report and behavioral measures. More fundamentally, this approach helps us to understand the brain basis of pain within individuals. Thus, integrative pain models allow the field of neuroimaging to move beyond pain concepts onto pain mechanisms.

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