CHAPTER

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Pharmacology of Economic and Social Decision Making

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s0010 INTRODUCTION TO PSYCHOPHARMACOLOGY

p0155 Perhaps the most consistent aspect of human decision making is its variability or state-dependency. Human preferences, and their expression in choices, are highly variable between individuals, and across situations. When hungry, under stress, or sleep-deprived, we often make rather different choices than when faced with the same options under different physiological conditions. One potential source of this variability, at a mechanistic level, is the context-sensitive modulation of neuronal activity by *neuromodulator* systems. These operate much like the synaptic neurotransmitters discussed in Chapter 5, but with two important specializations. First, they are long acting. While traditional neurotransmitters may bind to receptors for only fractions of a millisecond before being inactivated, these chemicals remain active for intervals ranging from seconds to hours. Second, the distribution of these neurochemicals tends to be diffuse; rather than acting synapse-by-synapse many of these compounds travel throughout the body interacting with receptor distributed throughout the nervous system. Classically, neuromodulators include, amongst others, the monoamine neurotransmitters serotonin, dopamine, and norepinephrine, as well as the hormones testosterone and oxytocin. These neuromodulator systems regulate the levels of these compounds in the blood and in the brain in response to events in the environment and subsequently influence information processing in local brain regions, presumably in a manner that renders the information processing appropriate to the state that provoked neuromodulator release (Robbins and Arnsten, 2009).

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p0160 In this chapter, we review the effects of neuromodulators on decision making, focusing on time preferences (the evaluation of future outcomes), risk preferences (the evaluation of uncertain outcomes), and social preferences (the evaluation of others' outcomes). Almost every human decision involves at least one of these valuation processes. Important background information on these topics is covered in Chapters 9–11 of this volume. Although we are principally concerned with human decision making, much of the research in this area has employed animal models, due to methodological limitations associated with the manipulation of neuromodulator function in humans. We focus, however, on those animal models that are most directly comparable to decision making paradigms studied in humans. We further limit our overview to those studies employing experimental manipulations of neuromodulators, and do not extensively consider studies examining correlations between neuromodulator levels and behavior, as we are primarily interested in the causal role of neuromodulators in decision making.

s0015 Neuromodulation: A Brief Overview

s0020 *Anatomy*

p0165 The neuronal cell bodies that produce and release the monoamine neurotransmitters serotonin, dopamine, and norepinephrine are housed in the brainstem (Figure 14.1). These clusters of cells project axons to discrete brain regions widely distributed in the brain. Importantly, different neuromodulator systems project to different, but overlapping, regions. Dopamine neurons project primarily to the striatum and prefrontal cortex. Norepinephrine neurons send projections to nearly all parts of the brain, with highest density in the cerebral cortex and hippocampus; notably, the striatum is devoid of norepinephrine. The projections of serotonin neurons are also highly diffuse, innervating the entire brain. The neuropeptide oxytocin is synthesized in the hypothalamus and released in the hippocampus, amgydala, striatum, hypothalamus, midbrain and into the general circulation. Testosterone, meanwhile, is synthesized in both males and females in the adrenal cortex above the kidney and gonads in the pelvic area; it is then carried by the bloodstream to the brain where it activates receptors in the hypothalamus, amygdala, and striatum.

s0025 *Mechanism of Action*

p0170 The synthesis of neuromodulators is influenced by several factors, including chemical precursor availability, synthetic enzyme activity, and end-product inhibition (where the final product of synthesis – the neuromodulator itself

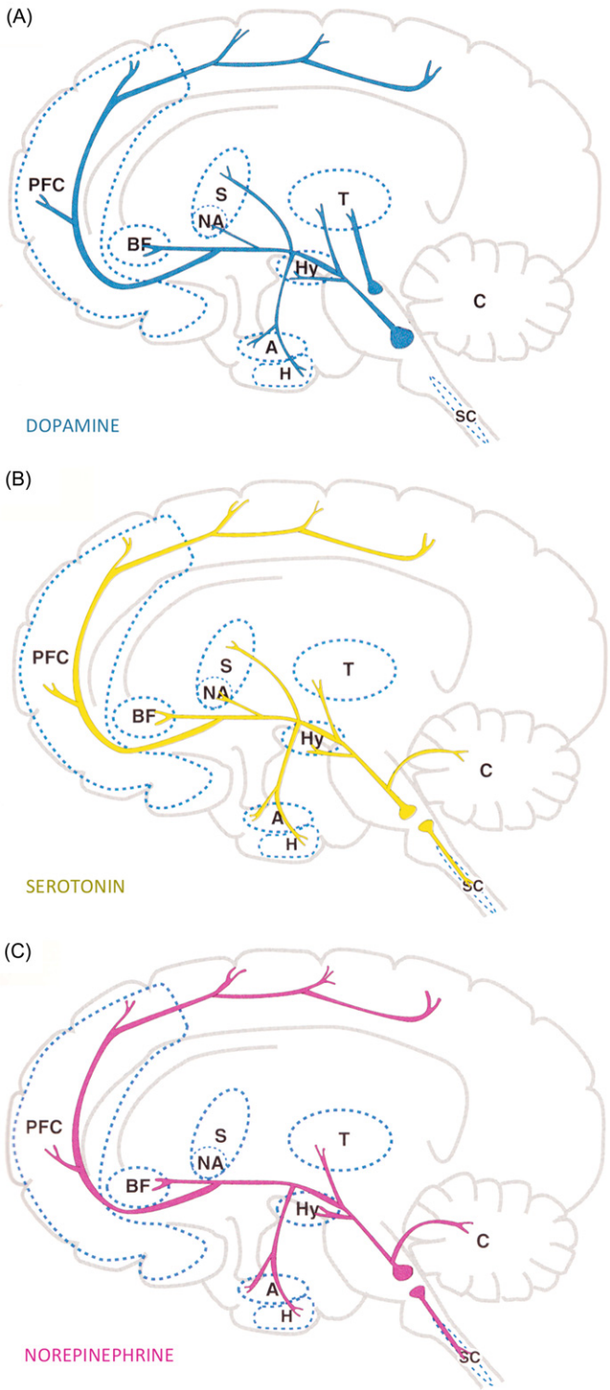
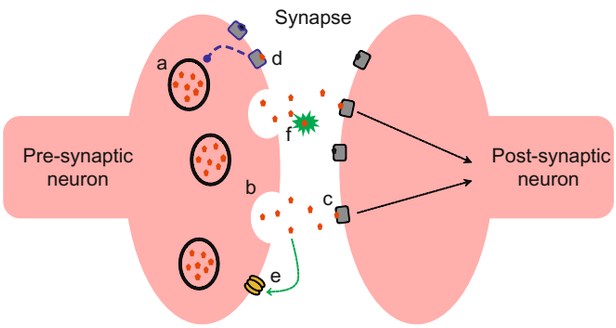


FIGURE 14.1 (A) Dopamine system. PFC, prefrontal cortex; BF, f0010 basal forebrain; S, striatum; NA, nucleus accumbens; A, amygdala; H, hippocampus; Hy, hypothalamus; T, thalamus; C, cerebellum; SC, spinal cord. (B) Serotonin system. (C) Noradrenaline system. *From Stahl (2008).*

– inhibits further synthesis). Once synthesized, the neuromodulator is stored in synaptic vesicles (Figure 14.2, see a) in the pre-synaptic neuron, just like a regular neurotransmitter, until it is released. After being released into the bloodstream, a region of the brain, or a specific synapse (Figure 14.2, see b), the neuromodulator activates post-synaptic receptors on the target neuron (Figure 14.2, see c) as well as under some conditions pre-synaptic receptors on the releasing neuron (Figure 14.2, see f). Following release, transporter machinery (akin to a cellular vacuum cleaner) removes the neuromodulator from the synaptic space into the releasing neuron (Figure 14.2, see d), where it is either recycled or broken down. Neuromodulators can also be broken down directly in the synapse by chemicals, called *catabolic enzymes*, that are specialized for this purpose (Figure 14.2, see e). All of these molecular mechanisms (precursor availability, synthesis, post- and pre-synaptic receptors, transporters, and catabolic enzymes) can be targeted by pharmacological agents to influence neuromodulator function, as described in the next section. (More details about these mechanisms and, neuropharmacology in general, can be found in Cooper *et al*., 2003).

p0175 There are many different types of receptor for each neuromodulator system, and different receptor types can have different effects on neuronal function when activated. For example, dopamine D_1 and D_2 receptors can have opposing effects on long-term potentiation and neuronal excitability (reviewed in Frank, 2005). The distribution of different receptor types can vary across the brain; so for instance, D_1 and D_2 receptors are found in roughly equal proportions in the striatum, whereas D_1 receptors outnumber D_2 receptors in much of the prefrontal cortex (Hall *et al*., 1994). The consequence of this neuronal architecture is that neuromodulators, when released, can have different effects in different brain regions according to the type of receptor activated.



f0015 **FIGURE 14.2** (a) Neurotransmitters are stored in synaptic vesicles in the pre-synaptic terminal. (b) Depolarization-dependent influx of Ca^{++} into the terminal causes synaptic vesicles to fuse with the plasma membrane, thereby releasing neurotransmitter into the synapse. (c) Neurotransmitter binds to post-synaptic receptors, which activate the post-synaptic neuron. (d) Transporter removes neurotransmitter from the synapse back into the pre-synaptic neuron. (e) Enzymes catabolize neurotransmitter within the synapse. (f) Neurotransmitter binds to pre-synaptic autoreceptors, which can down-regulate subsequent neurotransmitter release.

Phasic Versus Tonic Responses s0030

p0180 The neurotransmitter-releasing cells depicted in Figures 14.1 and 14.2 operate in at least two modes: *phasic* and *tonic*. Phasic neurotransmitter release is a form of fast, transient neurotransmission that is triggered by behaviorally relevant signals in the environment. These short-term changes in firing rate dramatically increase the level of the neuromodulator, resulting in intense stimulation of post-synaptic receptors. In contrast, tonic neurotransmission results refers to the sustained, slow levels of cell firing that maintain a constant "background" level of extracellular neurotransmitter and change along a much longer timescale. By maintaining a constant baseline stimulation of post-synaptic receptors, tonic neurotransmission can make it more difficult for neurons to detect changes in neurotransmitter levels, thus affecting their sensitivity to the phasic response (Grace, 1991).

Function s0035

p0185 As a consequence of all their complexity and flexibility, neuromodulators are well suited for orchestrating large-scale changes in neuronal network activity in line with the behavioral state of the organism (Andrade and Beck, 2010). Neuromodulators could therefore code for behavioral states and modulate information processing in neuronal networks in an adaptive manner (Robbins and Arnsten, 2009). In other words, neuromodulators can be thought of as *context encoders* that both signal the current context and shape neuronal activity to adaptively fit that context. Here *context* can be broadly construed to include features of the external environment (e.g., stressors, predators, competitors, or potential mates); internal states (e.g., reproductive status, emotions, arousal); and ongoing behavioral states (e.g., sleep/wake).

Methods for Manipulating Neuromodulator Systems s0040

Neurotoxic Lesions s0045

p0190 In animals, the cells that produce and release neuromodulators can be destroyed with neurotoxins that are selectively taken up by these neurons. This results in an irreversible, profound depletion (around 90%) of neuromodulator levels. Depending on the specific neurotoxin used and site of injection, depletion can be achieved throughout the entire brain, or localized to a particular brain region.

s0050 ***Precursor Manipulation***

p0195 In animals and humans, neuromodulator function for some of these chemicals can be enhanced by increasing the availability of precursor via pharmacological or dietary supplementation, or impaired by decreasing the availability of precursor via dietary depletion. Dietary depletion of precursor results in a reversible, partial global reduction in brain levels of the specific neuromodulator being depleted. In standard precursor depletion procedures, subjects drink a beverage that does not contain the amino acid precursor for, to take one common example, serotonin but which does include a surplus of closely related amino acids. This lowers the ratio of precursor to other amino acids in the blood and almost completely halts precursor transport into the brain (Booij *et al*., 2003). The effects of precursor manipulations on neuromodulator function are likely more subtle than those of neurotoxic lesions, and may have a stronger influence on tonic rather than phasic neurotransmission (Cools *et al*., 2008).

s0055 ***Receptor Agonists and Antagonists***

p0200 In animals and humans, it is also possible to directly stimulate or block neuromodulator receptors with pharmacological agents. These agents can be highly selective (targeting only a specific receptor type) or less so (targeting a general class of receptors and binding to multiple receptor types). *Antagonists* bind to the receptor and block the actions of the endogenous neuromodulators, thus impairing neuromodulator function. *Agonists* bind to the receptor and mimic the actions of the endogenous neuromodulator. When agonists bind to post-synaptic receptors (Figure 14.2c), their net effect is to increase neuromodulator function. However, agonists and antagonists can also influence neuromodulator function by binding to special receptors called *pre-synaptic autoreceptors*. Autoreceptors are located on the pre-synaptic neuron (Figure 14.2f). When activated, autoreceptors inhibit synthesis and release of neurotransmitter. Meanwhile, antagonism of autoreceptors can stimulate neurotransmitter synthesis and release by blocking negative feedback brought on by endogenous neurotransmitter. Thus, when they bind to autoreceptors, agonists have the net effect of decreasing neuromodulator function, while antagonists have the net effect of increasing neuromodulator function. The effects of agonists and antagonists on neuromodulator function therefore depend on whether they activate pre-synaptic (Figure 14.2f) or post-synaptic (Figure 14.2c) receptors.

s0060 ***Re-Uptake Inhibition***

p0205 In animals and humans, selective *re-uptake inhibitors* increase the concentration of neuromodulator by blocking its presynaptic re-uptake (Figure 14.2d). Consequently, the concentration of the neuromodulator is increased and thus its effect on post-synaptic receptors is enhanced. However, it is worth noting that re-uptake inhibitors can also increase neuromodulators' stimulation of pre-synaptic autoreceptors; this can have the paradoxical effect of *reducing* the overall release of neuromodulator. Whether re-uptake inhibitors have a net positive or negative effect on neuromodulator function may depend on the dosage used, with lower doses reducing neuromodulator function via pre-synaptic effects, and higher doses enhancing neuromodulator function via post-synaptic effects (Bari *et al*., 2010). However, the precise mechanisms governing these effects are not yet fully understood.

s0065 ***Direct Neuromodulator Administration***

p0210 Direct oral or intravenous administration of neuromodulators (e.g., serotonin, norepinephrine and dopamine) is not generally possible, because most of these molecules (testosterone is one important exception here) cannot cross the semi-permeable separation that prevents materials in the bloodstream from entering the brain (called the *blood–brain barrier*). For some neuromodulators like oxytocin, it may be possible to administer the compounds through the nasal passages, which bypass the blood−brain barrier. However, it remains unclear how intra-nasally administered neuromodulators enter the brain and reach the appropriate receptor sites (Churchland and Winkielman, 2012).

PHARMACOLOGY OF TIME PREFERENCES

s0070

p0215 When faced with a choice between a small immediate outcome and a larger delayed outcome, a decision maker must weigh the value of the immediate outcome against the time-discounted value of the delayed outcome. Time discounting plays a role in an array of counterproductive behaviors, including overeating, overspending, and procrastination. A preference for small immediate rewards is also seen as prominent in a variety of disorders such as addiction and attention-deficit/hyperactivity disorder (ADHD). These disorders are often treated with pharmacological agents targeting the serotonin and dopamine systems. For an overview of intertemporal choice, please refer to Chapter 10 of this volume. Here, we examine the effects of manipulating neuromodulator systems on intertemporal choice. We focus primarily on studies in animals and humans using simple tasks involving choices between small immediate rewards and larger delayed rewards, and define *impatient choice* as a preference for small immediate rewards over larger delayed rewards (note that some studies also refer to this preference as *impulsive choice*).

s0075 ## Dopamine

p0220 Initial interest in the relationship between dopamine and impatient choice came from the clinical observation that a class of drugs called *psychostimulants* are an effective treatment for ADHD, a disorder associated with steeper discounting of delayed rewards (Cardinal, 2006). Psychostimulants (amphetamine is one prominent example) have diverse effects on monoamine function, but their major effect is to enhance dopaminergic neurotransmission by stimulating dopamine release into the synapse and inhibiting its re-uptake. In line with the therapeutic effects of amphetamines in ADHD, several studies have reported that amphetamine reduces impatient choice in rodents (Bizot *et al*., 2011; Floresco *et al*., 2008; Richards and Sabol, 1999; van Gaalen *et al*., 2006; Wade *et al*., 2000) and humans (de Wit *et al*., 2002). Similar effects have been observed with the psychostimulant methylphenidate in rodents (Bizot *et al*., 2007, 2011; van Gaalen *et al*., 2006) as well as humans (Pietras *et al*., 2003).

p0225 However, not all studies have demonstrated straightforward effects of psychostimulants and amphetamines on intertemporal choice. The effects of amphetamines on impatient choice can be dose-dependent, with low, but not high doses reducing impatient choice (Floresco *et al*., 2008; Isles *et al*., 2003). Others have reported increased impatient choice following treatment with psychostimulants (Charrier and Thiébot, 1996; Evenden and Ryan, 1996). Cardinal (2006) pointed out that one potential explanatory factor for the differences between studies is the presence of cues during the delay to the larger reward. Such cues tend to increase choices for the delayed reward, as they themselves become associated with reinforcement (as conditioned reinforcers; Cardinal, 2006), and psychostimulants are known to potentiate the effects of conditioned reinforcers on behavior (Robbins, 1978). An explicit test of this hypothesis showed that amphetamine decreased impatient choice when a cue was present during the delay, but increased impatient choice when there was no cue (Cardinal *et al*., 2000). These findings suggest that psychostimulants may not influence impatient choice *per se*, but rather affect impatience indirectly by increasing the salience of conditioned reinforcers on behavior. However, other studies have shown that amphetamine decreases impatient choice even when no cue is present during the delay (van Gaalen *et al*., 2006; Wade *et al*., 2000; Winstanley *et al*., 2003), so the puzzle remains unresolved.

p0230 Studies examining the effects of more selective dopamine manipulations on intertemporal choice have also produced mixed results. Dopamine re-uptake inhibitors, which enhance dopamine function, have effects similar to those of psychostimulants, rendering subjects more patient (van Gaalen *et al*., 2006), whereas dopamine antagonists have the opposite effect, increasing impatient choice (Cardinal *et al*., 2000; van Gaalen *et al*., 2006; Wade *et al*., 2000).

p0235 It remains unclear whether the effects of dopamine on intertemporal choice are mediated by D_1 or D_2 type receptors. One study reported that systemically antagonizing D_2 receptors increased impatient choice, whereas antagonizing D_1 receptors did not (Wade *et al*., 2000). However, another study using a slightly different behavioral paradigm found the opposite effect: antagonizing D_1 receptors increased impatient choice, whereas antagonizing D_2 receptors did not, although the D_2 antagonist counteracted the patience-enhancing effects of amphetamine (van Gaalen *et al*., 2006). Although there is a high density of both D_1 and D_2 receptors in the nucleus accumbens, and lesions of this region increase impatient choice (Cardinal *et al*., 2001), neither D_1 nor D_2 antagonism specifically within the nucleus accumbens alters impatient choice (Wakabayashi and Fields 2004), and neurotoxin-induced dopamine depletion in the nucleus accumbens does not affect impatient choice (Winstanley *et al*., 2005).

p0240 An alternative possibility is that dopamine modulates time preferences via the orbitofrontal cortex (OFC). Kheramin and colleagues examined the effects of neurotoxin-induced dopamine depletion specifically within the OFC on impatient choice. Using a quantitative method that obtains separate measures of sensitivity to reward magnitude and sensitivity to delay, they found that OFC dopamine depletion increased both sensitivity to delay (increasing the rate of discounting) and sensitivity to reward magnitude (Kheramin *et al*., 2004). These findings suggest that dopamine within the OFC modulates the integration of delay and magnitude in the computation of subjective value.

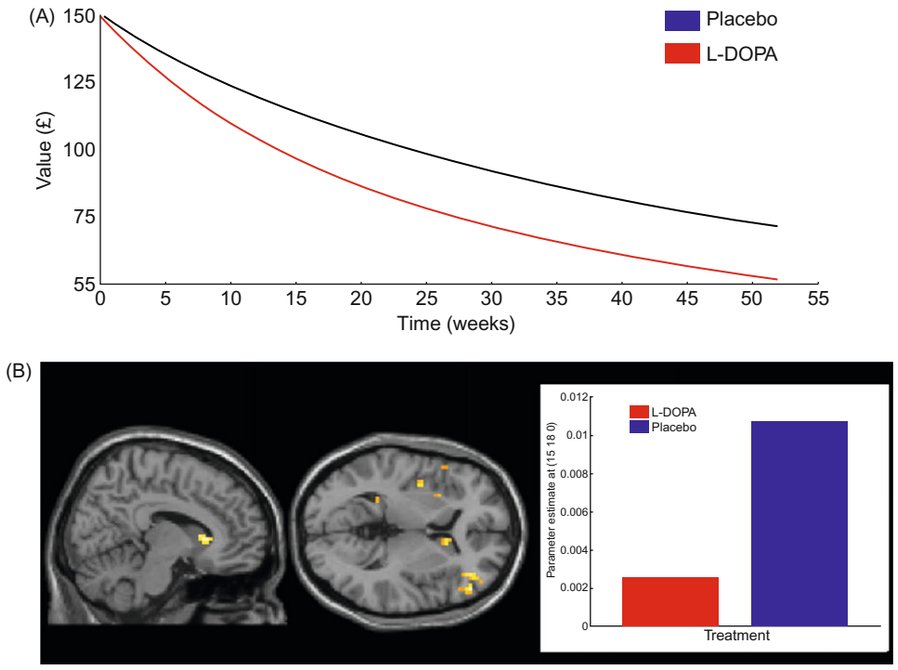
p0245 Although lesion studies in animals benefit from tight experimental control that enables inferences about the causal role of specific brain regions in intertemporal choice, they suffer from an important limitation: lesion studies target single brain regions, but the valuation of delayed outcomes involves multiple brain regions acting within a network. To probe the effects of neuromodulators on brain valuation networks in intertemporal choice, one potentially useful approach is combining computational models of temporal discounting with pharmacology and functional magnetic resonance imaging (fMRI). Pine and colleagues recently used this approach to examine the effects of the dopamine precursor L-DOPA and the D_1/D_2 antagonist haloperidol on intertemporal choice and its neural basis in humans (Pine *et al*., 2010). Healthy volunteers made a series of real choices between smaller-sooner versus larger-later monetary rewards following treatment with either placebo, haloperidol, or L-DOPA in a within-subjects design. Choice data were fit to a hyperbolic discounted utility model with free

parameters for time discounting (k) and magnitude discounting (i.e., the rate of diminishing marginal utility for gains; r). L-DOPA increased the proportion of impatient choices, relative to placebo, and increased the time discount rate k without affecting the magnitude discount rate r (Figure 14.3a), whereas haloperidol did not differ from placebo. Neuroimaging data revealed that activity in the striatum, insula, subgenual cingulate, and lateral orbitofrontal cortex decreased with increasing delays to the large reward. This effect was more pronounced on L-DOPA relative to placebo, paralleling the behavioral findings (Figure 14.3b). In addition, the subjective discounted value of delayed rewards, associated with activation in the caudate, insula, and lateral inferior frontal cortex, was reduced on L-DOPA relative to placebo. In other words, the data suggest that enhancing dopamine function with L-DOPA increased the discount rate, leading to a reduction in the subjective value of delayed rewards. The authors conclude that "dopamine controls how the timing of a reward is incorporated into the construction of its ultimate value" (Pine *et al.*, 2010, p. 8893).

Serotonin

p0250 Revisiting the effects of psychostimulants on intertemporal choice, it is worth noting that these compounds also influence serotonin function. In addition to stimulating dopamine release, amphetamine enhances serotonin neurotransmission by blocking the serotonin transporter. In a series of studies, Winstanley and colleagues provide evidence suggesting that the effects of amphetamines on impatient choice are at least partly mediated by changes in serotonin function. Global forebrain serotonin depletion, achieved via neurotoxic lesions, attenuated the ability of amphetamine to decrease impatient choice (Winstanley *et al.*, 2003). In the same study, a complete blockade of amphetamine's patience-enhancing effects was achieved by combining global serotonin depletion with dopamine antagonists, suggesting some redundancy in the roles of serotonin and dopamine in the control of intertemporal choice. Further experiments provided additional support for the idea that *interactions* between the serotonin and dopamine systems, rather than either system alone, play a key role in regulating the ability to make patient choices (Winstanley *et al.*, 2005).

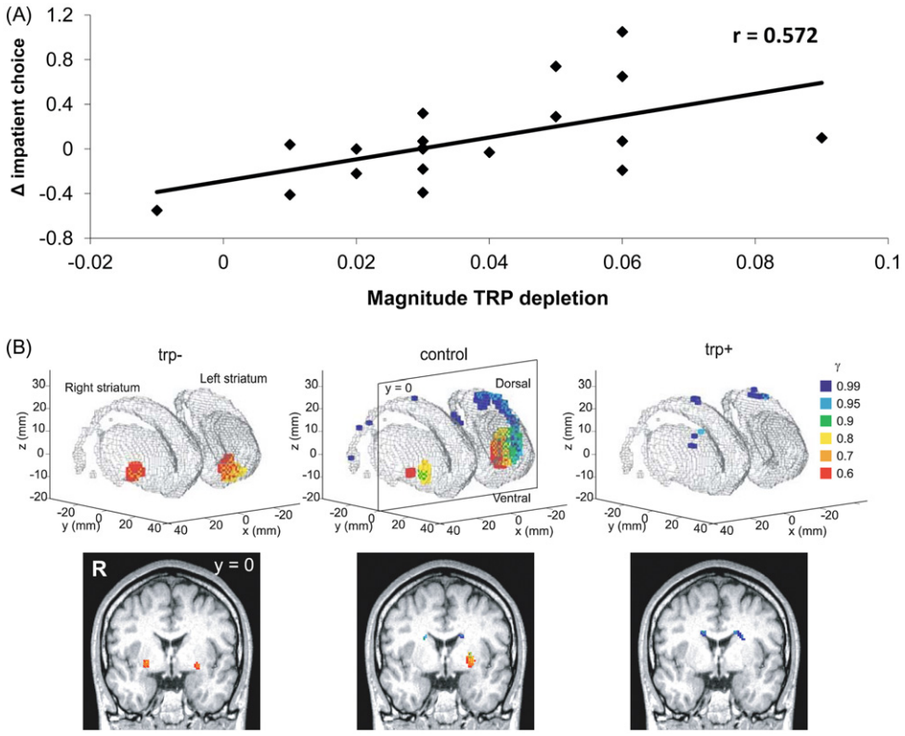
p0255 Still, other studies have shown that manipulations focusing directly on the serotonin system can influence intertemporal choice. Initial work in rodents using neurotoxin-induced global serotonin depletions indicated that impatient choices for small immediate rewards increase following serotonin depletion (Bizot *et al.*, 1999; Mobini *et al.*, 2000a,b; Wogar and Bradshaw 1993), suggesting that serotonin is critical for the ability to wait for delayed rewards. Converging evidence for this



f0020 **FIGURE 14.3** (A) L-DOPA reduced the discount rate k, relative to placebo. (B) Activity in the striatum, insula, subgenual cingulate, and lateral orbitofrontal cortex decreased with increasing delays to the large reward; this effect was more pronounced on L-DOPA relative to placebo. *From Pine* et al. *(2010).*

hypothesis comes from studies using alternative methods for manipulating serotonin function: impatient choices also increase following inhibition of serotonin synthesis (Bizot *et al*., 1999; Denk *et al*., 2004), and decrease following enhancement of serotonin with serotonin reuptake inhibitors (Bizot *et al*., 1999) or serotonin releasers (Poulos *et al*., 1996). However, other studies have failed to find effects of global serotonin manipulations on impatient choice in rodents (Evenden, 1999; Evenden and Ryan, 1996, 1999; Winstanley and Dalley, 2004). Examining the consequences of stimulating specific serotonin receptor subtypes, Evenden and colleagues reported increased impatient choice following stimulation of the 5-HT_2 class of receptors for serotonin (Evenden and Ryan, 1999), an effect likely mediated specifically by 5-HT_{2A} receptors (Hadamitzky *et al*., 2009). Stimulating 5-HT_{1A} receptors also tends to increase impatient choice, but the effects depend on the dosage used (Bizot *et al*., 1999; Liu *et al*., 2004; Poulos *et al*., 1996). As the 5-HT_{1A} receptor can regulate serotonin release when activated pre-synaptically, the complex consequences of 5-HT_{1A} stimulation may reflect a delicate balance between the effects of pre- and post-synaptic receptor activation.

In humans, the influence of serotonin on intertemporal choice has been studied using acute tryptophan depletion (ATD), a dietary precursor manipulation that results in a transient global reduction of brain serotonin. An early study found no effect of ATD on intertemporal choice (Crean *et al*., 2002). The authors suggested that the intertemporal choice task, which was questionnaire based, was perhaps insufficiently sensitive to detect effects of altered serotonin levels. A later study examined hypothetical choices for smaller-sooner versus larger-later monetary rewards, and fit intertemporal choice data to a hyperbolic discounted utility model. The discount rate, k was increased by ATD, but only to the extent that the ATD procedure resulted in effective depletion of tryptophan (measured in the plasma; Figure 14.4a; Crockett *et al*., 2010b). Another set of studies in humans used an intertemporal choice task with experiential delays (as are used in the animal studies reviewed above), and fit behavior to a reinforcement learning model with separate parameters for reward discounting (using an exponential discount function), learning rate, and choice variability. One study found that ATD increased choices for the smaller, sooner reward, as



f0025 **FIGURE 14.4** (A) Impairing serotonin function with acute tryptophan depletion increased the discount rate k, but only to the extent that the ATD procedure resulted in effective depletion of tryptophan (measured in the plasma). *Adapted from Crockett* et al. *(2010b)*. (B) Acute tryptophan depletion enhances activity in the ventral striatum during short-term reward prediction (left), while augmenting serotonin function with tryptophan supplementation enhances activity in the dorsal striatum during long-term reward prediction (right), relative to placebo (center). *Adapted from Tanaka* et al. *(2006)*.

well as the discount parameter, without affecting learning or choice variability (Schweighofer *et al.*, 2008). An fMRI study using the same task suggested that ATD increases impatient choice by enhancing activity in the ventral striatum during short-term reward prediction (Tanaka *et al.*, 2007). In the same study, augmenting serotonin function with tryptophan supplementation enhanced activity in the dorsal striatum during long-term reward prediction (Figure 14.4b). These findings fit with the animal literature suggesting that serotonin modulates intertemporal choice through its actions in the striatum, either alone or in concert with dopamine (Robbins and Crockett, 2010; Winstanley *et al.*, 2005) as well as with single-cell recording studies showing the activity of serotonin neurons is related to decisions to wait for delayed rewards (Miyazaki and Miyazaki, 2011a,b; Miyazaki *et al.*, 2012; see also Chapter 17).

Norepinephrine

There have been far fewer studies on the role of norepinephrine in intertemporal choice, but the fact that many psychostimulants also enhance norepinephrine function (by inhibiting the norepinephrine transporter) and that norepinephrine-enhancing drugs such as the norepinephrine reuptake inhibitor atomoxetine can be effective treatments for ADHD, implies a possible role for norepinephrine in regulating impatient choice. Existing research supports this notion. Enhancing norepinephrine function with atomoxetine reduced impatient choice in rodents (Bizot *et al.*, 2011; Robinson *et al.*, 2007), while impairing norepinephrine function had the opposite effect (van Gaalen *et al.*, 2006). Another study in primates demonstrated that stimulation of norepinephrine receptors with the ADHD medication guanfacine (an α-2_A agonist) reduced impatient choice (Kim *et al.*, 2011). No studies have yet examined how norepinephrine modulates intertemporal choice in humans.

Summary

Pharmacological manipulations targeting the monoamine neurotransmitters dopamine, serotonin and norepinephrine have profound effects on time preferences across species. Psychostimulants, which cause nonspecific, broad and global release of all three monoamines, generally reduce impatient choices for small immediate rewards; however, when considering the effects of individual neuromodulators, the picture appears far more complex. Enhancing serotonin and norepinephrine function reduces impatient choice, but the effects of dopamine manipulations are more nuanced, and appear to depend on the precise pharmacological tools employed as well as features of the behavioral task. There is also evidence that *interactions* between serotonin and dopamine, rather than the actions of either neurotransmitter in isolation, may be decisive in controlling impatient choice. Work in animals and humans suggests that serotonin and dopamine, either together or separately, influence intertemporal choice by modulating the rate of time discounting and its representation in the striatum.

PHARMACOLOGY OF RISK PREFERENCES

In an unpredictable world, decision makers often face choices between certain outcomes on the one hand, and risky or uncertain outcomes on the other hand. In the case of choices under *risk*, the probability of the uncertain outcome is known; however, in most real-world decision problems, the probability of the uncertain outcome is unknown, and subjects therefore face *ambiguity*. Valuation under risk and ambiguity are at least partially dissociable at the neural level (see Chapter 9 for an overview). Risky decision making shares several features with impatient decision making, in that decision makers must "discount" the value of the uncertain outcome, perhaps in a similar manner to discounting the value of delayed outcomes in intertemporal choice. Indeed, some behavioral studies have shown that impatience (time discounting) and risk aversion (risk discounting) are correlated (Andersen *et al.*, 2008; Eckel *et al.*, 2004; Leigh, 1986). Perhaps not surprisingly, then, the same neuromodulators that influence intertemporal choice – dopamine, serotonin, and noradrenaline – also appear to modulate decisions under risk. In the following sections, we review studies in animals and humans investigating the effects of manipulating monoamine neurotransmitter systems on risky decision making. We focus mainly on studies involving tasks where decision makers must choose between small certain rewards and larger uncertain rewards, and define "risky choice" as a preference for large uncertain rewards over small certain rewards.

Dopamine

Clinical evidence for dopaminergic modulation of risky decision making comes from the striking observation of pathological gambling in a subset of Parkinson's disease patients who are treated with dopamine-enhancing medications. These symptoms are selectively associated with dopamine agonist treatment, coincide with the onset of dopamine agonist therapy, and disappear with the termination of treatment (Imamura *et al.*, 2006). In line with clinical reports of pathological gambling behavior resulting from treatments with dopamine agonists, enhancing dopamine function in humans

appears to increase risk-taking behavior, although the effects are not entirely straightforward. Nonspecific dopamine stimulation in humans with the dopamine precursor L-DOPA increased the propensity to seek out larger uncertain rewards over smaller certain rewards, but the effect of L-DOPA depended on genotype: the drug only increased risky decision making in individuals possessing the 7-repeat variant of the dopamine D_4 receptor gene (Eisenegger *et al*., 2010), a polymorphism associated with pathological gambling and impulse control disorders (Faraone *et al*., 2005). Dopamine may promote risky choice specifically through actions on D_2 or D_3 receptors. One study examined the effects of the mixed D_2/D_3 agonist pramipexole on decision making in a task where one choice ("safe") could incur a gain or loss of 5 Euro cents, while the other option ("risky") could incur a larger gain or loss of 25 or 50 Euro cents, with unknown probabilities. Following large wins, participants were less likely to choose the risky option. Pramipexole abolished conservatism following wins, and reduced activation in the striatum and midbrain following large wins. The authors suggested that the increased risky choices on pramipexole stem from a need to seek higher rewards to overcome blunted responses in the reward network (Riba *et al*., 2008). Another study investigated the effects of pramipexole on the tendency to increase risky decisions following losses ("loss-chasing"). In this task, participants faced a choice between sustaining a certain loss, or gambling to recover the loss (at the risk of doubling its size). Following pramipexole, participants chased larger losses and surrendered smaller ones, relative to placebo, suggesting that D_2/D_3 receptor stimulation increased the marginal value of risky loss-chasing decisions by reducing sensitivity to losses (Campbell-Meiklejohn *et al*., 2010).

p0285 The above studies support a role for dopamine in modulating risky decision making, but the mechanisms involved are unclear, perhaps due to the complexity of the decision making tasks used. Experiments in animals provide a bit more precision into understanding how dopamine modulates risky choice. The majority of these studies have employed simple tasks similar to those used to study impatient choice, involving choices between a small certain reward, and a larger reward that is uncertain (rather than delayed). Fitting with the observation that the process of discounting uncertain outcomes shares certain features with the process of discounting delayed outcomes, dopaminergic manipulations produce effects on risky decision making that are somewhat comparable with those on impatient decision making.

p0290 Recall that psychostimulants and other treatments that enhance dopaminergic neurotransmission generally reduce preferences for small certain rewards over larger delayed rewards; in other words, they make decision makers less impatient. If discounting the value of uncertain rewards reflects a similar underlying mechanism to discounting the value of delayed rewards, we might expect that enhancing dopamine function may also reduce preferences for small certain rewards over larger uncertain rewards (i.e., they may make decision makers more risky). Indeed, this has been observed: psychostimulants and other pharmacological manipulations that enhance dopaminergic neurotransmission appears to make decision makers more risky, preferring larger uncertain rewards over small certain ones. Thus, neuromodulation by dopamine may provide an important unifying account of time and risk discounting. Several studies in rodents have shown that the nonspecific monoamine enhancer amphetamine increases risky choice (Onge and Chiu, 2010; Onge and Floresco, 2008; Zeeb *et al*., 2009), although in one study, the effect of amphetamine depended on whether the probability of the uncertain outcome increased or decreased across the experimental session, suggesting that increasing dopamine release perturbs behavioral adjustments in response to changes in the relative value of certain versus uncertain rewards (Onge and Chiu, 2010). The effects of amphetamine on risky choice are likely mediated through changes in dopaminergic neurotransmission, as nonspecific dopamine antagonists reduce risky choice (Onge and Chiu, 2010).

p0295 Dopamine appears to promote risky choice via both D_1 and D_2 receptors, as blockade of either of these types of receptors attenuated the effect of amphetamine on risky choice (Onge and Floresco, 2008). Systemic blockade of D_1 or D_2 receptors alone decreases risky choice (Onge and Floresco, 2008; Zeeb *et al*., 2009), whereas stimulation of D_1 or D_2 receptors alone increases risky choice (Onge and Floresco, 2008). Meanwhile, stimulation of D_3 receptors reduces risky choice, while D_3 receptor blockade enhances the effect of amphetamine on risky choice (Onge and Floresco, 2008). These findings may help to explain the complex and inconsistent effects of pramipexole on risky choice in humans, since this drug stimulates both D_2 and D_3 receptors.

p0300 Within the medial prefrontal cortex (mPFC), however, D_1 and D_2 receptors appear to play distinct roles, with D_1 antagonists reducing risky choice but D_2 antagonists increasing risky choice (Onge *et al*., 2011). Collectively, these results suggest that the complementary effects of stimulating different dopamine receptor types on risky choice enable dopamine to exert finely tuned control over the integration of risk and reward information in decision making.

Serotonin s0105

p0305 An early study showed that global serotonin depletion in rodents does not affect choices between small certain rewards and larger uncertain rewards (Mobini *et al*., 2000). However, a more recent study reported increased

risky choices following transient serotonin depletion with ATD; relative to a placebo treatment, rats on ATD preferred large uncertain rewards to small certain ones, even beyond the indifference point (Koot *et al*., 2011). These effects are consistent with a study in humans showing reduced choices of the most probably rewarded option following ATD (Rogers *et al*., 1999; but see also (Anderson *et al*., 2003)), as well as a study in monkeys investigating the effects of ATD on a gambling task involving choices between a "safe" option (offering a certain reward) and a "risky" option (offering a larger or smaller reward, delivered randomly). This task enabled the quantification of "risk preference", defined by choice when the two options were matched in expected value, and "safety premium", defined as the point of subjective equivalence between the risky and safe options (i.e., the difference in expected value between the risky and safe options when the monkeys were indifferent between the options). ATD both increased the likelihood of choosing the risky option when its expected value was equivalent to the safe option, and decreased the safety premium, suggesting that ATD increased the subjective value of the risky option (Long *et al*., 2009). Importantly, in this study ATD did not affect discrimination of reward magnitudes, measured with a separate task. Thus, in the gain domain, impairing serotonin function led to risk-seeking behavior.

p0310 In humans, serotonin appears to influence risky decision making through effects on more sophisticated cognitive processes such as the appraisal of value or the framing of decisions (Rogers, 2010), but many findings are inconsistent. Rogers and colleagues (2002) studied the effects of ATD on decision making in a task involving choices between simultaneously presented gambles that differed in their magnitude of expected rewards, magnitude of expected losses, and the probabilities with which these outcomes were realized. ATD did not affect risk aversion, but made choices "noisier"; relative to placebo, ATD made subjects less likely to choose gambles associated with large rewards, relative to smaller ones (Rogers *et al*., 2002). However, another study by the same group reported rather different effects on the same task when augmenting serotonin function with dietary tryptophan supplementation. Following placebo treatment, participants preferred small certain gains over larger uncertain gains, but large uncertain losses over smaller certain losses. This "framing effect" was reduced by tryptophan supplementation in the loss domain; in other words, enhancing serotonin made subjects more risk-averse for losses, without affecting risk preferences in the gain domain (Murphy *et al*., 2009).

p0315 Two other studies directly contradict these findings and instead support the hypothesis that impaired serotonin function is associated with increased risk aversion in the loss domain, particularly when the distinction between the certain and risky options involves a degree of cognitive appraisal. Campbell-Meikeljohn and colleagues. (2010) showed that ATD reduced loss-chasing behavior; relative to placebo, participants on ATD preferred to sustain a certain loss, rather than gamble to recover the loss at the risk of doubling its size. Crockett and colleagues (2011) showed a similar effect using an information-sampling task, in which participants could sample information at a small cost to avoid making incorrect decisions, which resulted in large losses. ATD abolished the suppressive effect of small local costs on information sampling behavior; relative to placebo, participants were more willing to incur small local costs in order to avoid large global losses. These findings fit with contemporary theories of serotonin function that suggest enhancing serotonin promotes the avoidance of aversive outcomes (Boureau and Dayan, 2010; Cools *et al*., 2010). In both studies, impairing serotonin function made subjects more willing to accept small certain losses, perhaps by reducing reflexive avoidance of these cognitively salient aversive outcomes.

p0320 However, additional inconsistencies arise when considering two studies in rodents showing that impairing serotonin function increases risky decisions in the Iowa Gambling Task, in which subjects must choose between "advantageous" options (which produce small gains and occasional small penalties) and "disadvantageous" options (which produce larger gains, but incur heavy long-term losses). Both ATD and the 5-HT_{1A} receptor agonist 8-OH-DPAT, which decreases serotonin release, increased disadvantageous choices (Koot *et al*., 2011; Zeeb *et al*., 2009), suggesting these treatments reduced the ability to integrate information about the magnitude and probability of punishments in the context of risky decision making.

Norepinephrine

s0110

p0325 As with intertemporal choice, there have been few studies investigating how norepinephrine modulates risky decision making. One study reported no effect of the α-2A receptor agonist guanfacine on risky choice in primates (Kim *et al*., 2011). Two studies examined the effects of the beta-receptor blocker propranolol on risky choice in humans. One found no effect of propranolol on choices for small certain losses versus larger uncertain ones (Campbell-Meiklejohn *et al*., 2010). The other reported no effect of propranolol on the overall proportion of risky choices, or the tendency to prefer certain over uncertain gains but uncertain over certain losses (i.e., framing effects). However, propranolol made choices "noisier" when the probability of losing was high; in other words, at high loss probabilities, propranolol made subjects less likely to avoid larger losses, relative to smaller ones (Rogers *et al*., 2004). A similar effect

was observed following dietary tyrosine and phenylalanine depletion, which impairs dopamine as well as norepinephrine function (Scarnà *et al.*, 2005).

s0115 ## Summary

p0330 Although there is a wealth of evidence demonstrating that manipulations of monoamine neurotransmitter systems influence risky choice, the precise effects of dopamine, serotonin and norepinephrine on valuation under risk and ambiguity are not well understood. Enhancing dopamine function appears to promote risky choice, but the underlying mechanisms remain unclear, with some studies suggesting dopamine alters risky choice through effects on reward processing, while others imply dopamine modulates sensitivity to losses. Work in animals indicates that D_1, D_2 and D_3 receptors make distinct contributions to decision making under risk. Studies of serotonin in risky decision making are similarly mixed; serotonin has been implicated in a wide range of processes in the context of decisions under risk, including reward processing, punishment processing, and risk preference itself. There are very few studies of norepinephrine on risky choice, with most showing no effect. Overall, this literature would greatly benefit from a more precise specification of valuation under risk and uncertainty, to better identify the computational mechanisms involved in risky choice and their modulation by the monoamines. Experimental approaches combining economic models of risky decision making (e.g., expected utility and risk-return models; see Chapter 9) with pharmacological manipulations and neuroimaging will be a fruitful approach to understanding how neuromodulators shape decisions under risk and uncertainty.

p0335 One aspect of risky decision making that has been conspicuously overlooked in this literature is the phenomenon of non-linear probability weighting, or the tendency to overweight low probabilities and underweight high probabilities. Overweighting of low probabilities leads to risk-seeking behavior, while underweighting of high probabilities leads to risk aversion. Pharmacological treatments that cause upward or downward shifts in the probability weighting function, or changes in its shape, could result in complex patterns of risky decision making such as those described above. Future studies in this area may benefit from a fuller exploration of the risky decision making landscape.

s0120 # PHARMACOLOGY OF SOCIAL PREFERENCES

p0340 Humans are motivated to maximize their own payoffs, but also care about the outcomes of others, and are sometimes willing to incur personal costs to help or harm other people. In other words, humans display "social preferences" – they value (either positively or negatively) others' material payoffs or well-being. Of all the classes of preferences discussed in this volume, social preferences are perhaps the most sensitive to context, and therefore predicted to be under tight control by neuromodulators. Indeed, regulation of social preferences (and social behavior more generally) by neuromodulators may have evolved as an efficient and reliable means of matching social behavior to the current context. An overview of the neuroeconomics of social preferences is provided in Chapter 11. Here, we examine recent studies in primates and humans investigating the effects of manipulating serotonin, oxytocin, and testosterone on social decision making. Unlike the more basic processes of intertemporal and risky choice discussed in the previous sections, social decisions are rather more complex, often incorporating elements of time, risk, reward and punishment processing, among others. Because neuromodulators are involved in all of these more basic processes, it is important to tightly control for these factors when designing studies to test for influences of neuromodulators specifically on social preferences. We will carefully consider this point when evaluating the existing literature on the neuromodulation of social decision making.

Serotonin s0125

p0345 Serotonin modulates social behavior across a wide range of species, from locusts (Anstey *et al.*, 2009) and lobsters (Kravitz, 2000) to monkeys (Higley and Linnoila, 1997) and men (Krakowski, 2003). Observational studies in primates have generally reported a positive relationship between serotonin function and prosocial behavior, with enhanced serotonin function associated with social cooperation and affiliation, and impaired serotonin function associated with aggression and antisocial behavior (Higley *et al.*, 1996; Mehlman *et al.*, 1995) (Raleigh *et al.*, 1991). The association between low serotonin function and aggression has been replicated in numerous clinical and nonclinical human studies (Krakowski, 2003). Dietary depletion of the serotonin precursor tryptophan increases aggression in laboratory settings (Bjork *et al.*, 1999, 2000; Dougherty *et al.*, 1999; Marsh *et al.*, 2002; Moeller *et al.*, 1996), while enhancing serotonin function with reuptake inhibitors or tryptophan augmentation has the opposite effect (Berman *et al.*, 2009; Marsh *et al.*, 2002). Augmenting serotonin function also seems to promote social cooperation in humans; in observational studies, tryptophan supplementation decreases quarrelsome behavior (Moskowitz *et al.*, 2001) while serotonin re-uptake inhibitors increase affiliative and cooperative behaviors (Knutson *et al.*, 1998).

p0350 The mechanisms underlying the effects of serotonin on social behavior have begun to be explored recently with more precision by incorporating economic models of social preferences into pharmacological experiments. One potential explanation for the observation that serotonin positively covaries with prosocial behavior is that enhancing serotonin shifts valuation of others' outcomes in the positive direction, while impairing serotonin shifts valuation of others' outcomes in the negative direction. Consistent with this idea, serotonin re-uptake inhibitors increase cooperation in a repeated Prisoner's Dilemma (Tse and Bond, 2002), while ATD has the opposite effect (Wood *et al*., 2006). However, because these studies employed repeated games, there are several alternative explanations for the effects of serotonin manipulations on cooperation. As discussed in the previous section, there is evidence that serotonin modulates intertemporal choice, a process that likely plays a role in cooperation in repeated games (Rachlin, 2002), since long-term cooperation requires foregoing immediate selfish gains in order to obtain delayed social benefits. Repeated games also involve learning the behavior patterns of one's interaction partner, and serotonin has been implicated in reward representation during reinforcement learning (Seymour *et al*., 2012).

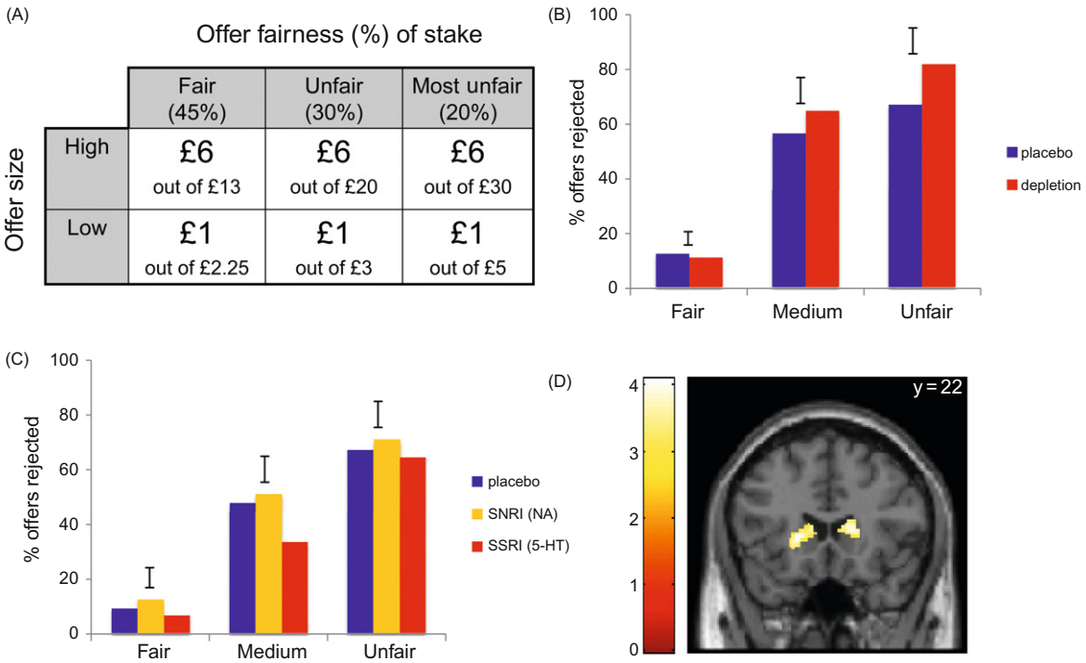
p0355 A cleaner test of the hypothesis that serotonin modulates social preferences is to use one-shot games, in which learning and intertemporal choice are less of a concern. Crockett and colleagues conducted a series of experiments demonstrating that manipulating serotonin alters social preferences in a one-shot ultimatum game (UG). In this game, two players must agree to share a sum of money (the stake), or neither player gets any money. One player, the proposer, suggests a way to split the sum. The other player, the responder, either accepts the offer and both players are paid accordingly, or rejects the offer and neither player is paid. Despite the fact that rejecting an offer means forfeiting payment, responders tend to punish proposers who behave selfishly by rejecting their unfair offers (usually less than 20–30% of the total stake; Güth and Schmittberger, 1982). Participants who reject offers in the UG display social preferences because they are willing to forego their own material payoff for the sake of decreasing the proposer's payoff.

p0360 One challenge in assessing the effects of pharmacological manipulations on complex phenomena such as social preferences is controlling for basic motivational processes that may also be affected by the neuromodulator of interest. In the case of economic games, one common confounding factor is monetary reward. Neuromodulators such as serotonin and dopamine are known to influence the representation of rewards (Jocham *et al*., 2011; Seymour *et al*., 2012). This is problematic because in many tests of social preferences, monetary reward is confounded with social factors such as fairness. For example, in the classic version of the UG, unfair offers (e.g., $2 out of $10) are both lower in monetary value and lower in social value relative to fair offers (e.g., $5 out of $10). Thus, suppose altering serotonin function affected rejection rates of unfair offers in the classic UG. While this may reflect a change in social preferences, the alternative possibility that altered serotonin function simply affected the valuation of money cannot be ruled out.

p0365 To circumvent this challenge, Crockett and colleagues (2008) used a version of the UG that independently manipulated offer size (monetary amount) and offer fairness (proportion of stake) by varying both the offer amount and the stake size across trials (Tabibnia *et al*., 2008; Figure 14.5a). Thus, the same amount of money (e.g., $5) could appear as an unfair offer (e.g., $5 out of $20) or a fair offer (e.g., $5 out of $10). By controlling for material value, the authors were able to demonstrate that impairing serotonin function with ATD altered social preferences: following ATD, participants were more likely to reject unfair offers, but not fair offers that were matched for material value (Crockett and colleagues 2008) (Figure 14.5b). In other words, impairing serotonin function appeared to shift social preferences in the negative direction; participants were more willing to forego material payoffs to decrease the payoffs of those who treated them unfairly.

p0370 Because pharmacological manipulations can have broad, global effects on mood, perception, and motor behavior, it is critical to collect additional measures of these processes within the same experiment to rule out these potential confounding factors when explaining the results of interest. In the study by Crockett and colleagues (2008), ATD did not affect mood, nor did it alter perceptions of fairness of the offers (assessed separately with a questionnaire) or the amount of money offered when subjects were in the role of proposer. Thus, the data suggest that serotonin directly modulates social preferences, rather than influencing them indirectly via mood or fairness perception. ATD did, however, increase impatient choice in the same subjects, an effect that was positively correlated with the effect of ATD on rejection of unfair offers (Crockett *et al*., 2010b). This finding underscores the importance of using one-shot games to test the effects of neuromodulators on social preferences, as global manipulations of neuromodulator systems can affect a variety of motivational processes as a consequence of their diverse ramifications throughout the brain.

p0375 A subsequent study tested whether the influence of serotonin on social preferences in the UG is bidirectional and neurochemically specific by comparing the effects of the serotonin re-uptake inhibitor citalopram with the norepinephrine re-uptake inhibitor atomoxetine and placebo. Using the same UG paradigm



f0030 **FIGURE 14.5** (A) Crockett and colleagues (2008) used a version of the UG that independently manipulated offer size (monetary amount) and offer fairness (proportion of stake) by varying both the offer amount and the stake size across trials. Thus, the same amount of money (e.g., £6) could appear as an unfair offer (e.g., £6 out of £30) or a fair offer (e.g., £6 out of £13). *Adapted from Crockett* et al. *(2008)*. (B) Impairing serotonin function with acute tryptophan depletion increased rejection of unfair, but not fair offers in the UG. *Adapted from Crockett* et al. *(2008)*. (C) Enhancing serotonin function with an SSRI reduced rejection of medium offers in the UG while an injection of a placebo nonspecific serotonin-norepinephrine reuptake inhibitor (SNRI) did not. *Adapted from Crockett* et al. *(2010a)*. (D) Impairing serotonin function with acute tryptophan depletion increased dorsal striatal responses during rejection of unfair offers. *Adapted from Crockett* et al. *(2013)*.

as in their previous study, Crockett and colleagues demonstrated that altering serotonin function with citalopram *reduced* rejection of unfair offers in the UG – an effect opposite to that of ATD (Crockett *et al*., 2010a; Figure 14.5c). Altering norepinephrine function with atomoxetine had no effect on social preferences, although it did improve performance on a separate test of sustained attention. Again, manipulating serotonin function had no effect on mood or perceptions of fairness of the offers. Additional tests showed that citalopram made participants less likely to endorse harming one person to save many others. These results suggest that citalopram increased harm aversion, consistent with a shift of social preferences in the positive direction following serotonin enhancement.

p0380 Previous neuroimaging studies have implicated the striatum in the computation of social preferences (Tabibnia *et al*., 2008; Tricomi *et al*., 2010). Thus, serotonin may modulate social preferences by altering striatal responses during social decision making. To test this hypothesis, Crockett *et al*. (2013) examined the effects of ATD on neural activity during the UG with fMRI (Crockett *et al*., 2013). Consistent with previous findings, ATD increased rejection of unfair offers. Neuroimaging revealed that during rejection of unfair offers, ATD increased responses in the dorsal striatum, relative to placebo (Figure 5d). The effects of ATD on dorsal striatal activity predicted the effects of ATD on rejection behavior: subjects showing the greatest increases in dorsal striatal activity during rejection on ATD were those that also showed the greatest increases in rejection rates on ATD. These findings are consistent with a role for serotonin in modulating the computation of social value.

Oxytocin s0130

The importance of oxytocin in social behavior became p0385 evident in the 1990s with Insel and Young's work on pair-bonding in two closely related species of voles. Prairie voles live in burrows with extended families and pair-bond monogamously, whereas montane voles live in solitary burrows and mate promiscuously. These two species show distinct patterns of oxytocin receptor distribution: monogamous prairie voles show a high density of oxytocin receptors in the nucleus accumbens, whereas promiscuous montane voles express oxytocin receptors more heavily in the lateral septum and the hypothalamus (Insel and Shapiro, 1992; Young and Wang, 2004).

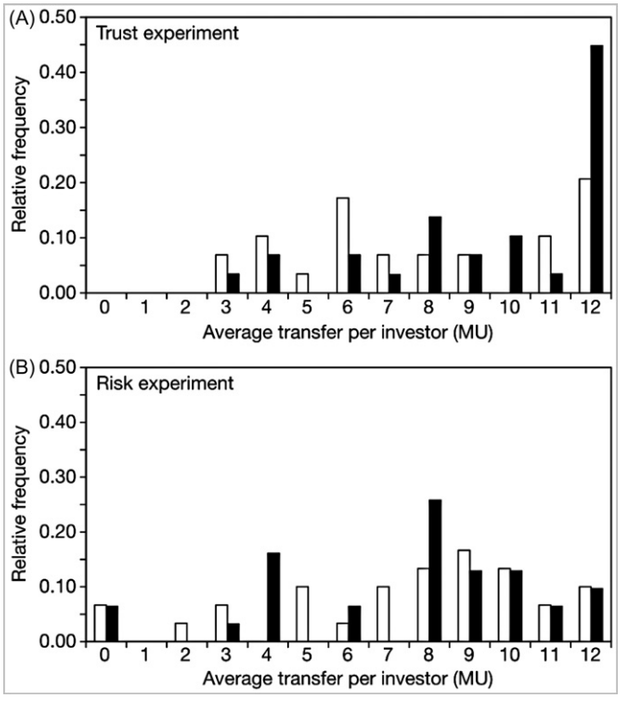
Oxytocin is released after mating, and the pattern of receptor expression in voles suggests that in monogamous species, mating is reinforcing and leads to long-term attachment (Insel, 2010). Other monogamous species, such as marmosets and California mice, also express oxytocin receptors in the nucleus accumbens (Insel *et al.*, 1991; Schorscher-Petcu and Dupré, 2009), and oxytocin administration enhances pair-bonding in marmosets (Smith *et al.*, 2010). In humans, oxytocin modulates a number of social processes, including social memory, emotion recognition, affect sharing, empathic accuracy, social emotions, social perception, social attention, affiliation, and communication (reviewed in Bartz *et al.*, 2011; Feldman, 2012; Graustella and MacLeod, 2012).

p0390 As in the case of serotonin, neuroeconomic approaches to understanding oxytocin function have begun to reveal how oxytocin modulates social decision making. The first study along these lines examined the influence of oxytocin on trust behavior. Social preference models predict that trusting other individuals by making investments that may not be repaid is not just a decision involving monetary risk. Reciprocal and inequity-averse subjects derive a special disutility from betrayal of trust, along with the associated economic loss; this is consistent with behavioral studies (Zeckhauser, 2004) indicating a pure aversion to social betrayal. Kosfeld and colleagues (2005) demonstrated that the brain distinguishes between social trust and monetary risk-taking by administering intranasal oxytocin to players in a trust game. In this game, one player (the investor) has the option to choose a costly trusting action by giving money to another player (the trustee). If the investor sends the money, the amount sent is tripled by the experimenter. The trustee is then informed about the investors transfer and has the option to either keep the full amount, or to send some money back to the investor. Thus, if the investor chooses to trust and the trustee shares the proceeds, both players end up with a higher amount than if the investor did not trust. However, trust involves a degree of risk for the investor, because the trustee may betray his trust and make him worse off than if he had not trusted.

p0395 In this experiment, oxytocin increased investors' trusting behavior by 17%, relative to a placebo control group (Figure 14.6a). But before the authors could conclude that oxytocin modulates trust specifically, they had to rule out the possibility that oxytocin simply altered sensitivity to risk, as trust involves a degree of risk-taking. To do this, they conducted a risk experiment, in which investors faced exactly the same decisions as in the trust game, but removed from a social context: the trustee was replaced with a computer. Critically, oxytocin did *not* affect behavior in the risk experiment (Figure 14.6b), indicating that the effects of oxytocin on trust are specific to the social context, nor did it affect investors' beliefs about the chances of being paid. Oxytocin also did not influence the behavior of trustees (a measure of altruistic preferences), demonstrating the remarkable specificity of oxytocin's effect on trusting behavior. The authors postulated that oxytocin limits the fear of betrayal in social interactions, consistent with animal evidence that it inhibits defensive behavior and facilitates maternal behavior and pair-bonding (Insel, 2010; Kosfeld *et al.*, 2005). The effect of oxytocin on trust has subsequently been replicated outside the context of a monetary game (Mikolajczak *et al.*, 2010).

p0400 To investigate the hypothesis that oxytocin facilitates trust by reducing the fear of betrayal, Baumgartner and colleagues (2008) examined the effects of oxytocin on investors' neural activity during the trust game with fMRI. Specifically, the authors were interested in oxytocin's effect on amygdala activity, as previous studies have indicated a role for the amygdala in evaluating the trustworthiness of faces (Adolphs *et al.*, 2005). Consistent with studies showing that oxytocin decreases fear responses by modulating activity in the amygdala (Domes *et al.*, 2007; Kirsch *et al.*, 2005), Baumgartner and colleagues found that oxytocin affected trusting behavior only in those situations where oxytocin also dampened amygdala activity (Baumgartner *et al.*, 2008). Further evidence that oxytocin modulates betrayal aversion comes from a study showing that oxytocin treatment interacts with individual differences in attachment avoidance, or the tendency to shy away from closeness and dependency in interpersonal relationships. Oxytocin increased trust and cooperation, and decreased betrayal aversion (measured with a questionnaire), specifically in subjects high in attachment avoidance (De Dreu, 2011).

p0405 In addition, the study by Baumgartner and colleagues suggests a crucial role of the caudate nucleus when subjects learn about the trustworthiness of a population of trustees. Subjects who were given oxytocin did not change their trusting behavior after they received information that many trustees had betrayed their trust in previous interactions, whereas subjects who received placebo reduced their trusting behavior after this information. During post-feedback trust decisions, oxytocin caused a specific activity reduction in the caudate nucleus, suggesting that the lack of trust adaptation in subjects with oxytocin may have been caused or modulated by the diminished recruitment of reward learning circuitry. One interpretation of this effect is that oxytocin facilitates social bonding by promoting "forgiveness" of trust violations, reflected in diminished caudate activity. Consistent with this interpretation, in a repeated Prisoner's Dilemma, oxytocin promoted cooperation following unreciprocated cooperation in the previous round (Rilling *et al.*, 2011). In the same study, oxytocin increased the caudate response to reciprocated cooperation, suggesting that oxytocin amplifies the reinforcing aspects of social exchange.



f0035 **FIGURE 14.6** (A) In the trust experiment, OT increased investors' trusting behavior by 17%, relative to a placebo control group. (B) OT did *not* affect behavior in the risk experiment, indicating that the effects of OT on trust are specific to the social context. *From Kosfeld* et al. *(2005)*.

p0410 As oxytocin has been implicated in social bonding, recent studies have begun to examine how oxytocin modulates trust and cooperation specifically with members of one's own social group. These studies show that the effects of oxytocin on trust and cooperation are far from universal; oxytocin appears to facilitate trust primarily with those who seem familiar or trustworthy. For example, Mikolajczak and colleagues manipulated social impressions of trustees in a trust game by describing them as either prosocial (e.g., studying philosophy, practicing first aid) or less prosocial (e.g., studying marketing, playing violent sports). Oxytocin increased trust behavior by investors (as in the study by Kosfeld *et al*., 2005), but *only* for those trustees described as prosocial. When trustees were described as less prosocial, oxytocin had no effect on investors' trust behavior: in other words, oxytocin makes people trusting, but not gullible (Mikolajczak *et al*., 2010). Similarly, Declerck and colleagues studied the effects of oxytocin on cooperation and found that oxytocin increased both expectations of cooperation by others and cooperative behavior when the participants had met one another beforehand, but actually *decreased* cooperation under conditions of complete anonymity (Declerck *et al*., 2010). In line with these findings, a recent meta-analysis showed that while oxytocin facilitates trust in members of one's own group ("in-group"), it does not significantly affect trust in members of outside groups ("out-group") (Van Ijzendoorn and Bakermans-Kranenburg, 2012).

p0415 A series of studies by De Dreu and colleagues (2011) suggests that oxytocin may promote trust of those in one's own group by enhancing the positive evaluation of in-group members ("in-group favoritism"). Dutch males received either oxytocin or placebo and evaluated photographs of in-group members (Dutch males) or out-group members (Middle-Eastern or German males) using implicit and explicit measures of affective associations. Across five experiments, the researchers found that oxytocin promoted in-group favoritism (De Dreu *et al*., 2011). These results imply that oxytocin may specifically promote prosocial behavior toward in-group members, i.e., "parochial altruism."

p0420 This claim was investigated directly in a pair of experiments by De Dreu *et al*. (2010), which tested the effects of oxytocin on behavior in an Intergroup Prisoner's Dilemma-Maximizing Differences Game (IPD-MD; De Dreu *et al*., 2010). The IPD-MD examines the motivational processes driving intergroup conflict, and can distinguish between an altruistic desire to help in-group members ("in-group love") and an

aggressive drive to hurt out-group members ("out-group hate"). In the IPD-MD, participants are arbitrarily divided into two groups. Each individual is given €10, and can allocate all or part of it to a within-group pool and a between-group pool. Each Euro kept is worth €1 for the individual; each Euro contributed to a within-group pool adds €0.50 to each in-group member, including the contributor; and each Euro contributed to the between-group pool adds €0.50 to each in-group member, including the contributor and, in addition, subtracts €0.50 from each out-group member. Thus, within-group pool allocations reflect in-group love, while between-group pool allocations reflect out-group hate. However, because the IPD-MD involves simultaneous moves by all players, behavior in this game necessarily reflects beliefs as well as preferences; subjects will contribute more to the group pools if they believe others will contribute as well (i.e., they will display "conditional cooperation").

p0425 De Dreu and colleagues (2010) reported that oxytocin (relative to placebo) increased allocations to the within-group pool (in-group love). Furthermore, oxytocin increased in-group trust, or expectations that other in-group members would contribute to the within-group pool. Because behavior in the IPD-MD both beliefs and preferences, it is unclear from these findings whether oxytocin actually affected preferences about in-group members' outcomes. Meanwhile, oxytocin had no effect on allocations to the between-group pool (out-group hate), nor did it influence out-group distrust (i.e., expectations that out-group members would contribute to the between-group pool).

p0430 However, two additional experiments suggest that oxytocin may additionally motivate defensive aggression or non-cooperation toward competitive outgroups. One study examined the effects of oxytocin on behavior in a series of between-group prisoner's dilemmas designed to distinguish between a desire to exploit out-group members ("greed"), and a desire to protect one's in-group from exploitation by out-group members ("protectionism"). Oxytocin selectively increased protectionist behavior, consistent with the idea that oxytocin triggers a "tend and defend" behavioral repertoire (De Dreu *et al*., 2010; Taylor *et al*., 2000).

p0435 The parochial effects of oxytocin on intergroup behavior may be restricted to competitive contexts, however. Israel and colleagues randomly assigned participants to arbitrary local groups (labeled "circles," "squares," "triangles," or "diamonds") and tested the effects of oxytocin on public goods provision to the local group (parochial altruism) as well as to the entire group (universal altruism). In this cooperative context, oxytocin increased both contributions to the local group and to the entire group, as well as expectations that others would contribute (Israel *et al*., 2012). These general effects of oxytocin on prosocial monetary allocations are in line with those of another study reporting increased donations to charity following oxytocin infusion (Barraza *et al*., 2011), as well as a study in monkeys demonstrating that intranasal oxytocin increased prosocial choices associated with reward to another monkey (Chang *et al*., 2012).

p0440 Collectively, these studies underscore the notion that context plays a key role in shaping the effects of oxytocin on social behavior (Bartz *et al*., 2011). Further research is needed to provide a clearer picture of how the effects of oxytocin on prosocial behavior interact with the social context, the identity of one's interaction partner, and individual differences in social cognition and motivation.

Testosterone

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p0445 As with serotonin and oxytocin, the hormone testosterone has long been implicated in many facets of social behavior, most notably aggression (Archer 1991) and social dominance and status-related behaviors (Eisenegger *et al*., 2011; Mazur and Booth 1998). Most of this work to date has been correlational in nature: for instance, among male and female prisoners, testosterone levels are much higher in those with a history of violent crimes, relative to those with a history of non-violent crimes (Dabbs, 1997; Dabbs *et al*., 1995), and testosterone levels are higher in winners of competitions, relative to losers (Mazur and Booth, 1998). The interpretation of these studies is complicated by the fact that the causal arrow between testosterone and status-related behaviors appears to run in both directions: testosterone modulates competitive behaviors, but competitive interactions also influence testosterone levels.

p0450 More recently, studies examining the effects of testosterone administration have enabled inferences about the causal role of testosterone in human social interactions. One study tested the effects of 4 weeks of daily administration of 40 mg testosterone in post-menopausal women, and reported no effects of testosterone on generosity, trust, or reciprocal fairness behavior (Zethraeus *et al*., 2009). However, more recent studies in pre-menopausal women have found significant effects of acutely administered testosterone on social behavior. Eisenegger and colleagues (2010) investigated how testosterone affects bargaining behavior. Following 0.5 mg testosterone administration, proposers in the UG made more generous offers to responders (Figure 14.6a); meanwhile, responders' behavior was unaffected by testosterone. The effects of testosterone on UG behavior therefore contrast with those of serotonin manipulations, which affect responders' but not proposers' behavior (Crockett *et al*., 2008, 2010a). Note that proposers' offers reflect not only altruism (i.e., positive social preferences) but also strategic concerns, as higher

offers are more likely to be accepted by responders. Responders' behavior in one-shot UGs, on the other hand, is a more direct reflection of social preferences. If testosterone increases the generosity of proposers via effects on social preferences, then it should also reduce rejection behavior in responders. The fact that it did not suggests that testosterone instead enhanced social status-seeking motives, making proposers more generous by increasing the concern that their offers would be rejected (Eisenegger *et al*., 2009).

p0455 Intriguingly, the same study showed an independent effect of beliefs on proposers' behavior: those who believed they received testosterone made *less* generous offers than those who believed they received placebo, regardless of which treatment they actually received (Figure 14.6b). The authors hypothesized that this belief effect reflects folk wisdom about testosterone: namely, that it causes antisocial or aggressive behavior. Thus, participants who believed they received testosterone may have felt "morally licensed" to make less generous offers in the UG. This finding underscores the importance of measuring beliefs in these kinds of experiments, particularly when studying complex social interactions where beliefs can play a decisive role.

p0460 Corroborating the findings of Eisenegger and colleagues (2010), a recent study demonstrated that 0.5 mg of testosterone increased cooperation in the public goods game, suggesting a more universal effect of testosterone on prosocial behavior than revealed by its effects on ultimatum bargaining (van Honk *et al*., 2012). The effects of testosterone on public goods contributions were strongest in subjects with low levels of prenatal testosterone during development (assessed by measuring the right hand's second-to-fourth-digit ration; (*2D:4D*). Note that in this study's version of public goods game, it is in one's own interest to contribute to the public good if one believes at least one other player has contributed as well; thus, the positive effect of testosterone on cooperativeness may be due to its effect on beliefs about the cooperativeness of others. Alternatively, testosterone may have affected social preferences directly. Either way, increased cooperation in the public goods game following testosterone administration is consistent with the hypothesis that testosterone enhances concerns about one's social status (Eisenegger *et al*., 2011), as people confer higher status to cooperative group members (Hardy, 2006; Willer, 2009).

p0465 One key aspect of status-seeking is protecting oneself from exploitation. If testosterone enhances status-seeking motives, then it should promote social vigilance. A study examining the effect of testosterone on interpersonal trust supports this idea. Testosterone administration reduced facial trustworthiness ratings, particularly in those individuals who displayed high levels of baseline trust (Bos *et al*., 2010). Another facet of status-seeking is the projection of self-confidence. Wright *et al*. (2012) demonstrated that testosterone disrupts social collaboration by increasing self-confidence during joint decision making. Pairs of subjects engaged in a visual perceptual decision making task following either 80 mg of testosterone or placebo. Subjects initially made their own perceptual decisions. On trials where they disagreed, subjects had to negotiate in order to reach a final collaborative decision. Successful collaboration required appropriately weighting self decisions against partner decisions. Testosterone did not affect individual decisions, but increased the weight subjects placed on their own decision, relative to that of their partner, which decreased the performance benefit that arose from collaboration under placebo (Wright *et al*., 2012). This bias may be a form of signaling one's confidence (or "saving face") in the context of a collective decision.

Summary s0140

p0470 Decades of research in animals and humans have shown that the neuromodulators serotonin oxytocin, and testosterone influence a range of social behaviors, but the underlying processes remain unclear. Neuroeconomic approaches to understanding social decision making have begun to shed light on the precise mechanisms through which these neuromodulators shape social interactions. Existing studies of serotonin and social decision making support a role for this neuromodulator in directly shaping social preferences; treatments that enhance serotonin function appear to increase the valuation of others' outcomes, while treatments that impair serotonin function shift social preferences in the negative direction. Importantly, the data do not support alternative explanations that serotonin alters social decision making by changing beliefs, social perceptions, or mood. Meanwhile, the hormones oxytocin and testosterone appear to have more complex effects on perceptual and motivational processes in social settings. Oxytocin administration increases trust and cooperative behavior, but these effects are strongly moderated by the social context and characteristics of the individual. In particular, oxytocin appears to promote trust and cooperation specifically with members of one's own social group, perhaps by enhancing positive affective evaluations of in-group members. The effects of testosterone on social decision making are consistent with a role for this hormone in enhancing the motivation to seek social status, rather than in directly shaping social preferences. Importantly, however, social preferences are not fixed, but respond to features of the social context and the interaction partner (see Chapter 11 for an overview), and future studies examining how neuromodulators shape social preferences will need to take these factors into account.

CONCLUSION

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p0475 Neuromodulators, such as monoamine neurotransmitters (serotonin, dopamine and norepinephrine) and hormones (oxytocin and testosterone) exert broad and multifaceted influences on decision making. In the domain of time preferences, serotonin and norepinephrine reduce impatient choices, while the effects of dopamine on intertemporal choice depend on the specific receptors involved. The study of the neuromodulation of risk preferences suggests that dopamine promotes risky choice, while serotonin modulates more complex facets of risky decisions such as framing and cognitive appraisal, though the precise mechanisms remain unclear. Research investigating the neuromodulation of social preferences suggests that serotonin promotes the positive valuation of others' outcomes, while oxytocin and testosterone modulate perceptual and motivational factors in the context of trust and cooperation. Overall, we recommend that future work in this area capitalize on economic and computational models of decision making to ascribe more precise roles for specific neuromodulators in shaping human preferences.

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NON-PRINT ITEM

Abstract

In this chapter we present a survey of studies employing pharmacological manipulations in humans to elucidate the psychological and neural mechanisms underlying the neuromodulation of economic and social preferences. We will review research examining the effects of changes in neurotransmitters (including serotonin, dopamine, and noradrenaline) and hormones (such as oxytocin and testosterone) on human decision-making. Recent studies have shown these neuromodulatory systems to play a key role in shaping time, risk, and social preferences. We will consider how the involvement of these evolutionarily ancient chemical systems in basic learning and affective processes scales up to impact complex decision-making in economic and social settings.

Keywords: Decision-making; Dopamine; Impatience; Intertemporal choice; Norepinephrine; Oxytocin; Risk; Serotonin; Social preferences; Testosterone.