

Comprehensive review

# Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction

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## ABSTRACT

Converging preclinical, and human epidemiological, neuroimaging, and genetic evidence suggests a central role for dopamine neurotransmission in modulating pain perception and analgesia. Dysregulation in dopamine signaling may modulate the experience of pain both directly, by enhancing or diminishing the propagation of nociceptive signals, and indirectly, by influencing affective and cognitive processes, which affect the expectation, experience, and interpretation of nociceptive signals. Hypersensitivity to pain and high rates of comorbid chronic pain are common in disorders linked with deficits in dopamine system function, including disorders of mood and affect, substance abuse, and Parkinson disease. Hyposensitivity to pain, however, is common in patients with schizophrenia, which has been linked with excessive dopamine neurotransmission. Although patients are typically affected most by the primary symptoms of their disorders, alterations in pain perception may further increase the burden of their illness, compromising their quality of life. The present review focuses on this relationship, and discusses clinical and potential therapeutic implications for both patients with dopamine-related disorders and those with chronic pain syndromes.

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## 1. Introduction

Individual differences in sensitivity to pain, and the capacity to recruit endogenous antinociceptive systems to counteract noxious stimuli, reflect natural variability in central pain-processing systems. While it is well established that endogenous opioids play a key role in modulating these systems [44,175], emerging research implicates central dopamine (DA) signaling as another important modulator of pain perception [10,45,86]. This view is consistent with observations of analgesic properties of drugs, including levodopa [51], morphine [119], nicotine [17], alcohol [120], and amphetamines [25], which enhance DA neurotransmission. Given this link between analgesia and DA signaling, one would expect that hyper-responsivity to pain may occur at unexpectedly high rates in patients with disorders that involve abnormalities in DA functioning, including disorders of mood and affect, schizophrenia, substance abuse, and Parkinson disease [16]. Although these patients are generally affected most by the primary symptoms of

their disorders, the impact of dysregulated DA signaling systems on pain perception may further increase the burden of their illness, compromising their quality of life. This review focuses on this relationship, and discusses clinical and therapeutic implications both for patients with DA-related disorders, and those with chronic pain syndromes.

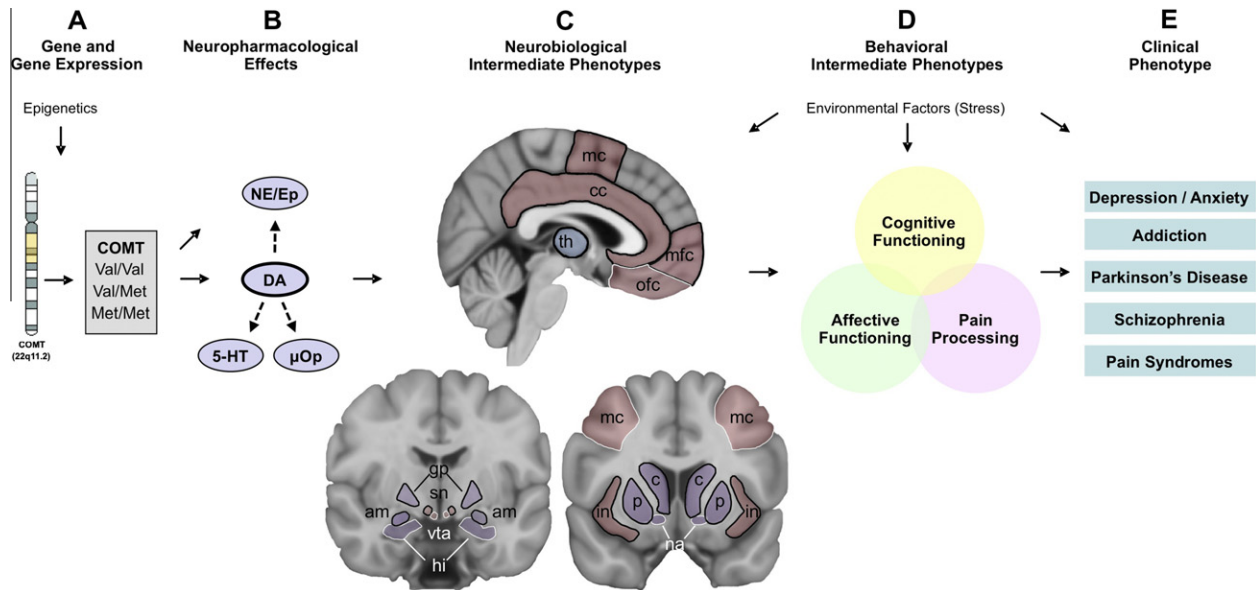
## 2. The cerebral dopamine system

### 2.1. The functional neuroanatomy of the dopamine system

Several neuroanatomical pathways, involving the brain regions illustrated in Fig. 1C, support DA signaling across the brain. Neurons that comprise the nigrostriatal DA pathway project from the substantia nigra to dorsal striatal structures, including globus pallidus, putamen, and caudate nucleus. This pathway, which degenerates in patients with Parkinson disease, has a well-established function in sensorimotor coordination and control. The mesocorticolimbic DA pathway is comprised of neurons that project from the ventral tegmental area of the midbrain to subcortical structures, such as the nucleus accumbens, thalamus, hippocampus, and amygdala. Distinct projections from the ventral tegmental area also innervate cortical regions, including ventromedial,

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**Fig. 1.** Pleiotropic effect of the valine (Val)/methionine (Met) polymorphism of the gene that codes for catechol-*O*-methyltransferase (COMT). (A) Epigenetic events influence the expression of the COMT gene. (B) Expression of Val and Met polymorphisms of the COMT gene primarily affects the rate at which dopamine (DA) is catabolized in the medial prefrontal cortex (PFC), directly influencing synthesis of norepinephrine (NE) and epinephrine (Ep), which are also catabolized by COMT. In addition, the rate at which DA is catabolized has indirect effects on serotonin (5-HT) and  $\mu$ -opioid ( $\mu$ Op) system activity. (C) Neurobiological intermediate phenotypes. Genetic variability in COMT polymorphisms has direct and indirect effects on DA activity across brain regions that comprise the DA system. This includes regions that have a relatively higher density of D1-like DA receptors (red), D2-like DA receptors (blue), or equal density of both receptor types (purple). There is a substantial overlap between these brain regions and those that are most commonly implicated in pain processing (outlined in black; Apkarian et al., 2004 [5]). Abbreviations: mc = motor cortex; cc = cingulate cortex; mfc = medial prefrontal cortex; ofc = orbitofrontal cortex; th = thalamus; gp = globus pallidus; sn = substantia nigra; am = amygdala; vta = ventral tegmental area; hi = hippocampus; c = caudate; p = putamen; in = insula; na = nucleus accumbens. (D) Behavioral intermediate phenotypes. Neurobiological intermediate phenotypes, as shown in C, can influence a cluster of behavioral intermediate phenotypes. (E) Clinical phenotypes. The cluster of behavioral phenotypes can result in differential clinical phenotypes, possibly through variations in environmental factors, including injury or psychosocial stressors.

dorsolateral, and orbitofrontal cortices, motor areas, anterior and posterior cingulate, and insular cortices. The mesocorticolimbic pathway participates in attention regulation, motivation, and reward processes (see the following for reviews of anatomy [12,83,133, 138,146]). DA neurotransmission in both pathways is linked with responses to salient or arousing cues, regardless of whether those cues are associated with reward or require motor responses (reviewed by [68]).

## 2.2. Mechanisms of dopamine neurotransmission

Occupancy of D1-like postsynaptic receptors by DA results in increased postsynaptic neuronal firing. In contrast, occupancy of D2-like receptors by DA inhibits the postsynaptic neuron from firing, thus preventing subsequent excitatory neurotransmission [3]. As depicted in Fig. 1C, the densities of D1- and D2-like DA receptors vary across the brain. Both receptor types are present in equally high density in the striatum, and in similar but lower densities in the amygdala and the hippocampus [60]. Differences in density occur in prefrontal and cingulate cortices, where D1-like receptors are more prevalent than D2-like receptors, while receptor density in the thalamus is higher for D2- than D1-like receptors [60].

As depicted in Fig. 2, 2 distinct modes of DA neurotransmission are proposed to regulate DA differentially in cortical and subcortical brain regions (reviewed by [53]). In subcortical regions, low-level background, tonic DA release occurs via the slow, irregular firing of DA neurons, which are regulated by glutamatergic cortico-striatal inputs. Tonic DA levels, which are defined by the amount of DA present at steady-state concentrations in extra-synaptic space [47,137], exert an enabling influence on post-synaptic receptors, which impact the motor, cognitive, and motivational systems often affected by Parkinson disease [137]. In contrast, phasic DA release

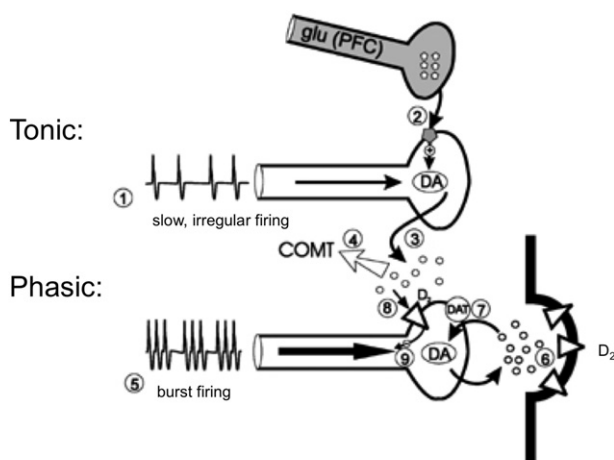
is driven by bursts of firing from DA neurons in response to more immediate, behaviorally relevant stimuli. The level of phasic DA release is linked to prediction of future outcomes, and plays an important role in motivating behavioral responses to appetitive and aversive stimuli (reviewed by [137]).

Tonic and phasic DA neurotransmission are inter-related, such that high levels of tonic DA attenuate phasic DA release, whereas low levels of tonic DA facilitate phasic DA release (reviewed by [14,47,53]). This relationship is maintained via a series of feedback loops that promote homeostatic balance within the DA system. Phasically released DA binds to postsynaptic D2-like DA receptors, inhibiting subsequent excitatory neurotransmission. The extent of this effect in the striatum is largely determined by the rate at which DA is removed from the synaptic cleft via rapid reuptake by the DA transporter (DAT) [47,53]. While tonic levels of DA are too low to activate postsynaptic DA receptors or engage DAT, tonic DA stimulates presynaptic D2-like DA autoreceptors, which constrain the synthesis and release of DA. In this way, tonically released DA downregulates the intensity of phasic DA release. Catechol-*O*-methyltransferase (COMT), an extracellular enzyme, catabolizes the relatively small amount of DA within the striatum that escapes the synaptic cleft (reviewed by [14]).

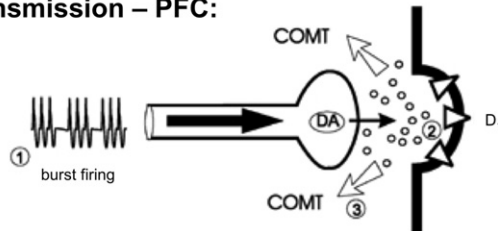
Burst firing of DA neurons that project to the medial prefrontal cortex (PFC) also produces high levels of phasic DA release, and high synaptic DA concentrations. However, unlike their subcortical counterparts, mesocortical DA neurons do not contain high levels of DAT [144]. Therefore, instead of undergoing reuptake within the synaptic cleft, DA diffuses to extrasynaptic space and stimulates postsynaptic, excitatory D1-like DA receptors, resulting in increased neuronal firing until DA is catabolized by COMT (reviewed by [14]).

Although COMT plays a more prominent role in modulating phasic DA activity in PFC than in subcortical regions, the rate at

### A. Tonic/Phasic DA Transmission – striatum:



### B. DA Transmission – PFC:



**Fig. 2.** Tonic–phasic regulation of dopamine (DA) transmission in the striatum and medial prefrontal cortex (PFC). (A) Tonic/phasic DA transmission – striatum. Tonic DA release is dependent on slow, irregular spike activity of ventral tegmental area (VTA) DA neurons (1) and is modulated by glutamatergic afferents from the PFC (2). Tonic DA releases low levels of DA (5–20 nM concentrations) into the extrasynaptic space (3), where it is subject to a limited degree of catabolism by catechol-O-methyltransferase (COMT) (4). Phasic DA transmission is evoked by behaviorally salient stimuli, and is triggered by burst firing of VTA neurons (5), which release very high levels of DA into the synaptic cleft (M concentrations), where it stimulates postsynaptic D2-like DA receptors (6). Phasic DA is inactivated by removal from the synaptic cleft via rapid uptake by the DA transporter (7), and therefore is not subject to catabolism by extrasynaptic COMT. Although tonic DA occurs in too low a concentration to stimulate intrasynaptic D2-like DA receptors, it stimulates presynaptic D2-like DA autoreceptors (8), which then inhibit phasic DA release (9). Therefore, tonic DA levels are controlled by an interaction of glutamatergic presynaptic stimulation and COMT catabolism; tonic DA in the extrasynaptic space, in turn, downregulates phasic DA release. (B) DA Transmission – PFC. Regulation of DA transmission in the PFC is markedly different. Burst firing of VTA DA neurons (1) releases high concentrations of DA into the synaptic cleft (2). Given that DA neurons in the PFC do not contain high levels of DAT, phasic DA transmission in the PFC is not restricted to the synaptic cleft. Instead, DA diffuses out of the synaptic cleft to stimulate nearby postsynaptic sites (3). Thus, in the PFC, COMT plays a more important role in the inactivation of DA following its release than in the striatum. Figure reproduced and adapted with permission from Bilder et al., 2004 [14].

which DA in PFC is catabolized has important downstream effects on DA function in subcortical regions. Neuronal firing activated by DA transmission in PFC is propagated across corticostriatal pathways, and produces increased activity in glutamatergic afferents in the striatum, which in turn results in higher levels of tonic striatal DA release. Since tonically released DA downregulates the amplitude of the phasic response via presynaptic D2-like DA autoreceptors, higher levels of tonic DA are associated with lower amplitude phasic DA release in response to behaviorally relevant stimuli, while lower levels of tonic DA release are associated with higher-amplitude phasic DA release [47,53].

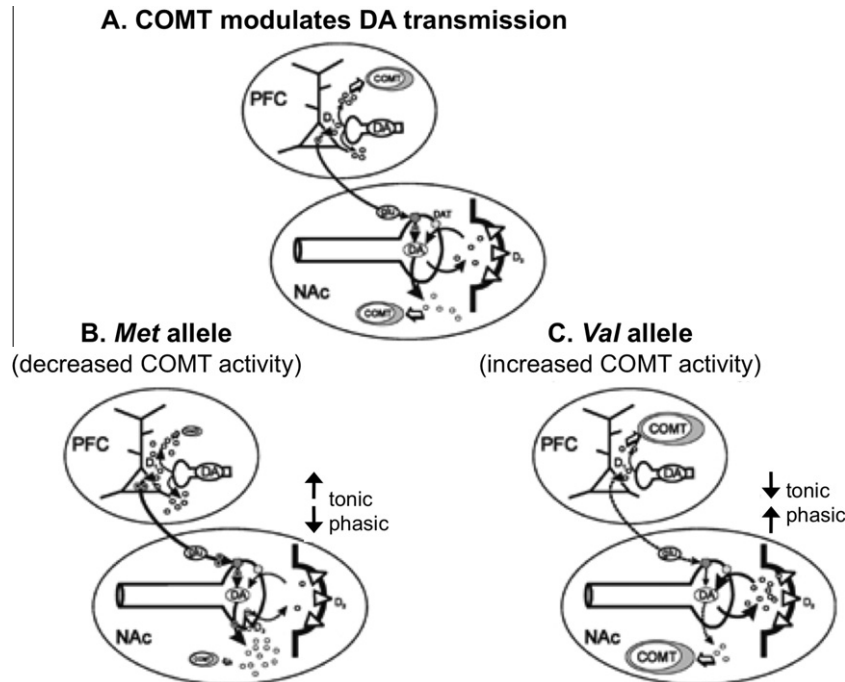
#### 2.3. Genetic influences on dopamine system function

Given their critical role in regulating DA system function, there has been increasing interest in investigating common functional

variants in genes that code for D2-like DA receptor density, and for DAT and COMT. Variability in the Taq1A restricted fragment length allele of DRD2, which codes for D2-like DA receptors, has been associated with levels of D2-like DA receptor density. Several studies suggest that carriers of the Taq1A A1 allele have lower density of striatal D2-like DA receptors compared with those homozygous for the A2 allele [73,110,118,129]. Additionally, carriers of the A1 allele have reduced glucose metabolism in many areas critical to DA neurotransmission, including the putamen, nucleus accumbens, and medial prefrontal cortex (PFC) [111], as well as significantly smaller midbrain volume [21]. However, one study by Laruelle et al. [82] found no relationship between the Taq1A and D2-like DA receptor density. Availability of DAT in the striatum is partially determined by a variable number of tandem repeats in the 3' untranslated region of the solute carrier family 6 member 3 (SLC6A3) gene. In some studies, individuals who are homozygous for the 10-repeat allele had significantly higher levels of striatal DAT expression than those who carried the 9-repeat allele [24,65]. Presumably, higher levels of DAT protein would result in more rapid reuptake of DA from the synapse; however, there are inconsistencies in reports describing the relationship between the expression of SLC6A3 variable number of tandem repeats and availability of striatal DAT (for alternate accounts, see [160,161]).

A common single nucleotide polymorphism in which a valine (Val)-to-methionine (Met) substitution at codon 158 in the gene that codes for COMT, accounts for a 3- to 4-fold variation in COMT enzyme activity and DA catabolism [92]. Given the critical role of COMT in DA neurotransmission in PFC, allelic variations in the gene that codes for COMT has a greater direct effect on DA neurotransmission in PFC than subcortical regions. The Met allele, associated with lower enzymatic activity, and thus slower catabolism of DA in PFC, allows for greater glutamatergic input to striatal regions, resulting in higher levels of tonic DA release, and in turn, lower amplitude of phasic DA neurotransmission. Conversely, the Val allele is associated with higher enzymatic activity, and thereby faster catabolism of DA in the PFC, which decreases tonic DA release in the striatum, and facilitates phasic DA neurotransmission. Thus, presence of the low-activity Met allele can facilitate DA system stability, but may impair the capacity to respond flexibly to behaviorally relevant stimuli. Conversely, presence of the Val allele may limit DA system stability, but promote flexible responses (Fig. 3).

Accumulating evidence suggests that variations in the COMT gene have substantial effects on DA system function as well as direct and indirect effects on other brain signaling systems. For instance, since COMT also plays an important role in degrading norepinephrine and epinephrine [7], it has been suggested that presence of the Val allele may promote more rapid degradation of norepinephrine and epinephrine [114]. Although DA and COMT do not have direct effects on endogenous opioids, allelic variations in COMT have downstream, indirect effects on the  $\mu$ -opioid system such that individuals homozygous for the Val allele of COMT have lower thalamic  $\mu$ -opioid receptor binding than carriers of the Met allele [174]. In addition, since DA activity is positively related to serotonin release [155], differences in availability of DA, conferred by allelic variations in COMT, may indirectly affect serotonergic function. Given that allelic variants of the COMT gene may have such wide-reaching influence on neuropharmacological functions, the COMT gene may have pleiotropic effects on a variety of cognitive, affective, and clinical phenotypes [102]. Indeed, the Met allele has been associated with enhanced capacity to perform tasks that require sustained executive functioning and working memory, but deficits in cognitive flexibility, as demonstrated by difficulties in updating or switching between cognitive sets, as compared with the Val allele [14]. Homozygosity of the Met allele is also associated with greater functional activity in limbic regions of



**Fig. 3.** Activity of catechol-O-methyltransferase (COMT) differentially affects dopamine (DA) transmission in the medial prefrontal cortex (PFC) and the striatum. (A) COMT modulates DA transmission. DA in the PFC stimulates postsynaptic D1-like DA receptors, producing an excitatory effect on neuronal firing, which is largely limited by the catabolism of DA by COMT. This neuronal firing increases striatal glutamate release, which in turn, stimulates presynaptic DA receptors, promoting tonic DA release in striatal regions, such as nucleus accumbens (NAc). Tonic DA stimulates DA autoreceptors and decreases phasic DA release. COMT plays only a minor role in the catabolism of DA in the striatum. (B) The Met allele of COMT decreases its overall activity, resulting in slower catabolism of DA in the PFC, and thus greater PFC neuron firing. This, in turn, leads to greater striatal glutamate transmission and thus greater tonic DA release, with lower levels of DA catabolism by COMT. The result is high levels of tonic DA and suppression of phasic DA. (C) In contrast, the Val allele of COMT increases its activity and produces a markedly different series of events. High COMT activity in the PFC increases DA catabolism, thereby limiting D1-mediated excitation of PFC neurons. This diminishes glutamate-stimulated tonic DA release in the striatum, which is further limited by increased tonic DA metabolism by COMT. Phasic DA transmission is thus released from tonic DA modulation, resulting in abnormally high phasic DA response. Fig. 3 is reproduced and adapted with permission from Bilder et al., 2004 [14].

the brain while processing aversive emotional stimuli compared with the Val/Val genotype [149], suggesting an enhanced response to negative affective cues in brain networks associated with emotional processing. This hyper-responsiveness may contribute to the higher levels of anxiety-related symptoms [41,112] and clinically significant anxiety disorders [169] that occur among individuals who carry the Met allele. Thus, allelic variability in the COMT gene has a variety of phenotypes, such that compared with carriers of the Val allele, Met carriers may have enhanced cognitive stability but impaired cognitive flexibility, dysregulated processing of negative affective stimuli, and increased likelihood of anxiety- and stress-related symptoms and syndromes.

### 3. Evidence linking the dopamine system and pain

#### 3.1. Preclinical research

While extensive research has demonstrated a primary relationship between opioid system activity and pain processing, opioid system activity has also been linked with DA neurotransmission. Preclinical studies utilizing microdialysis have demonstrated that endogenous opioids (such as met-enkephalin), which typically bind to  $\mu$ -opioid receptors, are released almost immediately in DA-rich regions of the brain, including nucleus accumbens, following the onset of noxious stimulation [79]. Administration of exogenous opioids [33,87] and  $\mu$ -opioid agonists [150], in turn, promote DA release within 10–30 minutes of their administration [33,119], with peak effects approximately 60 minutes post administration [33,87,150]. This time course suggests that the DA and opioid systems may work together in the context of pain processing, with

the opioid system responding rapidly to noxious stimuli, which in turn promotes DA release. Indeed, preclinical evidence has shown that release of the presynaptic DA metabolite, DOPAC, is greater in anterior cingulate cortex after prolonged (10-minute), compared with brief (5-minute), noxious stimulation [93]. Further, microdialysis in striatal and forebrain regions has revealed increases in DA neurotransmission during noxious stimuli, with peak effects in some regions occurring up to 20 minutes after stimulation has terminated [1,74]. Conversely, physical and pharmacological depletion of the DA system enhances responses to noxious stimuli [26].

Preclinical research that relies on administration of exogenous dopaminergic agents to assess the relationship between DA system function and pain processing have produced inconsistent results, potentially due to variability in dose and pharmacology of exogenous dopaminergic agents, infusion site, and modality of noxious stimuli. Consistencies begin to emerge when focusing on the relationship between pain processing and intraventricular or intracerebral administration of DA agonists and antagonists during noxious stimulation. For instance, acute pain evoked by thermal stimulation, and tonic pain evoked by formalin injection, are both augmented by intraventricular or striatal microinjection of the DA antagonist haloperidol, whereas microinjection of the DA agonist apomorphine results in a dose-dependent decrease in nociceptive responses [88,95]. The same pattern of enhanced nociceptive response is produced with striatal microinjection of the D2-like DA receptor antagonist eticlopride, and attenuated nociception with the agonist quinpirole, but not with D1-like DA-receptor-selective agonists or antagonists [18,95,154]. Moreover, administration of the D2-like DA-receptor selective antagonist raclopride diminishes the antinociceptive effects of D2-like DA-receptor

selective agonists [154]. These observations suggest that stimulation of D2-like DA receptors in the striatum inhibits nociception in response to acute and tonic pain.

Notably, however, cortical D2-like DA receptors have also been implicated in nociceptive processing. Microinjections of nonselective and selective D2-like DA-receptor agonists in ventrolateral orbital cortex produce dose-dependent decreases in acute pain and in the allodynic response to mechanical stimulation induced by spared nerve injury, effects that are eliminated by the D2-like DA-receptor antagonist, raclopride [30,145]. In addition, neuropathic pain associated with sciatic denervation is attenuated with microinjections of D2-like DA-receptor selective agonists, but not the D1-like DA receptor agonist SKF-38393, in anterior insula and anterior cingulate cortex [27,91]. Some evidence, however, suggests that D1-like DA receptors in the anterior insula may also play a role in pain modulation. For instance, microinjections of the D1-like DA receptor-selective antagonist SCH-23391 into the anterior insula resulted in thermal hyperalgesia [18]. Taken together, these data suggest that activation of DA receptors, and particularly D2-like DA receptors in striatum and cortex, contribute to antinociception.

### 3.2. Research with healthy human subjects

Human studies that have used functional magnetic imaging and positron emission tomography (PET) with <sup>15</sup>O-water to assess neurovascular activity in response to pain in healthy individuals, have identified substantial overlap between the network of brain regions most commonly implicated in pain processing [4] and brain regions that comprise the DA system [86] (see regions highlighted in Fig. 1C). PET studies with [<sup>11</sup>C]raclopride, a radiotracer that binds to D2-like DA receptors, have been used to assess tonic levels of striatal DA under baseline conditions, and phasic DA release associated with noxious stimulation. These studies have shown that healthy individuals with lower levels of tonic DA release in the striatum, indexed by higher levels of radiotracer binding under basal conditions, are more sensitive to noxious stimulation [59,98,117,139,171]. Other PET studies with [<sup>11</sup>C]raclopride have revealed that DA neurotransmission in the striatum increases during noxious stimulation, as indexed by decreased radiotracer binding [139,142]. This increase is, in turn, positively correlated with self-reported discomfort associated with the stimulus [139]. However, when endogenous mechanisms are employed to diminish the experience of pain, as is the case with placebo analgesia, reductions in pain are associated with greater striatal DA release [140,141]. Thus, data from healthy individuals mirror results from preclinical studies (reviewed above) such that an increase in DA release occurs with the introduction of noxious stimulation, and elevated levels of striatal DA in the presence of a noxious stimulus diminishes self-reported pain.

### 3.3. Research on patients with chronic pain syndromes

Evidence supporting the relationship between pain and function of the DA system in the brain is also derived from studies of patients with persistent pain syndromes. Such studies have employed a variety of experimental techniques in small samples of patients (groups of 8–11) with varying diagnoses. In most studies, the differential mechanisms engaged during the expectation and actual experience of noxious stimulation have not been addressed. While this may contribute to inconsistencies across studies, taken together, the findings suggest that patients with persistent pain syndromes have abnormalities in DA system function. For example, presynaptic DA activity, as measured using 6-[(18)F]fluoro-L-DOPA and PET, is lower in patients with burning mouth syndrome [71] and fibromyalgia [170] compared with healthy individuals, although no deficits are observed in patients with atypical face

pain [170]. Studies that used [<sup>11</sup>C]raclopride and PET have demonstrated that patients with burning mouth syndrome [58], atypical facial pain [57], and fibromyalgia [171] have lower tonic DA levels in striatum than healthy individuals, as indexed by greater radiotracer binding. The one study that assessed DA release associated with noxious stimulation among people with chronic pain found that, unlike healthy individuals, patients with fibromyalgia fail to exhibit significant decreases in radiotracer binding with stimulation, and also do not show a significant correlation between decreases in binding and self-reported experience of pain [171]. However, insufficient statistical power stemming from small sample size may have obscured 2 potentially important findings related to fibromyalgia. First, while fibromyalgia patients appear to lack a DA response to noxious stimulation, there may, in fact, have been 2 modes of response. One subset of patients exhibited the same pattern of decreased binding with noxious stimulation as healthy individuals, while another subset exhibited no change, or an increase in binding with noxious stimulation, suggesting ineffective recruitment of the DA system. Second, a change in binding with noxious stimulation across several brain regions among patients was positively correlated with self-reported pain ( $r_s > 0.4$ ), even though this relationship did not reach statistical significance [171]. Perhaps a larger sample size that would allow for statistical comparisons between the 2 subsets of fibromyalgia patients might reveal clinically significant differences. Even though further research is needed to characterize the relationship between DA system function and chronic pain syndromes appropriately, taken together, the available evidence suggests that deficits in presynaptic DA activity and tonic DA levels may be characteristic of patients who suffer from chronic pain syndromes, while a subset of these patients may have disruptions in DA responses to noxious stimulation.

### 3.4. Dopamine system influence on cognitive factors that affect pain

In addition to the anatomical overlap between brain regions associated with pain processing and those that comprise the DA system, there is also a substantial overlap between the cognitive and affective functions influenced by DA neurotransmission and the cognitive and affective factors that influence the subjective experience of pain. DA neurotransmission has an important influence on outcome prediction, attention, response inhibition, and motivation [109], as well as affective symptoms associated with anxiety [135,156] and depression [37]. While many of these factors also relate to the subjective experience of pain in healthy individuals [103,163], alterations in the same functions are common in patients with chronic pain syndromes [5,35,63]. For example, coping styles related to the prediction of positive or negative outcomes play an important role in severity of symptoms in chronic pain patients (e.g., [113,148]). For example, a copying style that assumes a high probability of worst outcomes (also referred to as catastrophizing), is highly correlated with pain symptom severity in a variety of chronic pain conditions (reviewed by [124]). Moreover, symptoms of anxiety [152] and depression [77] commonly exacerbate the experience of experimental pain in otherwise healthy individuals, while mood and affect-based disorders are often observed among patients with persistent pain syndromes [99].

### 3.5. Genetic influences on dopamine system function may affect pain

While some differences in DA system function [70], and cognitive [63] and affective symptoms [46] may be secondary to the prolonged experience of pain, other differences may be primary, resulting in altered pain sensitivity or increased vulnerability to developing chronic and persistent pain syndromes. For example, there are differences in allelic variation in the DRD2 gene that

codes for D2-like DA receptor density among those with and without migraine [32,115]. Individuals with the 10-repeat allele of the SLC6A3 gene, which may be associated with higher levels of striatal DAT [24,65], and thus potentially more rapid reuptake of synaptic DA than those with 9 repeats, are both more sensitive to pain [158] and more likely to suffer from chronic headache [22]. Likewise, individuals homozygous for the Met allele, associated with low COMT activity (affecting extracellular DA concentrations in the cortex) and therefore, restricted capacity to produce flexible phasic DA responses in striatum, are more sensitive to pain than those homozygous for the Val allele [174], and more likely to develop persistent pain syndromes [34,56] (see above discussion of COMT and effects on phasic and tonic DA release). Given its role in other monoaminergic signaling systems, polymorphisms in the COMT gene are likely to affect pain sensitivity and vulnerability for persistent pain syndromes through non-DA mechanisms as well. For instance, noradrenergic and adrenergic signaling systems play an important role in the peripheral nervous system, the spinal cord, and at supraspinal sites [105]. The  $\mu$ -opioid system, which also plays a critical role in nociceptive processing, may be another downstream mechanism by which genetic variants of COMT can affect the experience of pain. For example, individuals homozygous for the Met allele of COMT have a diminished  $\mu$ -opioid system response to a painful stimulus, which is accompanied by more negative affect and more discomfort, compared to carriers of the Val allele [174].

### 3.6. Potential mechanisms

Despite considerable preclinical and clinical evidence linking the DA and opioid systems to each other, and their interactions related to pain, the specific mechanisms by which DA neurotransmission alters nociception are not well understood. One limiting factor is a methodological constraint associated with the radiotracers used in conjunction with PET. [<sup>11</sup>C]raclopride is the most commonly used radioligand to study the DA system in humans, and it has only moderate affinity for D2-like DA receptors, limiting its utility to assessments in the striatum, where the density of D2-like DA receptors are high. Functional studies of other brain regions that comprise the DA system, including cortical and limbic structures, have revealed evidence that engagement of these regions is important in the subjective experience of pain (see above, and Fig. 1). This restriction to studies of the striatum can now be addressed using more recently developed radiotracers, such as [<sup>18</sup>F]fallypride [172,173] and [<sup>11</sup>C] and FLB -457 [106,107], which have higher affinities for D2-like DA receptors, enabling extrastriatal subcortical and cortical measurements. An additional challenge relates to the relatively poor temporal resolution of PET and rapid dynamics in DA system function. For instance, while basal levels of endogenous DA and tonic DA release associated with prolonged stimulation can be measured with PET, more rapid, phasic activity is unlikely to be captured with this imaging technique. Moreover, basal levels of endogenous DA as assessed with PET may also inadvertently capture DA activity related to expectations about forthcoming experimental stimulation, as has been noted in studies of placebo effects (for example: [61,140,141]). This problem poses a particularly difficult challenge given the importance of expectations in the experience of experimentally induced pain.

Available evidence suggests that the DA signaling system may affect the experience of pain and the vulnerability to develop chronic pain, by way of at least 3 mechanisms: first, as laid out in Fields' Motivation-Decision Model of pain, the DA system may play an important role in the unconscious decision process preceding the experience of a potentially noxious stimulus [45]. This decision process requires information about imminent threat and potential reward, the latter being based on memories of

previous pain experiences, and determines the engagement of selective attentional and pain modulation mechanisms. Variations in central DA signaling play an important role in making these predictions, and the resulting coping styles, with worst-case assumptions ("catastrophizing") being characteristic in many chronic pain patients. Second, there may be a direct effect on how noxious stimuli are processed via DA-based propagation or inhibition of nociceptive signals to a network of brain regions that are commonly implicated in processing pain, and subsumed by well-established DA pathways. Third, a combination of both direct and indirect factors may determine how the DA system influences the experience of pain. Pleiotropic effects of the COMT genotype may influence all 3 potential mechanisms and thus, may play a prominent role in determining the experience of pain symptoms and syndromes along with otherwise unrelated DA-based disorders (illustrated in Fig. 1). In the following section, we will discuss 4 such disorders.

## 4. Pain, cognitive deficits, and affective dysregulation in patients with dopamine-related disorders

### 4.1. Pain in disorders of mood and anxiety

There is extensive comorbidity between chronic pain syndromes and mood and anxiety disorders [9,99]. Given the high lifetime prevalence rate of mood and anxiety disorders [76], the cost associated with comorbid psychopathology and chronic pain is substantial. Key symptoms characteristic of mood and anxiety disorders are closely linked with cognitive processes influenced by the DA system. For instance, patients with major depressive disorder exhibit profound impairments in initiating motivation-based behavior and a reduced capacity to experience pleasure, functions typically driven by the DA system (reviewed by [108]). PET studies have supported the link between symptoms of depression and DA system function, revealing that compared with healthy individuals, patients with major depressive disorder have lower D1-like DA receptor binding potential in caudate, which is in turn associated with higher levels of anhedonia [20]. Moreover, patients with depression also exhibit lower levels of DA release than healthy individuals in response to monetary reward (reviewed by [123]).

Patients with anxiety disorders exhibit symptoms of catastrophizing, hypervigilance, and persistent fear, which have also been linked to DA system function [43]. This association is supported by findings that individuals with social phobia have lower levels of both DA re-uptake [156] and D2-like DA receptor binding in striatum [135] than healthy individuals. In addition, the Met allele of the COMT gene has been associated with the failure to extinguish the response to conditioned fear stimuli [90], a common characteristic of patients with anxiety disorders [89]. Given that patients with anxiety disorders are more likely than healthy individuals to carry the Met allele [62,71,113,169], the COMT genotype may be an additional mechanism by which the DA system influences anxiety-related symptoms.

There is evidence to suggest a reciprocal relationship between mood and anxiety disorders and pain, such that the experience of one can precipitate or exacerbate the symptoms of the other. Chronic pain can trigger anxiety [55] and depressed mood states [39], and is often accompanied by a marked reduction in the ability to enjoy life [9,78], and persistent symptom-specific fears [28]. Likewise, mood and anxiety disorders have been associated with increased likelihood of developing chronic pain symptoms [9,55,94], and of inducing greater sensitivity to experimentally induced noxious stimulation [127,153]. This reciprocal relationship may be partially due to shared dysfunctions in central DA signaling, which plays a role in both mood and anxiety disorders and in pain processing. On the other hand, it may also reflect the fact

that cognitive and affective symptoms associated with mood and anxiety disorders affect the perception of chronic and acute pain. As such, symptoms of mood and anxiety disorders that occur in the presence of typical DA-based disorders may further increase the likelihood of patients experiencing chronic pain.

#### 4.2. Pain in drug addiction and recovery

A majority of patients with substance abuse disorders experience chronic pain prior to entering treatment [19,157], even after controlling for discomfort associated with withdrawal [131]. Patients with pain are also more likely than those without pain to experience depressive symptoms [121]. In turn, both pain [19,80] and depression [64] are associated with negative treatment outcomes.

As observed in patients with chronic pain, individuals who have drug abuse disorders also exhibit dysregulation of DA system function. Alcoholics, tobacco smokers, and individuals who abuse methamphetamine, cocaine, and heroin have lower density of striatal D2-like DA receptors than healthy individuals (reviewed by [84,164]), a difference that can persist after months of abstinence from drugs such as cocaine [165]. Moreover, compared with healthy individuals, both alcoholics [167] and cocaine addicts [166] exhibit a blunted DA response to acute administration of methylphenidate, indicative of deficits in presynaptic DA function. Although some alterations in DA system function may result from drug use, individuals with addictions may have primary characteristics that predispose them towards dependence. For instance, Val variants in the COMT gene are more common among individuals with heroin addiction than nonaddicted at-risk individuals [67], as well as in individuals with high lifetime polysubstance use compared with those who have insignificant levels of substance use [162], suggesting that biological factors associated with DA system function may contribute to vulnerability for addiction.

Relevant human research has largely focused on the role of psychological stressors on exacerbating drug use and relapse. Corresponding animal studies, however, have focused more directly on nociception. They have shown that painful physical stressors, such as tail pinch or foot shock, increase self-administration of morphine and psychostimulants, and can promote reinstatement of drug-seeking behavior after extinction among animals previously dependent on heroin, cocaine, nicotine, or alcohol (reviewed by [147]).

These findings suggest that drug dependence may be a risk factor for developing chronic pain or diminished capacity to cope with pain, which may, in turn, increase likelihood of relapse. A diminished capacity to cope with physical stressors among individuals with drug dependence could potentially be linked to more general deficits in inhibitory control [8], and altered motivation- and attention-based processes [49]. These behavioral deficits are common in drug addiction, and linked with DA-system dysfunction (reviewed by [164]).

Large-scale prospective surveys in humans, along with preclinical data from animals, therefore suggest that it may be beneficial to treat primary symptoms of addiction along with secondary symptoms of chronic pain, cognitive deficits, and depression as a way of decreasing the likelihood of relapse. Such a treatment strategy, however, poses a problem for patients and clinicians, who have concerns that pharmacological treatments for pain may exacerbate symptoms of substance abuse disorders [130]. Given the relationship between pain, depression, and negative treatment outcome, the risk of addiction needs to be carefully weighed against possible benefits. A more thorough understanding of how the DA system contributes to the experience of pain may eventually help determine the most appropriate course of treatment for individuals with pain and addiction on a case-by-case basis.

#### 4.3. Pain in Parkinson disease

Chronic pain is one of the most common nonmotor symptoms of Parkinson disease (PD) [11,85]. PD is a progressive neurodegenerative disorder that affects multiple sites (enteric nervous system, brain stem, spinal cord, and cortical regions) and systems within the nervous system, including the nigrostriatal pathway of the central DA system, and results in a profound depletion of DA in the striatum. Degeneration within the nigrostriatal system typically affects motor function, resulting in tremor, rigidity, difficulty initiating movement, and impaired coordination. Stereotyped motor symptoms materialize only after extensive neurodegeneration has reduced central DA by nearly 80% [13], making early detection and treatment a challenge.

Although chronic pain among PD patients can be caused by primary motor symptoms [11], patients also report pain that is independent of these symptoms [85]. PD patients with chronic pain exhibit a variety of symptoms that differentiate them from patients without pain. They have a lower threshold for acute noxious stimulation than PD patients without chronic pain, a difference eliminated with administration of L-dopa, which increases levels of available DA [134]. Compared with PD patients without chronic pain, those with pain are also more likely to experience comorbid major depression [40], which often occurs in conjunction with anxiety [100], and diminished health-related quality of life [126]. These affective symptoms, along with the deficits in attention- [29] and motivation-based processes [23], are common in patients with PD, and may contribute to enhanced pain sensitivity. While the direct relationship between allelic variations in COMT and pain among PD patients has not been assessed, the Met allele of the COMT gene seems to impair implementation of cognitive strategies that allow for flexible attention shifting [168] and planning capabilities [48] among PD patients. Further research is needed to determine if the cognitive deficits associated with the Met allele among patients with PD also put patients at greater risk for developing pain symptoms.

Symptoms of chronic pain (as well as depression, anxiety, and cognitive deficits) often precede the manifestation of the stereotyped motor deficits associated with PD [23,31,48,151]. Unfortunately, physicians commonly overlook nonmotor symptoms, which typically go untreated throughout the course of the disease [23], and thus may contribute to diminished quality of life.

#### 4.4. Pain and schizophrenia

Anecdotal reports and clinical observations suggest that schizophrenics are less sensitive to pain than healthy control subjects. For example, schizophrenics experience surprisingly few pain-related symptoms associated with medical conditions, such as appendicitis, myocardial infarction, and peptic ulcer, with injuries including bone fractures and burns, as well as postoperative pain following surgery (reviewed by [38]). Patients with schizophrenia also exhibit higher pain thresholds and greater tolerance to acute noxious stimuli than healthy individuals [6,15,72] and patients with bipolar disorder [6]. Elevated threshold and tolerance cannot be solely attributed to treatment with antipsychotic medication, as the difference persists even in schizophrenics who are drug-free and those who are drug-naïve (reviewed by [81,122]), and extends to the first-degree relatives of schizophrenics without psychopathology [66].

Although the pathophysiology of schizophrenia is incompletely understood, alterations in the cortical DA system may play a role in mediating the cardinal symptom complex of delusions, hallucinations, disorganized behavior, and cognitive deficits. This cortical DA signaling abnormality has partially been attributed to the relatively high occurrence of the Val allele of the gene COMT, which is

accompanied by a relative deficit in phasic DA signaling in cortical regions (reviewed by [159]). In contrast, schizophrenics have higher basal levels of synaptic striatal DA [2] than healthy subjects, and exhibit greater amphetamine-induced striatal DA release than nonpatients (reviewed by [81]), indicative of a hyper-responsive or sensitized striatal DA system. Together with the demonstrated higher vulnerability of COMT Met allele carriers for persistent pain disorders, these data suggest that the pain hyposensitivity observed in schizophrenics is related to a genetically determined difference in DA signaling.

Pain hyposensitivity has important clinical implications. It poses a serious health risk to schizophrenics, and is associated with increased patient morbidity and mortality. Illnesses and injuries whose symptoms typically include pain, but that present without pain, can result in delayed diagnosis and treatment, and thus an otherwise preventable further deterioration in health. This type of delay has been documented for numerous serious medical conditions among schizophrenics, including perforated bowels [132], perforated ulcers [97], and acute appendicitis [52,97]. An absence of pain can mask the need to seek treatment entirely, and can result in death. Indeed, one of the leading causes of death in institutionalized schizophrenia patients is painless myocardial infarction [69]. Hyposensitivity to pain among schizophrenics may in fact be exacerbated by treatment with antipsychotic medications, many of which target the DA system, and have analgesic properties [143]. Given this situation, medical personnel should remain alert to the possibility that serious, potentially life-threatening medical conditions may occur in schizophrenic patients presenting with minimal symptoms of pain.

## 5. Implications for clinical management and drug development for chronic pain

As discussed above, there is considerable evidence supporting a role of the DA system in the altered pain sensitivity of patients with chronic central nervous system disorders, such as disorders of mood and anxiety, substance abuse, PD, and schizophrenia, as well as in the vulnerability to developing common persistent pain symptoms. Since genetically determined variations in several DA-dependent brain-based systems (including outcome predictions, attention, and engagement of endogenous pain modulations systems) appear to mediate variations in pain sensitivity and chronic pain prevalence across several clinical disorders, these DA-dependent signaling systems can be considered as general endophenotypes of chronic pain symptoms [101].

While awareness that altered pain sensitivity in patients with DA-based disorders by clinicians can have important implications for the management and treatment outcome (as outlined above), the possible role of altered DA signaling mechanisms in persistent pain disorders opens up the possibility of novel treatment approaches for these conditions. For example, levodopa, an indirect dopaminergic agonist used to treat PD, reduces pain-related symptoms in patients with PD [125], but also in patients with herpes zoster [75], symmetrical diabetic polyneuropathy [42], and some forms of cancer [36]. While long-term administration of levodopa could result in negative side effects, further study of its efficacy in the treatment of chronic pain is warranted. Additionally, there have been inconsistent reports about the usefulness of antipsychotic drugs on various forms of acute and chronic pain, including chronic headache, fibromyalgia, and painful diabetic neuropathy [50,128,143]. Typical antipsychotics antagonize D2-like DA receptors, and would therefore be expected to worsen, rather than relieve pain. However, with repeated administration, these drugs down-regulate reactivity of mesolimbic DA neurons [54], which diminishes both tonic DA levels and phasic DA release in the striatum [104]. It is possible that blunting both tonic and phasic striatal DA

activity may produce antinociception, but it is unclear whether the costs associated with such a profound alteration in DA neurotransmission would outweigh the benefit of pain relief. A recent review of 11 studies involving 770 patients with chronic pain conditions found beneficial effects of antipsychotic treatment in 5 studies, along with significant side effects in 7 studies; limitations in data reported did not permit a formal meta-analysis [143]. Despite these inconsistencies, one promising candidate pain treatment is amisulpride, an unusual atypical antipsychotic that at low doses selectively blocks D2-like DA presynaptic autoreceptors that control DA synthesis and release, thereby increasing DA neurotransmission, particularly in limbic regions of the brain [116,136]. An initial study revealed that an 8-week course of treatment with amisulpride produced significant relief among patients with burning mouth syndrome, both more rapidly than treatment with a selective serotonin reuptake inhibitor, and without side effects [96].

Given the continuing unmet medical need in the treatment of chronic pain conditions, and our better understanding of the role of the DA signaling system in the development and expression of chronic pain, formal evaluation of novel, atypical antipsychotic drugs as primary or adjuvant therapies may be warranted. One may speculate that, depending on the individual variations in the DA signaling system based on polymorphisms of the genes for COMT, DAT, and D2 receptors, subgroups of patients may greatly benefit from such treatments, while they may be of limited effectiveness in others. Also, given the evidence for sex-related differences in most persistent pain disorders, sex-gene interactions may have to be considered in such individualized DA therapy approaches.

## Conflict of interest statement

The authors declare no conflicts of interest.

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