

<sup>1</sup> Pain and value-based decision-making: An  
<sup>2</sup> introduction and implications for neuroeconomics

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<sup>16</sup> **Abstract**

<sup>17</sup> Pain is central to numerous clinical conditions and is the main reason that individuals seek  
<sup>18</sup> medical treatment. Although pain involves subjective decisions and the psychophysics  
<sup>19</sup> and neural basis of pain have been studied for decades, few have applied neuroeconomic  
<sup>20</sup> approaches to the study of pain and its modulation. In this chapter, we provide an  
<sup>21</sup> introduction to pain for those in the field of neuroeconomics. We focus on acute pain,  
<sup>22</sup> which can be experimentally manipulated and studied using neuroscience tools. We first  
<sup>23</sup> review aspects of pain-related decisions and the circuits that support different aspects of  
<sup>24</sup> pain. We then discuss the common neural pathways that support pain and reward, as well  
<sup>25</sup> as evidence of their interactions. Next, we introduce how pain might be viewed from a  
<sup>26</sup> neuroeconomic perspective, focusing on the value of pain. Finally, we address hypotheses  
<sup>27</sup> and outstanding questions for those at the intersection of pain and neuroeconomics. By  
<sup>28</sup> providing this introduction, our goal is to inspire a new generation of studies that bridge  
<sup>29</sup> neuroeconomics and pain to tackle critical challenges such as those brought about by the  
<sup>30</sup> opioid epidemic.

<sup>31</sup> **Keywords**

<sup>32</sup> pain, value, affect, decision-making, nociception, neuroeconomics

<sup>33</sup> **Introduction**

<sup>34</sup> Neuroeconomics has provided powerful insights on the brain mechanisms of decision-  
<sup>35</sup> making across a wide variety of domains, including primary and secondary reinforcers  
<sup>36</sup> [1, 2], social learning and cognition [3, 4], and even political preferences [5]. Although  
<sup>37</sup> it is widely accepted that a fundamental drive for all organisms is to seek pleasure and  
<sup>38</sup> avoid pain, and many have reviewed general relationships between pain and reward [6, 7],  
<sup>39</sup> only recently have researchers begun linking the vast literature on neuroeconomics with  
<sup>40</sup> the diverse neuroscience of pain. We believe that this is an essential path forward and  
<sup>41</sup> that neuroeconomic perspectives can provide important insights on pain and pain-related  
<sup>42</sup> decision-making, similar to the recent emphasis in the field of computational psychiatry.  
<sup>43</sup> Reward, pain, and decision-making can interact in ways that can be either devastating  
<sup>44</sup> (e.g., the opioid crisis) or beneficial (e.g., placebo effects). In this chapter, our goal is  
<sup>45</sup> to address ways in which economic theory can provide insights on the clinical problem  
<sup>46</sup> of pain and motivate those in the field of neuroeconomics to consider how their findings  
<sup>47</sup> may be relevant for pain. We first provide an introduction to pain for those in the field of  
<sup>48</sup> neuroeconomics, with a focus on pain-related decisions. We next address the relationship  
<sup>49</sup> between the neural systems that support pain and reward and their interaction, laying a  
<sup>50</sup> foundation for using economic theory to understand pain decision-making. From here, we  
<sup>51</sup> explore how the fundamentals of neuroeconomics are relevant to the study of pain from a  
<sup>52</sup> behavioral perspective, and highlight key studies that have evaluated the value function  
<sup>53</sup> of pain. Finally, we discuss outstanding questions and implications of this work for future  
<sup>54</sup> studies and the amelioration of pain and related clinical conditions.

55    **1 Pain-related decision-making and relationship with**  
56    **neural circuits**

57    While most of us have been asked by a clinician to rate our pain on a simple 0-10 scale  
58    ranging from "no pain" to "most pain imaginable", the psychophysics of pain and its  
59    measurement has been the subject of extensive study and debate for over 50 years. In  
60    fact, even the definition of pain remains hotly debated and regularly revised [8, 9]. For the  
61    purpose of this chapter, we focus on pain as defined most recently by the International  
62    Association for the Study of Pain (IASP) [9]: "An unpleasant sensory and emotional  
63    experience associated with, or resembling that associated with, actual or potential tissue  
64    damage". Pain is different from nociception, which is defined as "The neural process  
65    of encoding and processing noxious stimuli." [8]. Thus, from an economic standpoint,  
66    nociception is most analogous to objective value, while the conscious pain experience is  
67    most related to subjective value. Like valuation and perception, the mapping between  
68    objective noxious input (e.g., temperature in thermal pain; Figure 1A) and subjective  
69    pain appears to be a nonlinear and described by a power function [10], although the exact  
70    form of the power function can differ depending on many factors, including both aspects  
71    of the noxious stimulus itself (e.g., modality, duration) and how pain is measured [11, 12]  
72    . Unlike economic value, which is often evaluated with behavioral measures (e.g., choices,  
73    willingness-to-pay, etc.) and sometimes subjective ratings (e.g., desirability ratings), pain  
74    is based entirely on patients' subjective ratings. Even the revised definition of pain [9]  
75    states "A person's report of an experience as pain should be respected" while noting "Ver-  
76    bal description is only one of several behaviors to express pain; inability to communicate  
77    does not negate the possibility that a human or a nonhuman animal experiences pain."  
78    We return to the measurement of pain and relationship with economic principles later in  
79    section 3.

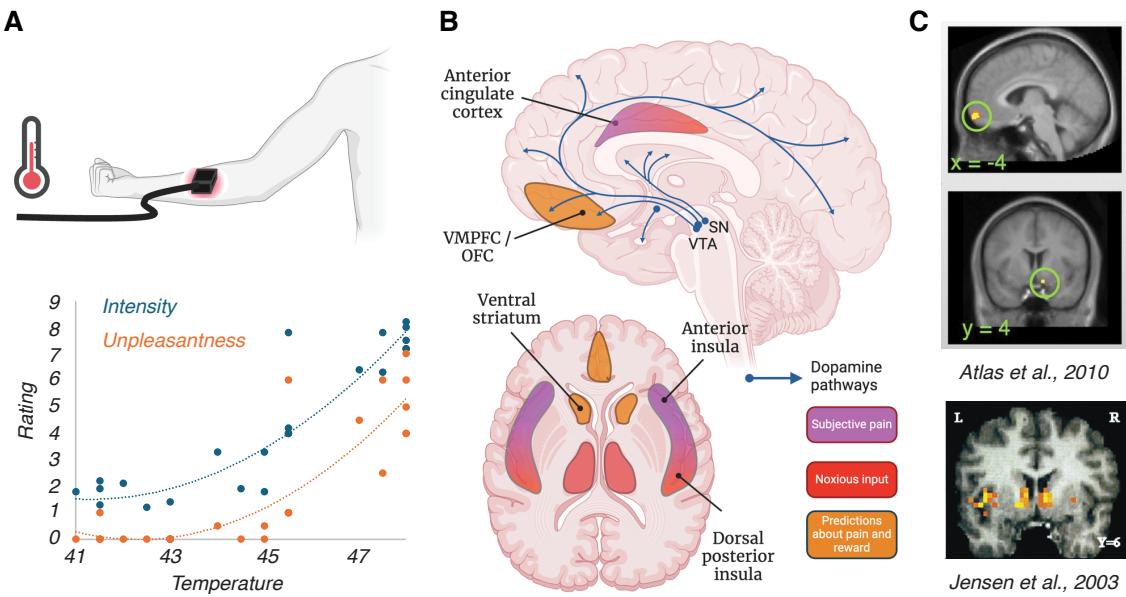
80    The distinction between pain and nociception is accompanied by segregation in the

81 central nervous system. Several studies [13–15] have revealed gradients within the insula  
82 and anterior cingulate cortex (ACC; Figure 1B) that map from objective nociceptive  
83 input (posterior) to subjective pain experience (anterior), and whole brain patterns have  
84 been identified that reliably predict pain, rather than nociception [16, 17]. Other studies  
85 indicate that brain regions show diverse stimulus-response functions with relationship to  
86 noxious stimulus intensity and subjective pain [18, 19]. Thus, the distinction between  
87 objective noxious input and subjective pain is meaningful, based on responses in the  
88 central nervous system and distinct brain circuits that respond to either noxious stimulus  
89 intensity or subjective pain.

90 Notably, pain is not only distinct from nociception, pain also contains two key com-  
91 ponents: intensity, which describes pain’s sensory features, and unpleasantness, or the  
92 affective and motivational features of pain. Although unpleasantness and intensity are  
93 highly correlated under normal circumstances (e.g., Figure 1A), the two can be disso-  
94 ciated behaviorally and anatomically. For example, intensity and unpleasantness have  
95 distinct stimulus-response functions [20–22] and opioid analgesics [23, 24], hypnosis [25],  
96 unpleasant odors [26], and some forms of meditation [27] and emotion regulation [28] can  
97 all influence pain unpleasantness while leaving pain intensity intact. Conversely, atten-  
98 tion can alter pain intensity without affecting unpleasantness [26]. These dissociations  
99 are also present in the central nervous system. Studies generally suggest that a medial  
100 pain system (e.g. ACC, insula) is involved primarily in affective components of pain  
101 while a lateral pain system (primary and secondary somatosensory cortex) is required for  
102 sensory components of pain. Variations in unpleasantness, controlling for intensity, are  
103 correlated with activation in the ACC [29, 30], while variations in intensity, controlling  
104 for unpleasantness, are associated with activation in primary somatosensory cortex (S1)  
105 [31]. ACC and insula lesions are associated with altered affective responses to pain [32,  
106 33], while patients with somatosensory lesions find noxious stimuli unpleasant without be-  
107 ing able to localize the stimulus [34]. The mechanisms that support pain unpleasantness

108 are likely to be shared across areas of negative affect, consistent with recent fMRI work  
 109 that used machine learning to identify a brain signature to predict negative affect across  
 110 modalities, including thermal pain, pressure pain, aversive sound, and aversive images  
 111 [35]. Responses in midline, forebrain, insular and somatosensory regions predicted un-  
 112 pleasantness regardless of modality, while stimulus-specific negative affect was predicted  
 113 by responses in primary and secondary sensory cortices. In the final section of this chap-  
 114 ter, we address how future work should use neuroeconomic theory to gain insights on the  
 115 functional significance of the dissociation between pain intensity and pain unpleasantness,  
 116 similar to work on wanting versus liking [36, 37].

117 Together, these studies indicate that there are important distinctions between a) pain  
 118 and nociception, and b) sensory and affective components of pain, and that pain-related  
 119 decision-making involves both specialized brain circuits (e.g., those that contain noci-  
 120 ceptive neurons) and systems that are likely to be conserved across domains of negative  
 121 affect. From this foundation, we now consider how neuroeconomic approaches may be  
 122 useful for the study of pain.



123  
 124 **Figure 1. Pain psychophysics and associated brain pathways.** A. *Top:* Studies  
 125 of acute pain use specialized devices to deliver noxious stimuli. Here, a thermode

126 delivers heat at different temperatures to a participant's forearm. *Bottom:* Participants  
127 are asked to rate pain in response to changes in noxious stimulus intensity. This figure  
128 depicts example data from a healthy participant who separately rated the intensity and  
129 unpleasantness of an 8-second thermal pain stimulus applied to the forearm at different  
130 temperatures. Both aspects of pain are fit with a power function. B. Cortical regions  
131 such as the anterior cingulate cortex and the insula differentiate between subjective pain  
132 (purple) and noxious input (red). Regions involved in subjective pain overlap with those  
133 involved in pain affect and affective processing more generally. In addition, targets of  
134 dopamine pathways such as the ventral striatum and the ventromedial prefrontal cortex  
135 (VMPFC) and orbitofrontal cortex (OFC) are involved in updating predictions about  
136 pain, similar to their role in error-driven reward learning. C. Traditional reward  
137 networks exhibit activation during anticipation of pain. *Top:* The ventral striatum and  
138 VMPFC show elevated activation in response to cues that predict high pain, relative to  
139 low pain (reprinted with permission from [38]). *Bottom:* The ventral striatum also  
140 shows elevated activation in response to conditioned cues that predict unpleasant  
141 electric shocks relative to neutral cues (reprinted with permission from [39]). Figure  
142 created in part using biorender.com.

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## 2 Pain and Reward: A Common Currency?

Many brain regions involved in reward and appetitive learning and decision-making play similar roles in pain and aversive learning (for reviews, see [6, 7]). In particular, dopaminergic mesolimbic / corticostriatal circuits involved in value processing, including the ventral striatum / nucleus accumbens (VS/NAc), ventromedial prefrontal cortex (VMPFC), and orbitofrontal cortex (OFC; Figure 1B), are implicated in both acute and chronic pain. Predictions about painful stimuli are associated with anticipatory responses in the VS [38–43] and VMPFC/OFC [38, 40] and value signals and prediction errors in these regions update during aversive learning in ways that are consistent with quantitative models of reinforcement learning [40–43], similar to reward learning. Studies that compare pain with monetary reward indicate that the VS responds similarly to the anticipation of pain and reward while the OFC and anterior insula seem to separately code valence [40]. Of course, value circuits are highly heterogeneous, and thus it is quite possible that pain and reward processing remain segregated at the level of individual neurons, even if they influence similar structures.

However, even if the neuronal underpinnings of appetitive and aversive value process-

ing remain separate, there are functional interactions between pain and reward processing at the level of both brain and behavior. This bidirectional, interactive relationship is evident both in basic laboratory studies of acute and chronic pain and when we consider the high rates of anhedonia in chronic pain [44] and comorbidity between chronic pain and depression [45]. Furthermore, although we can independently manipulate pain and reward, the two are actually intrinsically linked, as pain relief is rewarding (i.e. negative reinforcement; for review, see [46]). Relief can be operationalized experimentally as transient relief from tonic pain [43], responses at pain offset [47, 48], or relative relief based on the context surrounding pain (i.e. receiving a moderately painful stimulus when expecting high pain [49, 50]. In healthy volunteers, pain relief is associated with activation in the VS and OFC/VMPFC [43, 47–50]. Relative to healthy volunteers, people with chronic pain show reduced responses to pain offset in the NAc [47] and the dopaminergic ventral tegmental area (VTA) [51]. Animal models confirm that pain offset engages VTA dopamine neurons [52] and dopamine release in the NAc shell [53] and that inhibiting VTA dopamine prevents relief-related conditioned place preference [54]. Notably, reward is also associated with relief via analgesic treatments: Healthy individuals who report higher trait reward responsivity experience stronger opioid analgesia [55], and individuals who show stronger NAc responses to monetary reward experience stronger placebo analgesia and have higher placebo-induced dopamine binding in the VS [56].

Together this work highlights the many ways in which pain and reward are intrinsically linked. From this foundation, we now turn to direct consideration of how the basic tenets of neuroeconomics have the potential to lead to new insights in our understanding of pain.

200    **3 Neuroeconomic Approaches and their Utility to**  
201    **the Study of Pain**

202    Two main aspects of neuroeconomic theory are particularly helpful in conceptualizing  
203    decision-making in the context of pain and reward. First, value serves as a unifying signal  
204    for decision-making because it straddles both ends of the valence dimension (see Box 1).  
205    In other words, value is not only reward. The value of a stimulus or an action can be  
206    negative when the outcome is a loss and positive when the outcome is a gain. While most  
207    outcomes in behavioral economics studies are monetary losses and gains, the results from  
208    these studies could be generalized to aversive outcomes like pain when conceptualized as a  
209    loss or diminishment in well-being. Moreover, appetitive and aversive outcome values may  
210    be integrated through a cost-benefit computation into a net decision value [57]. A unified  
211    monotonic value signal has been consistently found to be encoded in the VMPFC and  
212    anterior part of VS [58, 59]. Critically, the brain's valuation signal in VMPFC appears  
213    to be invariant to the specific type of good or outcome that is evaluated [60, 61] (from  
214    monetary to consummatory rewards or consumer goods), while OFC seems to preserve  
215    information about the specific identity of the outcome [62–64]. This evaluation happens  
216    automatically even in the absence of a behavioral output or an overt choice, such as when  
217    passively viewing stimuli [65, 66].

218       The second aspect is that neuroeconomics rests on the premise that the brain "trans-  
219    forms" the objective value of the stimuli or options available (for example, monetary  
220    rewards or consummable goods) into a *subjective value* representation, which is used for  
221    decision-making. This is relevant to pain because it is also characterized by a *subjective*  
222    experience that is distinct from the objective parameters of the painful stimulus itself,  
223    such as its intensity or nature. The mapping between objective and subjective value  
224    is referred to in neuroeconomics as the *utility function* and is central to understanding  
225    both individual differences in decision-making and to making predictions about choice

226 behavior under uncertainty (Box 1). Drawing parallels between pain and reward-related  
227 decision-making is possible and application of approaches from neuroeconomics, as we will  
228 discuss below, have started to expand our understanding of the similarities and differences  
229 between the two.

## 230 4 The Value of Pain

231 Using a neuroeconomics approach to the study of pain implies inferring the subjective val-  
232 uation process by presenting the decision-maker with options of varying objective value.  
233 Park et al. [67] directly derived a participant-specific stimulus-response function by fit-  
234 ting a power model to pain ratings obtained as participants received shocks of increasing  
235 intensity. They found the shape of the objective stimulus to subjective experience func-  
236 tion to be nonlinear , such that increases in the intensity of the pain stimulus lead to  
237 exponentially increasing perceived pain (Box 1, panel A, left). Using this function to per-  
238 sonalize the pairing of monetary reward and pain, they tested different subjective value  
239 models against behavior and neural activity in VMPFC, OFC, and subgenual ACC. In  
240 all cases, the best model was one that performed a nonlinear integration of reward and  
241 pain. Evidence of pain and reward value integration as a cost-benefit computation has  
242 also been reported in the ACC and VS, such that these areas' responses to reward were  
243 attenuated in the presence of pain [68]. More recently, Slimani et al. [69] used the same  
244 approach as Park et al. [67] to personalize painful stimuli according to the participant-  
245 derived stimulus-response function, and created trials that tiled the space between pain  
246 detection and tolerance thresholds . They then evaluated the participants' willingness to  
247 accept monetary rewards paired with different levels of painful electrical stimulation, and  
248 estimated the utility function of pain from the points of indifference (50% probability of  
249 accepting a specific offer of combined monetary reward and pain). The best pain utility  
250 model was a quadratic function of experienced pain level (Box 1, panel A, right).

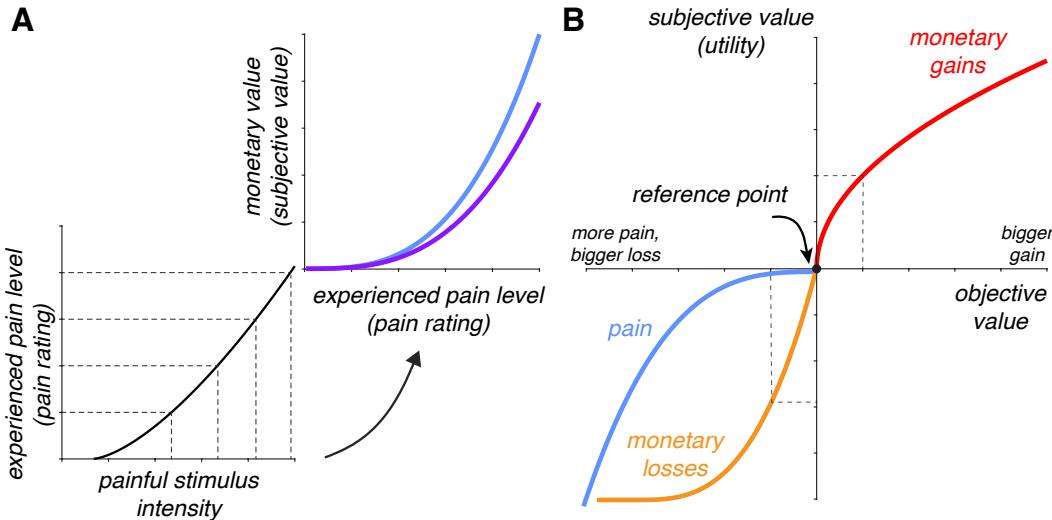
251 The shape of this utility function for pain has implications for decision-making under  
252 risk (see Box 1). A concave utility function means that the expected utility (probability  
253 \* utility) of a lottery is significantly lower than the utility of its expected value (prob-  
254 ability \* objective value), leading to the preference of a smaller more certain offer over  
255 a higher riskier one. Conversely, convexity is equivalent to the presence of risk-seeking  
256 preferences. As follows, a convex pain value function would predict that the individual  
257 is willing to take risk in order to avoid pain. Interestingly, while the outcomes in the  
258 Slimani et al. study were not probabilistic, the curvature of the pain value function they  
259 derived suggests a tendency for risk aversion for pain (willingness to accept some pain  
260 with certainty but avoid options that could lead to more pain with some probability  $< 1$ ).  
261 While nonlinearities have also been described for the utility function for monetary losses  
262 (Box 1, panel B), risk tolerance rather than risk aversion has been typically observed for  
263 monetary reinforcers. Few empirical studies have directly investigated the shape of the  
264 utility function for pain, but there is evidence that risk preferences may vary depending  
265 on the attribute of pain (intensity versus duration in a cold-pressor task) [70], with in-  
266 dividuals exhibiting risk aversion (concave function) for pain intensity but risk seeking  
267 (convex function) based on pain duration. This divergence has been considered in prior  
268 work that posits that the additional affective value of a reinforcer (such as pain) could be a  
269 separate input into the decision, thereby biasing it from its purely cognitive value [71, 72].  
270 There is also evidence that risk preferences for pain may vary depending on the object of  
271 pain, with individuals being more risk averse when pain is to be experienced by a stranger  
272 compared to themselves or their loved ones [73], contrary to what has been reported for  
273 monetary outcomes. More research is needed to resolve to what extend there are general  
274 or distinct mechanisms of valuation for aversive outcomes of different modalities such as  
275 primary (e.g. pain) and secondary (e.g. monetary losses) reinforcers, and how affective  
276 and social factors modulate these valuation processes.

277 Consistent with other predictions from the neuroeconomic framework, the pain value

278 function seems to be affected by monetary range (reward context) [69], such that availability  
279 of larger rewards decreased the willingness to accept pain offers that were previously  
280 tolerated and accepted. This feature of pain valuation recapitulates predictions from the  
281 efficient coding hypothesis, how optimal neuronal encoding according to reward availability  
282 in the environment leads to contextual changes in valuation, a phenomenon known as  
283 *range adaptation* [74, 75]. That reward context impacts the pain value function in this  
284 way further supports the notion that pain and reward interact and are integrated into a  
285 cost-benefit computation that guides choice behavior [68]. Range adaptation and another  
286 contextual mechanism known as reference-dependence (Box 1) have been proposed to explain  
287 irrational decision-making behavior [76] and have been identified in previous studies  
288 of appetitive and aversive value learning [77].

289 It is also possible to conceptualize the presence of pain as affecting the sensitivity to  
290 reward. This is consistent with the phenomenon of reference-dependence as described in  
291 Prospect Theory (Box 1, Panel B). Pain could thus shift the frame of reference to a worse  
292 state of the world. A leftward shift in the utility function could lead to a relative change  
293 in the utility perceived to be derived from the same reward [78, 79], potentially increasing  
294 reward seeking. Several studies have explored the effect of acute pain on economic choice  
295 and identified a tendency for acute pain to lead to increase in risk tolerance and delay  
296 discounting [80–82]. Moreover, individuals with chronic pain exhibit difficulties in distin-  
297 guishing high versus low risk [83] and have an increased preference for immediate rewards  
298 [84–86]. One study has reported that a prospective procedure aimed at reducing delay  
299 discounting—episodic future thinking—may be lower pain severity in chronic pain patients  
300 through a decrease in impulsive decision-making [87]. The neural mechanisms of these  
301 pain-induced shifts in reward related behavior are not known. One possibility is that pain  
302 is impacting the valuation itself through a sort of gain modulation, as has been posited  
303 for other internal states such as craving [88]. Future work could address this question by  
304 combining careful neuroeconomic modeling combined with brain measures of valuation.

BOX 1:



A. *Left:* Pain stimulus-response function mapping the objective stimulus intensity (nociception) to the subjective pain experience. *Right:* Resulting pain ratings can be used to derive a theoretical utility function that maps the subjective experience of pain to monetary value (adapted from [67, 69]). The pain value function can vary across individuals (blue vs. purple). B. Utility functions for monetary gains (red) and losses (yellow) as described by Prospect Theory [89]. Utility function for pain (blue) as derived from A [69].

While Prospect Theory's prediction of a "reflection effect" for monetary outcomes (concavity for gains and convexity for losses) seems to generalize to feelings [90], the pain utility function described in panel A (right) does not show the same pattern. The shape of the pain function indicates that willingness-to-accept decreases with each increase in pain level (more and more money is needed to accept). Individuals thus seem to exhibit risk aversion for experienced pain level [70, 91].

## 306 5 Conclusions and Future Directions

307 The central thesis that avoiding pain and procuring reward as two essential motivators of  
308 animal behavior is present in philosophy, economics, and neuroscience. In the utilitarian  
309 theory advanced by Jeremy Bentham, the pains and pleasures we experience should not  
310 only be quantifiable, but most importantly, contribute jointly to constructing the organiz-  
311 ing force of behavior—utility [92]. Recent behavioral and neural studies have started to  
312 test the limits of this old idea, and begun to paint a more complex picture of interrelated  
313 affective and cognitive processes involved in pain-related decision-making.

314 Several open questions remain. First, given the focus of neuroeconomics on choice be-  
315 havior should pain research adopt behavioral rather than self-reported measures of pain for  
316 the development of objective biomarkers? A similar discussion emerged in the field of psy-  
317 chiatry recently, which has had to wrestle with poor correlation between self-report scales  
318 and task-based behavioral measures, and worse prediction of real-world outcomes from  
319 behavior compared to self-report [93, 94]. Rather than task-based behavioral measures  
320 replacing self-report, they may complement each other, by providing different sources of  
321 information. Research is needed to disambiguate what each type of measure is useful for.  
322 Second, while the distinction between pain and nociception might parallel the mapping  
323 between value and subjective value, how can we think of the distinction between intensity  
324 and unpleasantness in the realm of pain? If pain value can be indirectly linked to intensity  
325 (through subjective pain ratings, for example), is the derived value function also capturing  
326 unpleasantness or the hedonic aspect of pain? Neuroeconomics has encountered a similar  
327 dichotomy in thinking about the difference between "wanting" versus "linking" a reward  
328 [36, 95]. Just as pain intensity and unpleasantness can be uncorrelated, a reinforcer can  
329 be intensely "wanted" but not necessarily "liked", or vice versa. Clinical examples of  
330 this difference are often seen in individuals with chronic substance disorders whose drug  
331 consumption is sought (wanted) despite no longer leading to a positive hedonic experience  
332 [96]. Neuroeconomists have proposed this divergence can be resolved through multiple

333 utility functions [97] or posited "liking" as an early stage of value learning [37], but this  
334 remains an issue of active inquiry and interest in the field. Finally, given the interrelated  
335 nature of pain relief and reward, it is fruitful to measure how interventions that specif-  
336 ically target pain unpleasantness, such as opioid analgesics, impact economic decisions.  
337 Mu-opioid receptor activation has been shown to increase choices for high-value / high-  
338 probability targets [98], and individuals receiving treatment for opioid use disorder with  
339 medications such as buprenorphine or methadone become more tolerant of uncertainty  
340 prior to a reuse event [99]. More research is needed in bridging the neuroeconomics of  
341 pain relief and that of opioid addiction.

342 The devastating consequences of the opioid use disorder epidemic in the United States  
343 and the lack of tangible solutions for the safe treatment of chronic pain conditions have  
344 made more urgent the call for progress in this research. Similar to recent efforts in  
345 computational psychiatry that apply neuroeconomics and computational neuroscience  
346 frameworks to clinical problems in mental health, a new generation of studies should use  
347 these methods to advance our understanding of pain and pain-related behaviors.

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