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A neurobehavioral model of affiliative bonding: Implications for conceptualizing a human trait of affiliation

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Abstract: Because little is known about the human trait of *affiliation*, we provide a novel neurobehavioral model of affiliative bonding. Discussion is organized around processes of reward and memory formation that occur during approach and consummatory phases of affiliation. Appetitive and consummatory reward processes are mediated independently by the activity of the ventral tegmental area (VTA) dopamine (DA)–nucleus accumbens shell (NAS) pathway and the central corticolimbic projections of the *u*-opiate system of the medial basal arcuate nucleus, respectively, although these two projection systems functionally interact across time. We next explicate the manner in which DA and glutamate interact in both the VTA and NAS to form incentive-encoded contextual memory ensembles that are predictive of reward derived from affiliative objects. Affiliative stimuli, *in particular*, are incorporated within contextual ensembles predictive of affiliative reward via: (a) the binding of affiliative stimuli in the rostral circuit of the medial extended amygdala and subsequent transmission to the NAS shell; (b) affiliative stimulus-induced opiate potentiation of DA processes in the VTA and NAS; and (c) permissive or facilitatory effects of gonadal steroids, oxytocin (in interaction with DA), and vasopressin on (i) sensory, perceptual, and attentional processing of affiliative stimuli and (ii) formation of social memories. Among these various processes, we propose that the capacity to experience affiliative reward via opiate functioning has a disproportionate weight in determining individual differences in affiliation. We delineate sources of these individual differences, and provide the first human data that support an association between opiate functioning and variation in trait affiliation.

Keywords: affiliation corticolimbic-striatal networks; appetitive and consummatory reward; dopamine; oxytocin; personality; social bonds; social memory; *u*-opiates

1. Overview

Because of the length of this target article, the reader is provided with a brief overview. Moreover, several of the longer sections in the article begin with a brief introduction, which attempts to guide the reader through the major topics covered in those sections.

The goal of this article is to provide a detailed analysis of a human trait of affiliation, a trait that has received relatively little attention in terms of its psychobiological foundation. There are three major components to the article: (i) delineation of the construct of affiliation from the standpoint of its place in the trait structure of personality, its central behavioral and affective features, and the core behavioral-motivational processes underlying the construct (sects. 2–5); (ii) analysis of the neurobehavioral foundation of the core processes defined in component (i) and exploration of the neurodevelopmental sources of individual differences in trait affiliation (sects. 6 and 7); and (iii) modeling the behavioral effects of individual differences in the neurochemistry posited to be critical for the acquisition and maintenance of affiliative bonds (sect. 8).

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In the first component of the article, affiliation is seen to represent but one domain of interpersonal behavior, and we attempt in Section 2 ("Interpersonal behavior and the structure of personality") to position the affiliative domain within the structure of personality as defined by psychometric analyses. Because of the variation in the descriptions of the construct of affiliation in psychological and trait literatures, Section 3 ("Trait affiliation"), relying on the content of personality measures of affiliation, delineates which phenotypic features we believe to be central rather than peripheral to the construct. This analysis is critical, because the definition of the construct of affiliation will lead in certain directions in attempting to posit which core behavioral-motivational processes underlie affiliative behavior. As discussed in Section 4 ("Core behavioral-motivational processes underlying affiliation"), we conclude that three core processes underlie affiliation: appetitive and consummatory phases of reward processes, and the formation of affiliative memories, which depends in part on the former reward processes. Section 5 ("Hierarchical structure of an affiliation trait") integrates the preceding discussion by providing a hierarchical structure of an affiliation trait that delineates the critical eliciting stimuli, the core behavioral and affective processes, and the resulting affiliative behavior and affect.

The second major component of the article provides a neurobehavioral foundation for the core processes defined in the first major component (sect. 6, "Neurobehavioral foundation of the core processes underlying trait affiliation"). First, the neurochemistry associated with the appetitive phase of affiliation is explored, with emphasis on the role of dopamine in incentive-reward motivation. Next, opiates are discussed as being a critical part of the reward processes associated with the consummatory phase of affiliation. Third, a major affective consequence of consummatory processes accompanies the physiological quiescence associated with consummation. We discuss the neurobiology of this quiescence and how opiates may facilitate it. Finally, the basic neurobehavioral foundation of the formation of affiliative memories is presented, with the focus being on the neural integration or binding of all contextual elements accompanying, and hence predicting, affiliative reward. The binding of context into an ensemble that represents the context of reward, and attributing an incentive-reward salience to that ensemble, represents the basis of forming affiliative memories. The interaction of dopamine and glutamate in this process is described. As we are concerned with affiliative behavior, our interest is in how, neurobiologically, affiliative stimuli are enhanced when the contextual ensemble is formed. We discuss three ways in which affiliative stimuli may be enhanced: (1) by being neurally integrated in the medial extended amygdala, (2) by interactions of opiates with glutamate and dopamine in the nucleus accumbens, where the ensemble is compressed and formed, and (3) by the role of gonadal steroids, oxytocin, and vasopressin in enhancing perception and memory of affiliative stimuli and in interacting with opiates and dopamine. Finally, the neurobehavioral treatment of affiliation would be incomplete from a trait perspective unless we specify how individual differences arise within the relevant neurobiological processes. Therefore, Section 7 attempts to define the neurodevelopmental sources of individual differences in trait affiliation. This discussion focuses on genetic influences on opiate and dopamine functioning, but subsequently explores how experiential processes, especially experience-dependent ones, may influence the neurobehavioral processes described in Section 6.

The third component of the article models the behavioral effects of individual differences in opiate functioning on the acquisition and maintenance of affiliative bonds (sect. 8: "Modeling Behavioral Effects of Individual Differences in *u*-Opiate Functioning on the Acquisition and Maintenance of Affiliative Bonds"). The focus on opiate functioning comes from our proposition that opiates mediate a capacity for affiliative reward, which to us is the sine qua non for forming an affiliative bond. The article concludes with the presentation of our initial study of the association of opiate functioning with a human trait of affiliation (sect. 8.3: "Preliminary Support for Opiate Involvement in Trait Affiliation"), followed by concluding remarks (sect. 9).

2. Interpersonal behavior and the structure of personality

The structure of temperament and personality is comprised of a relatively small number (4–5) of higher-order traits. As originally proposed by Gray (1973) and extended by others (Cloninger 1986; Depue & Collins 1999; Netter et al. 1996; White & Depue 1999; Zuckerman 1991), higher-order traits reflect emotional-motivational systems that evolved to increase adaptation to classes of stimuli associated with positive and negative reinforcement. For example, fear evolved to motivate escape behavior in the presence of unconditioned aversive stimuli that threaten survival. Individual differences in personality traits thereby reflect variation in the sensitivity to such stimuli and, overall, personality represents the relative strength of sensitivities to various stimulus classes. Within this framework, sensitivity ultimately means reactivity of neurobiological processes closely associated with a motivational system.

In view of the interdependence of personality traits, reinforcing stimuli, and motivational systems, it is not surprising that the higher-order structure of personality is substantially associated with the domain of interpersonal behavior. Other people are critical to the preservation of our species in mating, caring of offspring, and social cooperation required in tasks critical to survival, such as protection and food procurement. Until relatively recently, the interpersonal domain of personality was embodied largely in one higher-order trait termed *extraversion* which, despite terminological variation, is identified in virtually every taxonomy of personality (Buss & Plomin 1984; Cattell et al. 1980; Cloninger et al. 1993; Comrey 1970; Costa & McCrae 1985; 1992; Digman 1990; Eysenck & Eysenck 1975; 1985; Goldberg 1981; Guilford & Zimmerman 1949; Jackson 1984; Tellegen & Waller, in press; Zuckerman 1994a).

More recent structural work in personality, including a five-factor structure of personality (Digman 1990), has demonstrated that the interpersonal nature of extraversion is not unitary, but rather is composed of two independent higher-order traits (Digman 1990; Tellegen & Waller, in press). One trait has been variably called communion, social closeness, and agreeableness (in the five-factor model), but we prefer the more generic term *affiliation* to maintain a conceptual bridge to animal neurobehavioral work (Carter et al. 1997). Affiliation reflects enjoying and valuing close interpersonal bonds and being warm and affectionate; whereas the other trait associated with extroversion, *agency*,

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reflects social dominance and the enjoyment of leadership roles, assertiveness, and a subjective sense of potency in accomplishing goals. Prior to the more recent recognition of their independence, these two traits were represented, respectively, as different aspects of extraversion, such as Warmth-Gregariousness versus Assertiveness (Costa & McCrae 1992), Social Closeness versus Social Potency (Tellegen & Waller, in press), Sociability versus Ascendance-Dominance (in Social Activity; Guilford & Zimmerman 1949), Warmth (in Agreeableness) versus Assertion (in Surgency) (Goldberg & Rosolack 1994), Warmhearted-Socially Enmeshed versus Dominant-Ascendant (Cattell et al. 1980), and Sociability versus Ambition (in Surgency) (Hogan 1983). These two traits are also consistent with the two major independent traits identified in the theory of interpersonal behavior: Warm-Agreeable versus Assured-Dominant (Wiggins 1991; Wiggins et al. 1988). These latter two traits form the two major orthogonal dimensions in Figure 1, and they are accompanied by two additional dimensions identified by Wiggins that further characterize interpersonal behavior (Gregarious and Extraverted – Aloof, Arrogant, Unassuming). Within this multidimensional structure (referred to as a circumplex), much of interpersonal behavior can be represented as a combination of the two major traits, affiliation and agency.

Church and Burke (1994) supported a two-trait structure of extraversion by demonstrating that the lower-order traits of extraversion measured by Costa and McCrae's (1992) questionnaire factored into agency (assertiveness, activity) and affiliation (warmth, positive emotions, agreeableness). Furthermore, when general affiliation and agency traits were derived in joint factor analyses of several multidimensional personality questionnaires (Church 1994; Costa & McCrae 1989; Tellegen & Waller, in press) – two general traits were identified in each case as affiliation and agency. This made it possible to plot the loadings of lower-order traits from several studies in relation to the general affiliation and agency traits (see Appendix A). When trait loadings are plotted from different studies, the interrelations among traits will only be approximations in a quantitative sense, but the pattern with respect to the general affiliation and agency traits is instructive. For purposes of comparison, the lower-order traits are plotted within the interpersonal trait structure of Wiggins in Figure 1. Lower-order traits of achievement, persistence, social dominance, and activity all load much more strongly on agency than on affiliation, whereas traits of sociability and agreeableness show a reverse pattern. Lower-order traits of well-being and positive emotions are associated with both agency and affiliation about equally (see also Helgeson 1994), which is likely why affiliation and agency were combined in extroversion previously. But when positive emotion components are statistically removed, the associations among affiliative and agentic scales approach zero (range = 0.11 to −0.08; Watson & Clark 1997). Similar independence of affiliative and agentic traits have been demonstrated by analysis of peer ratings after extensive social interaction experience (Hurley 1998) and the human psychometric studies are supported by comparative studies in nonhuman personality, including the use of primates, wherein independent affiliative and agentic traits have been demonstrated (Byrne & Suomi 1998; Capitanio 1999; Capitanio et al. 1998; Champoux et al. 1997). Indeed, Gosling (2001) has argued that the dimensions of Sociability (affiliation) and Confidence (agency) are fairly widespread in the animal kingdom.

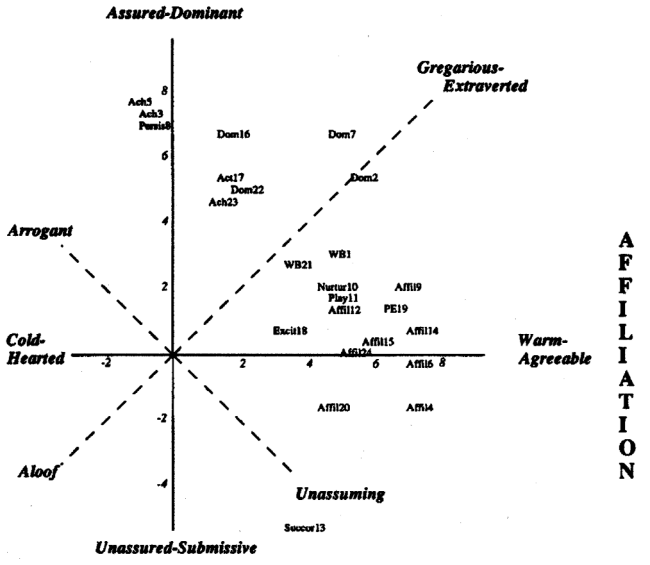

Figure 1. A structure of interpersonal behavior composed of four adjective-labeled dimensions, with the two predominant orthogonal dimensions labeled Agency and Affiliation. The figure illustrates that the interpersonal engagement characteristic of extraversion is composed of two different dispositions: affiliation and agency. Within the structure, lower-order traits representing either agency or affiliation components of extraversion are plotted according to their loadings on general Agency and Affiliation traits derived in several studies. See the Appendix for the identity of the abbreviations of trait measures (shown with numbers), the questionnaires to which the abbreviations correspond, and the studies providing the trait loadings.

In a comprehensive analysis, we (Depue & Collins 1999) demonstrated that affiliation and agency represent distinct dispositions. Whereas affiliation is clearly interpersonal in nature, agency represents a more general disposition encompassing dominance, ambition, mastery, and efficacy that is manifest in a range of achievement-related, as well as interpersonal, contexts. The focus of that analysis was on the incentive motivational and neurobiological nature of the agentic form of extraversion (Depue & Collins 1999). In this current analysis, we focus on the psychobiological nature of the affiliative form of extraversion, or simply, on a trait of affiliation.

A comprehensive neurobehavioral model of an affiliation trait must specify at least five points: (1) behavioral and emotional characteristics of the trait, particularly those that are central to its definition, (2) core behavioral-motivational processes inferred to underlie those central characteristics, (3) neuroanatomical brain networks and neuromodulators that integrate those core processes, (4) neurobiological variables that account for individual differences in the functioning of the networks, and (5) sources of those individual differences. This target article specifies all five points. As a guide to defining each of these points, we used the analytic strategy outlined in Figure 2, one that is similar to one used in primate personality research (Itoh 2002). Personality psychology, discussed previously, was used to define the broad nature and independence of trait affiliation within the structure of personality, and is also used in Section 3 to delineate its central behavioral and emotional characteristics. We next identify mammalian behavioral processes

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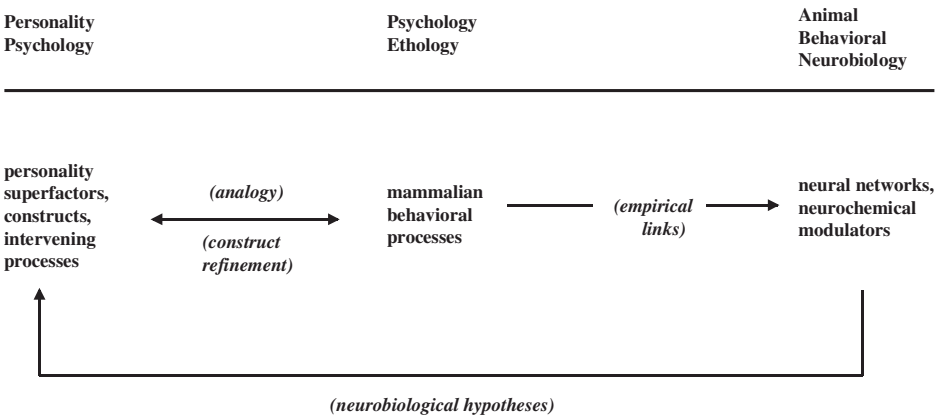

Figure 2. A modeling strategy for deriving neurobiological hypotheses about higher-order traits of personality. See text for details.

(sect. 4) that are believed to underlie those characteristics as described in the psychological and ethological literatures (see Itoh 2002; Timberlake & Silva 1995). Once these processes are identified, animal behavioral neurobiology research provided empirical links to their neural organization and neurochemical modulation, as discussed in Section 6. These behavioral-biology links represent hypotheses concerning the nature of affiliation, which can then be extended to human affiliation and subjected to empirical testing, as described in Section 8.

3. Trait affiliation: Central behavioral-emotional characteristics and differentiation from other constructs of interpersonal behavior

3.1. Central characteristics of trait affiliation

In accord with the strategy outlined in Figure 2, a critical first step is to define the central behavioral-emotional characteristics of trait affiliation, which then may be used to delineate behavioral-motivational processes underlying affiliation. One approach to this problem is to assess the content of items comprising affiliation trait measures. Tellegen's Multidimensional Personality Questionnaire identifies a higher-order affiliation trait termed Social Closeness (Tellegen et al. 1988; Tellegen & Waller, in press), which is independent of the higher-order trait of agentic extraversion. It incorporates two main areas of content. One area, which represents the strongest markers of the trait, assesses subjective feelings and attitudes of affectionateness and warmth versus being cool and distant, and a strong preference for close personal ties, all of which presumably reflect the emotional-cognitive experience that is correlated with neurobiological processes activated by affiliative stimuli. A second area assesses self-reported interpersonal behavior that is sociable, gregarious, and involves turning to others for comfort and support versus being solitary in nature. Together, this content is consistent with the major dimensional trait of Warm-Agreeable versus Cold-Hearted, illustrated in Figure 1 (Wiggins 1991; Wiggins et al. 1988), as well as with the content of other affiliation trait scales of Warmth, Positive Emotions, and Agreeableness (Costa & McCrae 1992), Warm-Hearted, Socially Enmeshed (Cattell et al. 1980), and Sociability (Guilford & Zimmerman 1949; Hogan 1983). Furthermore, in the five-factor model of the higher-order structure of personality, such interpersonal characteristics are assessed in large part by a trait termed Agreeableness. Agreeableness incorporates at least two components (Costa & McCrae 1992; Digman 1990; Goldberg & Rosolack 1994). The first component is consistent with the content of the affiliation measure of Social Closeness. It includes positive subjective feelings and attitudes toward other individuals, and is characterized most strongly by two groups of adjectives (Goldberg & Rosolack 1994): (a) a *Warmth* group, including warm, affectionate, kind, compassionate, and sympathetic, which is different from the construct of empathy (Preston & de Waal 2001); and (b) an *Amiable* group, including amiable, cordial, and friendly. These groups provide the strongest adjectival markers of the Agreeableness trait (Goldberg & Rosolack 1994). The second component represents social cooperation, which is defined most strongly by adjectives such as helpful, cooperative, accommodating, and agreeable, the latter adjective also being identified in the Warm-Agreeable trait dimension in Figure 1. Perhaps this second component reflects, in part, competitive aggression, which would be important in determining social group formation and cohesion, in that very high levels of competitive aggression (disagreeableness, lack of cooperation) can interfere with the development of social cooperation. Importantly, all of these sets of adjectives correlate near zero with agentic extraversion adjectives such as assertive, bold, excited, strong, peppy, and talkative (Goldberg & Rosolack 1994; Tellegen & Waller, in press), again indicating their independence.

The core content of affiliation scales seems to reflect the operation of neurobehavioral processes that (i) create a warm, affectionate, gratifying subjective emotional state elicited by others, which (ii) motivates close interpersonal behavior. Our hypothesis is that the subjective experience of warmth and affection reflects the *capacity to experience* reward *that is elicited by a broad array of affiliative stimuli*. This capacity is viewed as providing the key element utilized in additional psychobiological processes that permits the development and maintenance of longer-term affective bonds, defined as long-term selective social attachments observed most intensely between infants and parents and between adult mates, and that are characteristic of social organization in human and other primate societies (Gingrich et al. 2000; Wang et al. 1999). It is important to emphasize that a core capacity for affiliative reward and bonding is not

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viewed as a sufficient determinant of close social relationships, only as a necessary one, a sine qua non. We discuss other factors in subsequent sections.

3.2. Differentiation from other constructs of interpersonal behavior

Because the broad domain of interpersonal behavior encompasses multiple traits, we differentiate four trait issues relative to the more narrowly defined affiliation trait posited here. First, *sociability* is *quantitative* in nature and refers behaviorally to the frequency of engaging in interpersonal activities with a number of group members. Although most primates are disposed to high sociability, the evolution of sociality reflects a trade-off between costs and benefits of living in close proximity to conspecifics. There are, nevertheless, major benefits that accrue from social integration, because such behavior may increase, to varying degrees, depending on environmental and group circumstances, the ability to gather food, build shelter, obtain coalitionary support in within-group contests, learn about the environment, and gain access to a group of others with whom they may eventually mate (Cassidy 1999; Silk et al. 2003). That social relationships and social integration have adaptive value for baboon primate females was demonstrated recently for the first time in that offspring of the more socially integrated females had higher survival rates, independent of female dominance rank and variation in ecological conditions (Silk et al. 2003). Furthermore, social relationships with adult primate males may be valuable to females because male associates shield females from harassment, support their offspring in agonistic interactions, and can protect the females' infants from predators or infanticidal attacks (Silk et al. 2003). Moreover, in humans, primates, and other species, much literature supports the positive effects of sociality on health and well-being across the life span, including giving birth to heavier infants, delays in reproductive senescence, enhanced longevity, reduced stress responses, and enhanced immune responsiveness (Silk et al. 2003).

These findings suggest that there may be a fundamental behavioral system of sociability based on social cooperation that evolved to promote alliances with others, even in the absence of affective affiliative bonds. Thus, sociability is a broader construct than trait affiliation, which involves *quality* of interactions, based particularly on social reward derived from close interpersonal bonds with specific individuals (Lucas et al. 2000). Indeed, when these two different aspects of interaction (i.e., sociability vs. affiliation) are psychometrically separated, they correlate near zero (Lucas et al. 2000). Sociability can, therefore, be viewed as a higher-order interpersonal trait that may reflect several social motivational processes, including: (a) social approach and social dominance that are part of the incentive motivation underlying agentic extraversion (Depue & Collins 1999); (b) seeking of intimate social contact that is a result of affiliative reward (i.e., trait affiliation); (c) social cooperation (competitive aggression); and (d) avoidance of social isolation, which we posit in more detail below is an unconditionally aversive state because of its evolutionary association with a reduced probability of survival (White & Depue 1999). Thus, it is possible for one to be high on trait affiliation, thereby deriving significant reward from interpersonal contact, but low on a sociability trait (i.e., being engaged in few interpersonal relationships) because, for example, one shows low levels of social approach associated with agentic extraversion (e.g., see Fig. 1).

3.2.1. Dimensionality of affective bonding. There is disagreement over whether the type of affiliation that occurs in mother–infant pairs and between mates is quantitatively or qualitatively different from that experienced in intimate relationships between close friends. This disagreement may result in part from the fact that this issue involves at least two aspects: (a) whether the basic mechanisms that promote affiliative bonds are the same or different across different types of relationships, and (b) whether all types of affiliative relationships are capable of developing attachment characteristics. In this section, we are specifically referring to aspect (a), whereas attachment is discussed shortly. We, as well as others (Insel 1997; Nelson & Panksepp 1998; Panksepp et al. 1994; 1997; Young et al. 1998), take the position that the basic mechanisms that promote affiliative bonding, particularly a capacity for affiliative reward, provide the foundation for establishing all types of close interpersonal relationships *that have a positive affective component*, and that these mechanisms are elicited by the same modalities of sensory stimuli, even if the social activities that generate the sensory stimulation are different (Crews 1998; Insel 1997; Mason & Mendoza 1998). Certainly, prosocial interactions (e.g., allogrooming, play) and social bonds among nonhuman primates are strengthened by affiliative reward processes, and are necessary for the formation and maintenance of social groups (Silk et al. 2003; Young et al. 1998). Thus, for us, the positive emotional expression of affiliation-induced reward facilitates affiliative tendencies and bonding, and is manifested by nurturance in mother–infant relationships, support in close friendships, and by elements of both, in addition to sexual behavior in mates.

Furthermore, affiliative behavior enables physiological adaptations that facilitate trophotropic processes, such as calmness, relaxation, digestion, metabolism, growth, and healing, and also may foster physiological coregulation of bonding partners (Di Chiara & North 1992; Hofer 1995; Porges 1998; 2001; Uvnas-Moberg 1998). These effects may be experienced in all affectively close affiliative relationships. For example, after a two-month separation period, the mere visual presence (where tactile and auditory cues were isolated) of male mouse *siblings*, but not of unfamiliar mice, decreased tactile pain sensitivity and physiologic arousal to painful stressors, two variables that, similar to affiliative reward, are modulated by opiates (see sects. 6.1.2 and 6.1.3; D'Amato & Provone 1993; 1995). Also, oxytocin, which is released by many sociosexual stimuli (see sect. 6.3.3), is also released during social interaction between conspecifics outside of mate and mother–infant interactions, including interaction between female prairie voles, rats of both sexes, and male squirrel monkeys (Carter et al. 1995). Moreover, non-noxious touch applied by friends, such as gentle stroking, lowers blood pressure and sympathetic activity, and increases pain thresholds and the release of gastrointestinal hormones during delivery of human infants (Knox & Uvnas-Moberg 1998; Uvnas-Moberg 1997). Thus, we believe that the only difference between various affiliative relationships that have a positive affective component is one of degree rather than of kind.

3.2.2. Social attachment. We would argue that trait affiliation as previously defined is a narrower construct than that

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of *social attachment*, which is usually applied in a limited manner only to parent–offspring and mate relationships. For us, affiliative reward is one factor that contributes to social attachment and is critical to the development of *secure* attachment. From a neurobehavioral perspective, social attachment appears to be a heterogeneous, higher-order construct, the manifestation of which emerges from the interaction of several neurobehavioral systems (Kraemer 1992) and social experiences (Meaney 2001). For instance, the criteria for attachment in children include proximity-seeking, secure base, and separation distress. *Proximity-seeking*, which means the child seeks to be near the parent, appears to be a complex criterion itself. Proximity can be sought because of a positive desire to be near the source of reward and positive feelings. This is essentially the expression of a preference for a known, rewarding affiliative object, an expression that can be manifested by maintaining a close proximity to the parent or by an incentive-motivated approach to the parent from a distance. Alternatively, seeking proximity can also occur when conditioned cues of punishment arise, where the rewarding affiliative object serves as a safety cue (protection) that elicits incentive-motivated active avoidance and approach to the parent (Depue & Collins 1999). Thus, in this sense, proximity-seeking can reflect the operation of both incentive-motivational and affiliative reward processes. On the other hand, *secure base* can be viewed as a consistency variable, reflecting the consistency with which reward in ratio to nonreward and/or punishment is obtained from the affiliative object. Complexity is increased by the fact that the two criteria of secure base and proximity-seeking are likely to interact at the behavioral level. For example, a child could experience a lack of secure base as a result of inconsistent reward–punishment, while at the same time maintain close proximity based on: (a) an intermittent, variable (unpredictable) schedule of reinforcement, and/or (b) removal or omission of potential aversive circumstances provided by parental protection (passive and active avoidance).

The attachment criterion of *separation anxiety or distress* may be complex, as well, as is the issue of its biological modifiers (see review by Nelson & Panksepp 1998). Although manifestation of separation anxiety or distress is correlated with the existence of an affiliative bond, we take the position, along with others (Insel 1997; Nelson & Panksepp 1998; Panksepp 1998; Panksepp et al. 1994; Young et al. 1998), that processes underlying affiliative bonding are not the same as those involved in social separation distress. Affectively, affiliation and separation are distinctly different and not two sides of a coin. Separation is characterized by the presence of frustration, protest, and anxiety, and not just the absence of warmth and pleasure (and vice versa). In fact, there are data that support a bidimensional organization of affiliation and separation distress, because the neural pathways underlying affiliative engagement (e.g., maternal behavior) may be different from those that allow for inhibition of separation distress (Eisenberger et al. 2003; Insel 1997; Nelson & Panksepp 1998; Winslow & Insel 1991a).

3.2.3. Separation distress. In behavioral terms, separation anxiety or distress may reflect both (a) the anxiety of *uncertainty* generated by removal of protective, supportive, safety cues, and (b) the agitated dysphoria that accompanies loss of a significant source of reward when no chance of reacquiring the rewarding object appears to exist (Gray 1973; 1992). From a broader evolutionary perspective, separation leading to social isolation can be characterized as unconditionally aversive, having *no discrete, explicit stimulus source* – similar to the human experience of being in the dark (or being in bright light in nocturnal mammals) (Davis et al. 1997; Davis & Shi 1999; White & Depue 1999). That this aversiveness is severe is indicated by the fact that socially isolated nonhuman primates do not survive in the wild, dying of exposure, lack of nourishment, or predation within days to weeks (Steklis & Kling 1985). In humans, social isolation, rejection, and/or ostracization generate a sense of anxiety and apprehension. Put differently, separation anxiety or distress may, in part, reflect a very basic neurobehavioral anxiety system that serves to motivate attempts to reverse social isolation via reintegration into a social group (Barlow 2002; White & Depue 1999). It may be that separation anxiety or distress is associated with other related traits such as rejection sensitivity and dependency, both of which reflect anxiety related to social isolation. This system would be associated with neural networks involved in recognition of social uncertainty and rejection, experience of psychic pain (Eisenberger et al. 2003), and expression of anxiety as opposed to affiliative reward per se.

In sum, we view a capacity to experience affiliative reward as the necessary component in acquiring and maintaining affiliative bonds. Affiliative reward is hypothesized to underlie all human social relationships having a positive affective component, whereby such relationships are viewed as qualitatively similar, varying in affiliative strength but not in kind. Other interpersonal constructs of sociability, attachment, and separation anxiety are accordingly viewed as either broader than affiliation as defined here, and/or as based on different neurobehavioral systems.

4. Core behavioral-motivational processes underlying affiliation

The need to preserve the human species through reproduction and group cohesion has given rise to a number of mammalian neurobehavioral processes that support different aspects of sociosexual interaction. These processes may be arbitrarily divided into four components: (a) *preparation or approach*, whereby individuals are brought together for an affiliative exchange; (b) *consummation*, whereby individuals (i) display and engage in specific social, courtship, and mating behaviors, and (ii) experience relaxation and satiety as a result of the sensory exchange during, and reduced physiological arousal following, consummation (Porges 1998; 2001; Uvnas-Moberg 1997); (c) *short-term affective bonding*, involving parturition, lactation, and maternal and paternal parenting behavior as a means of ensuring immediate offspring survival; and (d) *longer-term affective bonding* to maintain bonds (i) between parent–infant and mate pairs during more prolonged offspring developmental periods, and (ii) more generally, between individuals to promote formation of social groups that are necessary for tasks critical to survival.

We suggest that these four components rely on at least two major core behavioral-motivational processes: reward and formation of affiliative memories. More specifically, human trait affiliation is proposed to rely on (a) an underlying capacity to experience reward elicited by affiliative stimuli, as reflected in the subjective emotional state assessed in trait measures of affiliation; and (b) the establish-

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ment of conditioned preferences for specific individuals, which is dependent on a reward capacity and is reflected in the close interpersonal preferences tapped by trait measures of affiliation. The outcome of these integrated processes is the development and maintenance of longer-term affective bonds. We now describe these two core processes in more detail.

4.1. Reward processes across two phases of affiliation

Affiliative bonding is a critical process for infants having relatively long developmental periods, because they will not survive without intense, prolonged support from parents. Indeed, such processes developed to the greatest extent in birds and mammals, and are surmised to have been functional in the therapsids, their common ancestor which survived until 150 million years ago (Insel & Winslow 1998). Therefore, at the very least, a behavioral process is required to assure maternal bonding to infant, as well as infant bonding to mother in species with developmental periods that fully extend into offspring locomotion. This may be one reason that females have a greater disposition to express attachment-caregiving behavior than males (Taylor et al. 2000). Furthermore, although mother–infant bonding most likely represents the initial pressure for the development of affiliative bonding, in species in which the father's contribution to familial nourishment and protection is required, paternal bonding to infants and mates would also be advantageous.

If the mother–infant pair is used as the prototypic affiliative bonding condition, the most basic process that would contribute to the formation of bonds is one in which specific classes of stimuli inherently activate reward in both mother and infant, thereby motivating contact and performance of critical affiliative behaviors such as nursing (Di Chiara & North 1992). Tactile stimulation may be particularly effective in activating affiliative reward processes, as it induces the strongest reinforcement in rat mothers exposed to pups (Fleming et al. 1994). Despite the display of maternal behavior, without tactile sensation either on the ventrum or the snout, conditioned place preference, which involves the pairing of context with reward, does not develop as a result of exposure to pups (Fleming et al. 1994; Morgan et al. 1992; Stern 1990). Exposure of maternal dams to visual, auditory, or olfactory pup cues is not sufficient to establish conditioned place preference, whereas licking or touching is a necessary sensory input (Fleming et al. 1994). In humans, many forms of sensory stimulation are likely to promote bond formation, although tactile stimulation does potently release several important sociosexually-related hormones (see sect. 6). Significantly, light, pleasant touch, that occurs to caress, like skin-to-skin contact between individuals, is transmitted by different afferents than hard or unpleasant touch (Olausson et al. 2002). Light, pleasant touch is transmitted by slow-conducting unmyelinated tactile afferents that project to the insular cortex but not to somatosensory areas S1 and S2, whereas hard, unpleasant touch is transmitted by fast-conducting myelinated afferents to S1 and S2. The insular cortex is a paralimbic region known to integrate several sensory modalities, including autonomic, gustatory, visual, auditory, and somatosensory, in order to characterize the emotional nature of sensory input (Damasio 1999; Mesulam 1990).

As illustrated in Figure 3, reward involves several dynamically interacting neurobehavioral processes occurring across two phases of affiliation: appetitive and consummatory. Although both phases are elicited by unconditioned affiliative stimuli, their temporal onset, behavioral manifestations, and putative neural systems differ (Berridge 1999; Blackburn et al. 1989; Depue & Collins 1999; Di Chiara & North 1992; Ikemoto & Panksepp 1996; Robinson & Berridge 1993; van Furth et al. 1994; Wyvell & Berridge 2000), and are dissociated in factor analytic studies based on behavioral characteristics of animals (Pfaus et al. 1999).

4.1.1. Appetitive phase. An appetitive, preparatory phase of affiliation is based on a mammalian behavioral system, which from an evolutionary biology perspective represents a behavior pattern that evolved to adapt to stimuli critical for survival and species preservation (Gray 1973; MacLean 1986; Panksepp 1986; Schneirla 1959; Timberlake & Silva 1995). Linkage of behavioral systems to critical stimulus conditions suggests that their neurobiology is integrated with brain networks responsible for both the recognition of stimulus significance and the activation of effector systems (locomotor, facial, vocal, autonomic, hormonal). Collectively, this group of interrelated brain functions is referred to as emotion (LeDoux 1987; 1998). Thus, behavioral systems are fundamentally emotional systems that incorporate a motivational state and emotional experience that is concordant with the reinforcement properties of critical stimuli (Gray 1973; Rolls 1999).

One behavioral system is activated by, and serves to bring an animal in contact with, unconditioned and conditioned rewarding incentive stimuli (Depue & Collins 1999; Gray 1973; Hebb 1949; Koob et al. 1993; Panksepp 1986; Schneirla 1959; Stewart et al. 1984). This system is consistently described in all animals across phylogeny (Hebb 1949; Schneirla 1959), but has been defined at two conceptual levels: (a) the behavioral level, as a search (MacLean 1986), foraging (Panksepp 1986), and approach system (Gray 1973; Schneirla 1959); and (b) the underlying process, as an incentive (Depue & Collins 1999), expectancy (Panksepp 1986), preparatory (Blackburn et al. 1989), and activation system (Fowles 1987; Gray 1973; 1992). We define this system as *behavioral approach based on incentive motivation* (Depue & Collins 1999). Incentive motivation theory concerns how goal-directed behavior is elicited and guided by the perception of incentive stimuli, or central representations of those stimuli, in interaction with the central drive states of the organism, such as hunger (Bindra 1978; Panksepp 1986; Toates 1986). Incentive motivation may involve aversive or pleasant stimulus contexts, but we will refer only to the latter, given the positive affective nature of affiliative bonding.

The appetitive phase of affiliation represents the first step toward attaining biologically important goals (Blackburn et al. 1989; Hilliard et al. 1998). Specific, *distal* affiliative stimuli of potential bonding partners – such as facial features and smiles, friendly vocalizations and gestures, and bodily features (Porges 1998) – serve as unconditioned incentive stimuli based on their distinct patterns of sensory properties, such as smell, color, shape, and temperature (Di Chiara & North, 1992; Hilliard et al., 1998). For example, Breiter et al. (2001) and Aharon et al. (2001) have shown that even passive viewing of attractive female faces unconditionally activates the anatomical areas that integrate reward, incentive motivation, and approach in heterosexual males. These incentives are inherently evaluated as positive in valence (the magnitude of which likely varies with cultural differences in

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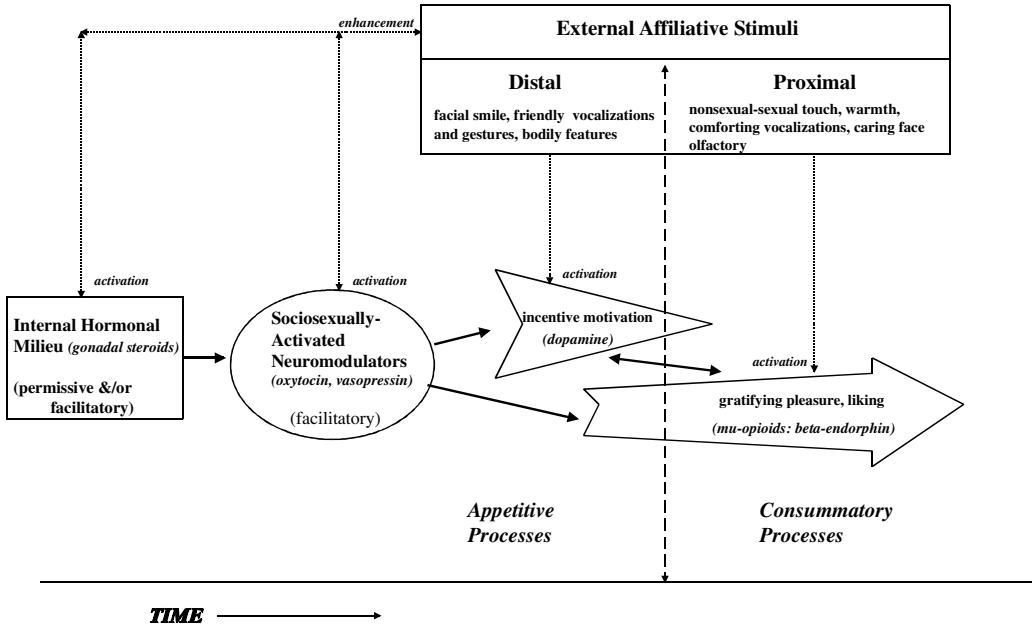

Figure 3. The development and maintenance of affiliative bonds across two phases of reward. Distal affiliative stimuli elicit an incentive-motivated approach to an affiliative goal, accompanied by strong emotional-motivational feelings of wanting, desire, and positive activation. The approach phase not only ensures sociosexual interaction with an affiliative object, but also acquisition of a memory ensemble or network of the context in which approach, reward, and goal acquisition occur. Next, proximal affiliative stimuli emanating from interaction with the affiliative object elicit strong feelings of consummatory reward, liking, and physiological quiescence, all of which become associated with these stimuli, as well as the context predictive of reward. Dopamine encodes the incentive salience of contextual stimuli predictive of reward during the approach phase and, in collaboration with μ-opiate mediated consummatory reward, encodes the incentive salience of proximal stimuli directly linked to the affiliative object. The end result of this sequence of processes is an incentive-encoded affiliative memory network that continues to motivate approach toward and interaction with the affiliative object. Specialized processes ensure that affiliative stimuli are weighted as significant elements in the contextual ensembles representing affiliative memory networks. These specialized processes include the construction of a contextual ensemble via affiliative stimulus-induced opiate potentiation of dopamine processes, and the influence of permissive and/or facilitatory factors, such as gonadal steroids, oxytocin, and vasopressin on (i) sensory, perceptual, and attentional processing of affiliative stimuli and (ii) formation of social memories. See text for details.

what is attractive), and activate incentive motivation, increased energy through sympathetic nervous system activity, and forward locomotion as a means of bringing individuals into close proximity (Di Chiara & North 1992). Moreover, the incentive state is inherently rewarding, but in a highly activated manner, and animals will work intensively to obtain that reward without evidence of satiety (Depue & Collins 1999). In humans, the incentive state is associated with subjective feelings of desire, wanting, excitement, elation, enthusiasm, energy, potency, and self-efficacy that are distinct from, but typically co-occur with, feelings of pleasure and liking (Berridge 1999; MacLean 1986; Robinson & Berridge 1993; Watson & Tellegen 1985).

4.1.2. Consummatory phase. When close proximity to a rewarding goal is achieved, the incentive-motivational approach gives way to a consummatory phase of affiliation (Herbert 1993). In this phase, specific *interoceptive* and *proximal exteroceptive* stimuli related to critical primary biological aims elicit behavioral patterns that are relatively specific to those conditions (e.g., sexual, social, or food-related) (Blackburn et al. 1989; Hilliard et al. 1998; MacLean 1986; McNaughton 1989; Panksepp 1986; Timberlake & Silva 1995). These behavioral patterns have relatively fixed topographies and immediate objectives, and are highly specialized for direct interaction with the specific stimuli associated with the biological goal. Performance of these behavioral patterns is inherently rewarding (Berridge 1999). Affiliation examples are courtship, gentle stroking and grooming, mating, and certain maternal patterns such as breastfeeding, all of which may include facial, caressive tactile, gestural, and certain vocal behaviors (Polan & Hofer 1998). Indeed, rat pups find physical contact with the mother inherently rewarding (Hofer et al. 1989).

As opposed to an incentive motivational state of activation, desire, and wanting, the expression of consummatory behavioral patterns elicits intense feelings of pleasure, gratification, and liking, plus physiological quiescence characterized by rest, sedation, anabolism, and parasympathetic nervous system activity, thereby reinforcing the production and repetition of those behaviors (Berridge 1999; Di Chiara & North 1992; Porges 1998; 2001; Robinson & Berridge 1993; Uvnas-Moberg 1997). Uvnas-Moberg (1997) suggested that the relaxation and satiety effects induced by activation of sensory neurons during the consummatory phase of social behavior likely evolved from a response pattern originally elicited by benign physical or chemical influences from the environment. The relaxation and sedation of the breastfeeding mother or of pups lying close together could therefore be related to the satiety and sedation induced by the intake of a meal or simply to pleasantly warm surroundings. Furthermore, both the pleasurable feelings and physiologic quiescence may serve an important feedback status. For example, in human mothers the pleasurable

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feelings resulting from interactions with their infants (e.g., nursing) inform them that the behaviors they are engaging in are benefiting their offspring and contribute to their survival (Panksepp et al. 1994; Porges 1998; 2001). Thus, whereas appetitive approach processes bring an individual into contact with unconditioned incentive stimuli, consummatory processes bring behavior to a gratifying conclusion (Hilliard et al. 1998). Whether the pleasurable state generated in affiliative interactions shares a common neurobiology with the pleasure generated by other consummatory behaviors (e.g., feeding) is not certain, but it is assumed by some to be so (Di Chiara & North 1992; Ikemoto & Panksepp 1996; Panksepp 1998; van Furth et al. 1994).

4.2. Formation of affiliative memories

Through Pavlovian associative learning, the experience of reward generated throughout appetitive and consummatory phases is associated with previously affectively-neutral stimulus contexts (objects, acts, events, places) in which pleasure occurred, thereby forming conditioned incentive stimuli that are predictive of reward, and that have gained the capacity to elicit anticipatory pleasure and incentive motivation (Berridge 1999; Bindra 1978; Ostrowski 1998; Timberlake & Silva 1995). Because of the predominance of symbolic (conditioned) processes in guiding human behavior in the absence of unconditioned stimuli, conditioned incentives are likely to be particularly important elicitors of *enduring* reward processes that underlie the trait of affiliation (Fowles 1987). Indeed, Pavlovian conditioning has been demonstrated in various aspects of sexual behavior, maternal lactation, and infant suckling, and may be similarly involved in social play and social grooming (Domjan et al. 2000). Similarly, the acquisition and maintenance of human partner preference, a marker used in animal work as an indication of affiliative bonding between mates (Insel 1997), also depends closely on Pavlovian associative learning between a mate's individualistic cues and reward.

The association of a salient context with reward is complex and involves at least three different but integrated processes. They are specified here because they are modeled neurobiologically later in our discussion. First, context includes distinctive attributes of incentive stimuli (modality, size, color, scent, texture, etc.) as well as their immediate sensory surround (position, location of targets of action, etc.), both of which are integrated with respect to internal drive states, desirability of action, and intended actions in the near future. Affiliative behavior is guided by both exteroceptive and interoceptive (e.g., visceral feelings, Porges 1998; 2001) sensory cues that are present during approach to and interaction with affiliative objects. For instance, in both human sexual and maternal exchanges the participating individuals often inspect each other closely, thereby enhancing tactile sensations, odors, vocalizations, and physical recognition cues (Cruz & Del Cerro 1998). Thus, in view of the enormous number of external and internal contextual cues associated with affiliative behavior, a critical process in constructing the context of reward is neural binding, whereby the elementary bits of contextual information are compressed and bound together into a *contextual ensemble* that is predictive of reward.

Second, the specific contextual stimuli that are selected for inclusion in an ensemble must be weighted or enhanced as a function of the target class of stimuli that currently define the behavioral goal. In a sociosexual context, it is advantageous relative to other sensory cues to weight affiliative stimuli as particularly salient elements of the total context as a means of *ensuring their incorporation in contextual ensembles*. Third, the contextual ensemble must also be encoded with incentive value proportional to the magnitude of reward experienced. This process imparts a relative motivational value to the contextual ensemble, thereby scaling its modulatory influence on affective and behavioral responses elicited subsequently by those conditioned incentive stimuli. Thus, subsequent perception of this particular contextual ensemble (or salient components of it), or activation of central representations of that ensemble, elicits an incentive motivational state proportional to the encoded incentive salience of the ensemble.

Taken together, these processes support acquisition of affiliative memories, whereby contextual ensembles are formed and weighted in association with the reward provided by interaction with the affiliative object (infant, mate, parent, close friends). Because many brain regions are involved in these processes, affiliative memories are represented as a network of nodes and connections among various brain regions (LeDoux 1998; McGaugh 2000; Schacter 1996). Thus, affiliative memories may be elicited by various elements of the salient context (if such elements are sufficiently strong to activate the entire network of connections), and then serve to motivate and guide the individual to the affiliative goal.

5. Hierarchical structure of an affiliation trait

Higher-order personality traits can be modeled in a hierarchical structure for affiliation, shown in Figure 4. This structure illustrates the interrelations among affiliative stimuli and the characteristics and core underlying processes of trait affiliation discussed in Sections 3 and 4. As illustrated in Figure 4, the higher-order trait of affiliation is defined by its core underlying processes of affiliative reward, emotional experience, physiological quiescence, and formation of affiliative contextual memories. We believe that the capacity to experience affiliative reward is the sine qua non of the higher-order trait, because other core underlying processes depend on it (e.g., emotional experience and formation of affiliative memories). Activation of the underlying processes leads in varying degrees to behaviors associated with *intimate social engagement*. In Figure 4, lower-order traits are each associated with the higher-order trait of affiliation, because each lower-order trait reflects the influence of the processes underlying the higher-order trait. Some of the lower-order traits, such as warm, affectionate, sympathetic, and positive emotion, reflect underlying processes more directly (e.g., emotional experience is the subjective expression of reward and physiological quiescence processes), whereas others reflect their influence as manifested in affiliative contexts (e.g., agreeable, sociable, and amiable). Not shown in Figure 4, but illustrated in Figure 3, are the permissive and faciliatory modulators of the core processes underlying trait affiliation.

6. Neurobehavioral foundation of the core processes underlying trait affiliation

Our discussion has attempted to delineate the behavioral-emotional characteristics underlying a human trait of affil-

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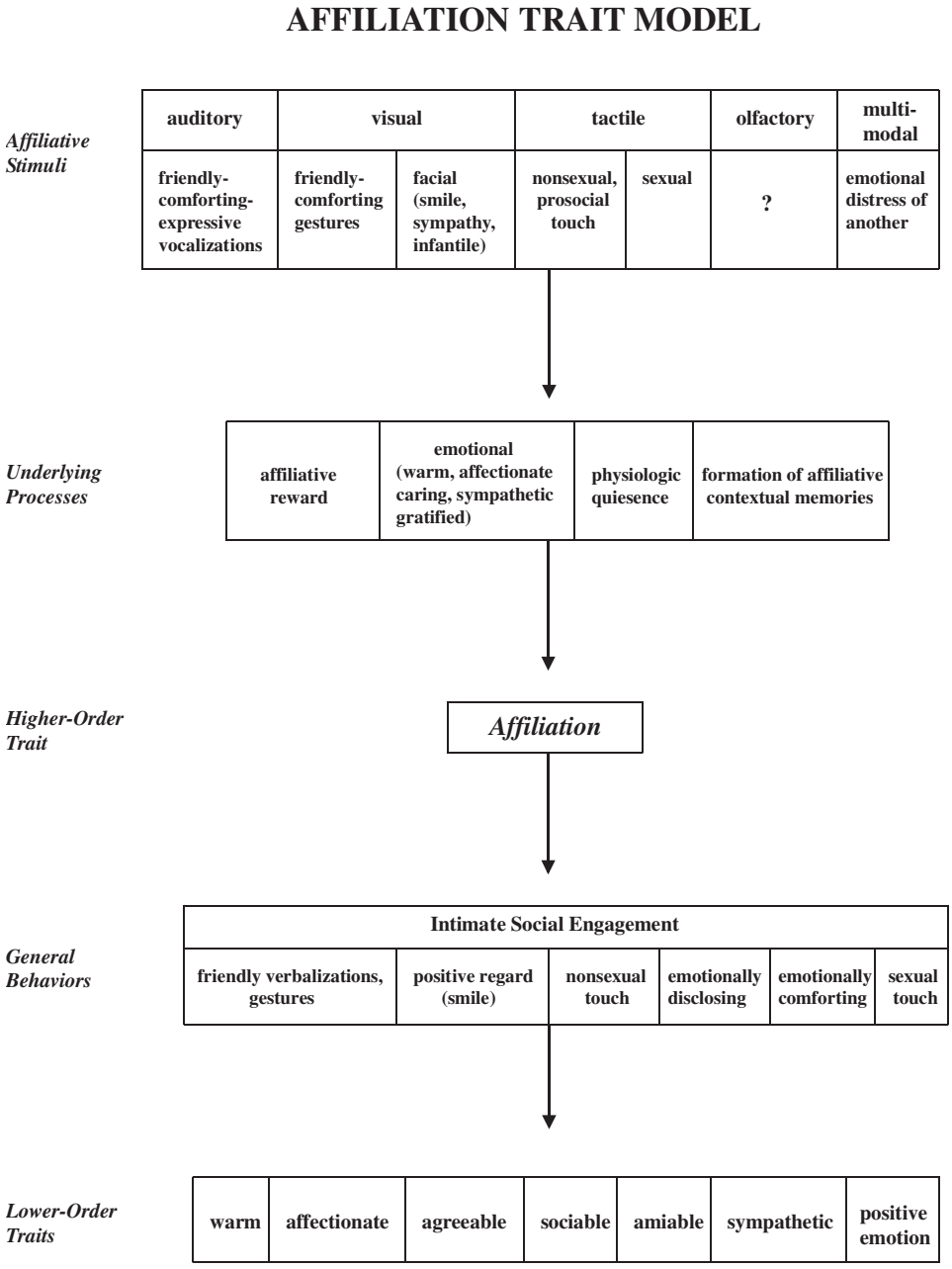

Figure 4. Path diagram representing the hierarchical structure of affiliation, which illustrates the interrelations among affiliative stimuli and the characteristics and core underlying processes of trait affiliation. See text for details.

iation, which at its core is characterized by emotional feelings of warmth and affection and valuing close interpersonal relations. We have suggested that these characteristics reflect an underlying capacity to experience reward elicited by affiliative stimuli, a capacity that allows for the development of contextual associative memory networks that establish and maintain affiliative bonds. The development and maintenance of affiliative bonds was organized within a sequence of two phases of reward in Figure 3. In section 6.1, we explore the neurobehavioral processes that are associated with these two phases of reward. In section 6.1.1, the role of dopamine neurotransmission in appetitive incentive reward processes is detailed, whereas in section 6.1.2, the role of opiates in the consummatory phase of reward is reviewed. A major component of the experience of reward in the consummatory phase is physiological quiescence that follows consummatory behavior. In section 6.1.3, we outline the brain structures involved in physiological quiescence and comment on the role of opiates in modulating the activity of those structures.

6.1. Neurobehaivoral processes of reward across two phases of affiliation

6.1.1. Dopamine, appetitive processes, and incentive reward. As reviewed recently (Depue & Collins 1999), animal research demonstrates that the positive incentive motivation and experience of reward that underlies a behavioral system of approach is dependent on the functional properties of the ventral tegmental area (VTA)

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dopamine (DA) projection system. DA agonists or antagonists in the VTA or nucleus accumbens (NAS), which is a major terminal area of VTA DA projections, in rats and monkeys facilitate or markedly impair, respectively, a broad array of incentive motivated behaviors, including locomotor activity to novelty and food; exploratory, aggressive, affiliative, and sexual behavior; acquisition and maintenance of approach and active avoidance behavior; food-hoarding; and maternal nursing behavior. More specifically, DA agonists injected in the NAS reduce, whereas both DA D_1 and D_2 antagonists increase, the threshold for electrical intracranial self-stimulation reward, a response model of incentive motivation (Bozarth 1987; Everitt & Robbins 1992; Fibiger & Phillips 1987; Knapp & Kornetsky 1994; Koob et al. 1993; Le Moal & Simon 1991; Mogenson et al. 1993). Furthermore, dose-dependent DA D_1, D_2, and D_3 receptor activation in the VTA-NAS pathway facilitates the acute rewarding effects of stimulants, and the NAS is a particularly strong site for intracranial self-administration of DA agonists (Hoebel et al. 1983; Le Moal & Simon 1991; Pich et al. 1997). More recent evidence suggests that the D_1 receptor may be most critical for the rewarding effects of cocaine and specifically its euphoric effects in humans (Koob 1999; Romach et al. 1999). D_1 and D_2 agonists injected in the NAS also modulate behavioral responses to *conditioned* incentive stimuli in a dose-dependent fashion (Cador et al. 1991; Robbins et al. 1989; Wolterink et al. 1989). Conversely, DA lesions (using the DA neurotoxin 6-OHDA with terminal field ablations of 95% or more) in the NAS or VTA create a reduction in motivation to work for reward, extinction-like responding, and long-lasting reductions in self-administration of stimulants (Caine & Koob 1993; Fibiger & Phillips 1987; Koob 1992; Koob et al. 1993; Phillips & Fibiger 1978; Pich et al. 1997; Robledo et al. 1992), whereas lesions of other DA terminal fields affect stimulant self-administration very little, if at all (Roberts & Zito 1987). In single-unit recording studies, VTA DA neurons are activated preferentially by appetitive incentive stimuli (Mirenowicz & Schultz 1996; Schultz et al. 1995b; 1997). DA cells, most numerously in the VTA, respond vigorously to and in proportion to the magnitude of both conditioned and unconditioned incentive stimuli and in anticipation of reward (Bowman et al. 1996; Henriksen & Giacchino 1993; Houk et al. 1995; Koob et al. 1993; Le Moal & Simon 1991; Mark et al. 1991; Mitchell & Gratton 1992a; Mirenowicz & Schultz 1996; Nishino et al. 1987; Pfaus et al. 1990; Schultz et al. 1993; Schultz et al. 1995b; Schultz et al. 1997; Weiss et al. 1992).

Finally, incentive motivation is associated in humans with both positive *emotional* feelings, such as elation and euphoria, and *motivational* feelings of desire, wanting, craving, potency, and self-efficacy. In humans, DA-activating psychostimulant drugs induce both sets of feelings (Drevets et al. 2001; Koob et al. 1993; Stewart et al. 1984). Also, neuroimaging studies of cocaine addicts found that during acute administration the intensity of a subject's subjective euphoria increased in a dose-dependent manner in proportion to cocaine binding to the DA uptake transporter (and hence DA levels) in the striatum (Volkow et al. 1997). Moreover, cocaine-induced activity in the NAS was linked equally strongly (if not more strongly) to motivational feelings of desire, wanting, and craving, as to the emotional experience of euphoric rush (Breiter et al. 1997). And the degree of amphetamine-induced DA release in healthy human ventral striatum assessed by PET was correlated strongly with feelings of euphoria (Drevets et al. 2001). Hence, taken together, the animal and human evidence demonstrates that the VTA DA–NAS pathway is a primary neural circuit for incentive reward.

6.1.2. Opiates, consummatory processes, and reward. A broad range of evidence suggests a role for endogenous opiates in sociosexual behavior. Endogenous opiate release or receptor binding is increased in rats, monkeys, and humans by parturition, lactation and nursing, sexual activity, vaginocervical stimulation, maternal social interaction, brief social isolation, and grooming and other nonsexual tactile stimulation such as play (Insel 1992; Keverne 1996; Keverne et al. 1989; Mansour et al. 1988; Nelson & Panksepp 1998; Niesink et al. 1996; Nissen et al. 1998; Olson et al. 1997; Silk et al. 2003; Vanderschuren et al. 1995). Moreover, the opiate receptor (OR) agonist morphine versus the OR antagonists naltrexone or naloxone increase or reduce, respectively, the ability of vaginocervical stimulation to induce maternal behavior and mother–infant bonds in sheep and humans (Keverne 1996), as well as time spent by juvenile rats with their mothers after a brief separation – indicating that opiates modulate the reward value of mothers (Agmo et al. 1997). Naloxone or naltrexone in small doses apparently reduces the reward derived from social interactions, because these substances increase attempts to obtain such reward, manifested as increases in (a) the amount of maternal contact by young monkeys, and (b) solicitations for grooming and frequency of being groomed in mature female monkeys, which has been associated with increased cerebrospinal fluid levels of β-endorphin (Graves et al. 2002; Keverne et al. 1989; Martel et al. 1995). Also, even prenatally administered morphine increases the frequency of subsequent play behavior in juvenile rats (Niesink et al. 1996). In addition, the endogenous opiate β-endorphin stimulates play behavior and grooming in juvenile rats, whereas naltrexone leads to reduced grooming of infants and other group members in monkeys and rats, and to maternal neglect in monkeys and sheep that is similar to the neglect shown by human mothers who abuse opiates (Kendrick & Keverne 1989; Keverne 1996; Martel et al. 1993; Niesink & van Ree 1989). Similarly, human females administered the opiate antagonist naltrexone showed an increased amount of time spent alone, a reduced amount of time spent with friends, and a reduced frequency and pleasantness of their social interactions relative to placebo (Jamner & Leigh 1999). Such findings suggest that opiates provide a critical part of the neural basis on which primate sociality has evolved (Keverne et al. 1989; Nelson & Panksepp 1998; Panksepp et al. 1994). Particularly important is the relation between *u*-opiates and grooming, because the primary function of primate grooming may well be to establish and maintain social bonds, which are subsequently used to act jointly on whatever environmental challenges occur (Matheson & Bernstein 2000).

Effects of opiate drugs are mediated by at least three OR families, having as many as nine subtypes (i.e., mu, delta, and kappa), and opiate peptides, as well as opiate alkaloids, may bind to more than one opiate-receptor subtype (Khachaturian et al. 1993; Mansour et al. 1988; Olson et al. 1997; Schlaepfer et al. 1998; Simon & Gioannini 1993; Stefano et al. 2000; Strand 1999; Uhl et al. 1999; Zubieta et al. 2001). Perhaps most relevant to sociosexual behavior is the

mu (μ) opiate receptor (μOR) family, which is the main site of exogenously administered opiate drugs (e.g., morphine), of endogenous endorphins (particularly *B*-endorphin), and whose u_3 receptor subtype may be the receptor for the newly discovered endogenous morphine (La Buda et al. 2000; Mathes et al. 1996; Olson et al. 1997; Schlaepfer et al. 1998; Shippenberg & Elmer 1998; Sora et al. 1997; Stefano et al. 1996; 2000; Stefano & Scharrer 1994; Wiedenmayer & Barr 2000). *u*ORs also appear to be the main site for the effects of endogenous β-endorphins and endogenous morphine on the subjective feelings in humans of *increased* interpersonal warmth, euphoria, well-being, and peaceful calmness, as well as of *decreased* elation, energy, and incentive motivation (Cleeland et al. 1996; Ferrante 1996; Greenwald et al. 1996; Olson et al. 1997; Schlaepfer et al. 1998; Shippenberg & Elmer 1998; Stefano et al. 2000; Uhl et al. 1999). The delta (δ)OR family may also be important in sociosexual behavior, in that B-endorphin also displays affinity for these receptors (Raynor et al. 1994; Shippenberg & Elmer 1998).

The facilitatory effects of opiates on sociosexual behavior are thought to be exerted by fibers that arise mainly from the hypothalamic arcuate nucleus and terminate in brain regions that typically express ORs, such as brainstem, basal ganglia, and corticolimbic regions, as well as in hypothalamic nuclei where the neurons of other sociosexually-related neuropeptides reside (e.g., oxytocin, vasopressin) (Brown et al. 2000; Keverne 1996; Mansour et al. 1988; Shippenberg & Elmer 1998; Stefano et al. 2000; Strand 1999). Endogenous opiate *B*-endorphin neurons located in the medial basal arcuate nucleus of the hypothalamus project anteriorally to the dorsomedial and anterior hypothalamus, medial preoptic area (mPOA), septum, diagonal band, NAS, and bed nucleus of the stria terminalis (Herbert 1993; Mann et al. 1991; Strand 1999). There are also lateral projections to the amygdala, most prominently to the central and medial nuclei, with less dense projections to the basolateral nuclei (Herbert 1993). Furthermore, there are dorsal projections that terminate in the paraventricular nuclei of the thalamus, which then proceed caudally to the brainstem periaquiductal gray (PAG), reticular formation nuclei, and nucleus of the solitary tract and other areas related to visceral and autonomic activity (Herbert 1993). Similarly, in postmortem examination of human brains, high, *u*OR concentrations were observed in the cingulate gyrus, NAS, VTA, cerebellum, thalamus, hypothalamus, mPOA, PAG, and raphe nuclei (Schlaepfer et al. 1998; Wellmann et al. 1997). Evidence for the functional importance of opiates in human limbic areas was demonstrated by Schlaepfer et al. (1998), who showed, using brain imaging, that *u*OR agonists increase regional CBF in the anterior cingulate cortex, pericentral cortex, the amygdala, and thalamus.

*u*ORs and perhaps *d*ORs may facilitate the rewarding effects associated with many motivated behaviors (Agmo & Berenfeld 1990; Agmo & Gomez 1993; Blake et al. 1987; Bozarth 1994; Keverne 1996; Koob & Le Moal 1997; Koob et al. 1993; Nelson & Panksepp 1998; Niesink et al. 1996; Olive et al. 2001; Olson et al. 1997; Stefano et al. 2000; Strand 1999; van Furth et al. 1994). For example, whereas DA antagonists block appetitive behaviors in pursuit of reward, but not the actual consumption of reward (e.g., sucrose; Ikemoto & Panksepp 1996), *u*OR-antagonists block rewarding effects of sucrose and sexual behavior, and in neonatal rats persistently impair the response to the inherently rewarding properties of novel stimulation (Herz 1998). Rewarding properties of *u*OR agonists are directly indicated by the fact that animals will work for the prototypical *u*-agonists morphine and heroin, and that they are dose-dependently self-administered in animals and humans (Di Chiara 1995; Nelson & Panksepp 1998; Olson et al. 1997; Shippenberg & Elmer 1998; Wise 1996). There is a significant correlation between an agonist's affinity at the *u*OR and the dose that maintains maximal rates of drug self-administration behavior (Shippenberg & Elmer 1998). Conversely, *u*OR antagonists can lead to extinction of self-administration of *u*OR agonists, but often lead to increased self-administration of *u*OR agonists, mimicking self-administration behavior seen when the unit dose of agonist is decreased (Shippenberg & Elmer 1998).

The rewarding effect of opiates may be especially mediated by *u*ORs and to a lesser extent by *d*ORs located in the NAS and VTA, both of which support self-administration of *u*OR agonists that is attenuated by intracranially administered *u*OR antagonists (Davis & Cazala 2000; Duvauchelle et al. 1996; Herz 1998; Koob 1992; Koob & Le Moal 1997; Schlaepfer et al. 1998; Shippenberg & Elmer 1998). Opiate mechanisms in the amygdala, extended amygdala, lateral hypothalamus, and PAG also likely contribute to rewarding properties of drugs of abuse such as ethanol (Heyser et al. 1999; Shippenberg & Elmer 1998). Particularly in the rostral shell region of the NAS, DA agonists (ethanol, cocaine, d-amphetamine) administered intraperitoneally in rats markedly increased the extracellular levels of endogenous endorphins (Olive et al. 2001), whereas intracerebroventricular administration of *B*-endorphin enhances NAS DA release (Spanagel et al. 1991). Moreover, *u*-opiate reward is markedly enhanced in DA D3 receptor knockout mice (Narita et al. 2003), a receptor that contributes to the postsynaptically inhibitory modualtion of the mesolimbic DA pathway. Whereas these findings suggest an interaction with DA in the rewarding effects of opiates, when opiate and mixed DA, D1, or D2 specific antagonists were given prior to cocaine or heroin self-administration, the opiate antagonist selectively altered opiate self-administration, while DA antagonists selectively altered the response to the DA agonist cocaine (Ettenberg et al. 1982; Gerber & Wise 1989; Gerrits et al. 1994; Shippenberg & Elmer 1998). Destruction of DA terminals in the NAS via the regional administration of 6-hydroxydopamine (OHDA) also showed that opiate self-administration is independent of DA function, at least at the level of the NAS (Dworkin et al. 1988; Pettit et al. 1984; Smith et al. 1985). Furthermore, NAS DA functioning was specifically related to the incentive salience of reward cues, but was unrelated to the hedonic state generated by consuming the rewards or response reinforcement (Wyvell & Berridge 2000). *Thus, DA and opiates appear to functionally interact in the NAS, but they apparently provide independent contributions to rewarding effects*. This appears to be particularly the case for the *acute* rewarding effects of opiates, which are thought to occur through a DA-independent system that is mediated through brainstem reward circuits, including the tegmental pedunculopontine nucleus (Laviolette et al. 2004; Olmstead et al. 1999).

Rewarding effects of opiates are also directly indicated by the fact that a range of μOR agonists, including morphine, heroin, DAMGO, and *B*-endorphin, when injected intracerebroventricularly or directly into the NAS, serve as

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unconditioned rewarding stimuli in a dose-dependent manner by producing a conditioned place preference, a behavioral measure of reward (Bals-Kubik et al. 1993; Carr et al. 1989; Mucha et al. 1982; Narita et al. 2000; Nelson & Panksepp 1998; Olds 1982; Olson et al. 1997; Shippenberg & Elmer 1998; van der Kooy et al. 1982). In the VTA, *u*ORs predominate, although self-administration of *d*OR agonists in the VTA has been demonstrated (Shippenberg & Herz 1988). VTA-localized *u*ORs, particularly in the rostral zone of the VTA (Carlezon et al. 2000), mediate: (a) rewarding effects such as self-administration behavior and conditioned place preference (Bozarth 1994; Carlezon et al. 2000; Panagis et al. 1998; Ramsey et al. 1999; Shippenberg & Elmer 1998; Wise 1998); (b) increased sexual activity and maternal behaviors (Callahan et al. 1996; Leyton & Stewart 1992; van Furth & van Ree 1996); and (c) the persistently increased play behavior, social grooming, and social approach of rats subjected to morphine in utero (Hol et al. 1996). Indeed, microinjections of morphine or the selective *u*OR agonist DAMGO into but not around the VTA produced marked place preferences, whereas selective antagonism of *u*ORs prevented morphine-induced conditioned place preference (Olmstead & Franklin 1997). *u*OR and *d*OR antagonists also attenuate psychostimulant-induced conditioned place preference (Houdi et al. 1989; Menkens et al. 1992; Shippenberg & Elmer 1998; Suzuki et al. 1994; Trujillo et al. 1991). Indeed, transgenic mice lacking the *u*OR gene show no morphine-induced place preferences or physical dependence from morphine consumption, whereas morphine induces both of these behaviors in wild-type mice (Matthes et al. 1996; Simonin et al. 1998). And significantly, opiate, but not oxytocin, antagonists block the development of partner preference that is induced specifically by *repeated* exposure and *repeated* sexual activity in rodents (Carter et al. 1997).

Taken together, these results indicate that activation of VTA *u*ORs (with perhaps *d*ORs) is sufficient for the establishment of place conditioning (Bals-Kubik et al. 1993; Baumeister et al. 1993; Bozarth 1987). These VTA *u*OR-mediated conditioning effects, however, are dependent on DA D1, but not D2, receptor activation in the NAS, as is *B*-endorphin-facilitated grooming in rodents (Drago et al. 1999). 6-OHDA lesions of DA terminals in the NAS, or infusion into the NAS, but not the caudate-putamen, region of selective DA D1 receptor antagonists during place conditioning, resulted in prevention or dose-related attenuation of the conditioned response to systemically administered morphine, respectively (Shippenberg & Elmer 1998). Activation of the DA D3 receptor, which may be an autoreceptor in the VTA and thereby inhibit activation of DA release in the NAS, also prevents the acquisition of morphine-induced place conditioning (DeFonseca et al. 1995). Whereas *u*OR agonists administered in the NAS do not elevate responding for conditioned reward, they do sensitize DA receptor reactivity to DA agonists in the NAS (Cunningham & Kelley 1992). The reason for opiate dependence on NAS D1 receptor activation in place conditioning is discussed in section 6.2.1.6

An interaction of DA and *u*-opiates, discussed further in section 6.3.2, in the experience of reward throughout appetitive and consummatory phases of affiliative engagement appears to involve two processes. During the anticipatory phase of goal acquisition, *u*OR activation in the VTA can increase DA release in the NAS, and hence the experience of reward (Bozarth 1994; Callahan et al. 1996; Jaeger & van der Kooy 1996; Marinelli & White 2000; Olson et al. 1997; Panagis et al. 1998). Subsequently, the firing rate of VTA neurons decreases following delivery and consumption of appetitive reinforcers (e.g., food, sex, liquid) (Kosobud et al. 1994; Schultz et al. 1997). At the same time, *u*OR and *d*OR (Churchill et al. 1995) activation in the NAS (perhaps by opiate release from higher-threshold NAS terminals that colocalize DA and opiates [Le Moal & Simon 1991]) decreases NAS DA release, creating an opiate-mediated experience of reward associated with consummation that is independent of DA. Thus, in contrast to the incentive motivational effects of DA during the anticipation of reward, opiates may subsequently induce calm pleasure and bring consummatory behavior to a gratifying conclusion (Bozarth 1994). This may explain the fact that higher doses of both *u*OR and *d*OR agonists administered into the NAS can block the self-administration of certain psychostimulant drugs of abuse in animals and reduce appetitive behaviors (Amalric et al. 1987; Corrigall & Vaccaccarino 1988; Heyser et al. 1999; Hyztia & Kiianmaa 2001; Johnson & Ait-Daoud 2000; Kelley et al. 1996; Kranzler 2000).

Although beyond the main focus of our discussion, *u*ORs are also the main site for the supraspinal antinociceptive systems, because mice lacking *d*ORs and kappa (*k*) ORs exhibit analgesia in response to morphine (Simonin et al. 1998; Stefano et al. 2000; Zubieta et al. 2001). Analgesic effects, however, may be mediated by different *u*ORs or different ligands of *u*ORs than rewarding effects (Wilson et al. 2000). Nelson and Panksepp (1998) creatively suggest that an analgesic function of *u*ORs is based on tactile (touch) elicitation of opiates as a means of reducing pain-induced emotional distress (Reisine & Pasternak 1996; Zubieta et al. 2001), and that this tactile–opiate relation was conserved throughout evolution to incorporate other opiate-induced functions by gentle touch, such as reduction of separation-induced emotional distress, and reward and physiological calming during prosocial engagement. Recent research supports this notion (Eisenberger et al. 2003).

6.1.3. Opiates, consummatory processes, and physiological quiescence. The consummatory phase of reward is typically accompanied by a state of physiological quiescence and behavioral calmness that contributes to the subjective feelings of liking and pleasure (Berridge 1999; Wyvell & Berridge 2000). Porges (1998; 2001) has integrated the literature on neural processes that contribute to physiological quiescence in mammals and especially primates, processes that he views as important components of social engagement, communication, and affiliative bonding. In particular, the more recently evolved myelinated efferents from ventral vagal neurons in mammals, arising from visceromotor portions of the nucleus ambiguous located in the rostral ventrolateral medulla, are capable of providing rapid inhibitory regulation of the autonomic nervous system, supradiaphragmatic visceral organs, and the sinoatrial node of the heart, as well as of striated musculature involved in facial and vocal communication. This vagal *brake* conserves biological resources by allowing for rapid changes in sympathetic tone without widespread autonomic nervous system and adrenal endocrine activation.

In addition, primates in particular can rapidly regulate sympathetic and adrenal activity via prefrontal regions (see review by Sullivan & Gratton 2002). Anterior cingulate and

dorsal prefrontal cortex in primates have a particularly dense distribution of glucocorticoid (type II) receptors that detect phasic changes in circulating cortisol levels. Activation of type II receptors in these regions engages an inhibitory feedback mechanism that modulates further hypothalamic-pituitary-adrenal cortex (HPA) stress responsivity (but not basal levels). Thus, in nonthreatening, nonstressful contexts, these prefrontal areas provide strong inhibitory regulation of rat right-hemispheric ventral infralimbic cortex (homologous to right hemispheric ventral orbital cortex in humans), a region that provides strong activation of sympathetic and adrenal activity (Sullivan & Gratton 2002). Under repeated stressful conditions, the ventral orbital cortex, proposed to sit at the apex of a stress response system (Schore 1996; 1997), activates sympathetic and adrenal activity via projections to the HPA axis, the lateral hypothalamic region controlling sympathetic activity, and the rostral ventrolateral medullary zone for integration of arousal information. But of importance here is that, under conditions of social engagement, dorsal prefrontal inhibition of ventral orbital cortex, together with ventral vagal output (Porges 2001), can jointly create a state of physiological quiescence and behavioral calm that promotes prosocial interactions and consummatory processes.

*u*ORs may facilitate this state of physiological quiescence and behavioral calm, although additional functional studies are required. A parallel distribution of endogenous morphine and the *u*OR gene is found in the PAG, rostral ventrolateral medulla, parabrachial nuclei, and locus coeruleus (Stefano et al. 2000). In the area of the rostral ventrolateral medulla, this parallel distribution occurred in the nucleus paragiganticocellularis, which is a major integration zone for arousal information and that provides the major source of activation to: (a) the autonomic nervous system, and (b) to locus coeruleus neurons, which in turn induce central arousal via norepinephrine release (Aston-Jones et al. 1996; Davis et al. 1996). Indeed, disinhibition of the locus coeruleus cells is implicated in the excessive arousal that accompanies the opiate withdrawal syndrome (Legradi et al. 1996). Furthermore, *B*-endorphin neurons in the medial basal arcuate nucleus of the hypothalamus send dorsal projections that terminate in the paraventricular nuclei of the hypothalamus, which then proceed caudally to the brainstem PAG, reticular formation nuclei, and nucleus of the solitary tract and other areas related to visceral and autonomic activity (Herbert 1993). Moreover, in the human brain, high *u*OR and endogenous opioid concentrations were observed in the anterior cingulate gyrus, NAS, VTA, amygdala, hypothalamus, mPOA, PAG, and raphe nuclei (Price 1999; Price et al. 1996; Schlaepfer et al. 1998; Stefano et al. 2000; Strand 1999; Wellmann et al. 1997).

The simultaneous presence of endogenous opiates and the *u*OR gene in these regions is consistent with the ability of opiate alkaloids to alter autonomic and neuroendocrine responses (Krzanowska et al. 1998; Stefano et al. 2000; Willis & Westlund 1997). In addition, their joint presence in both the anterior cingulate gyrus, which can inhibit ventral orbital activation of stress responses, and in the paraventricular hypothalamus, which is the site of corticotrophin-releasing hormone and the initiation of subsequent cortisol release, could also modulate sympathetic and adrenal activity. Although this modulation of arousal effector systems is utilized as part of an analgesic response system, it is also utilized to induce physiological quiescence at the time of consummatory behavior. Subsequently, the calming, inhibitory effects of endogenous morphine are diminished in a relatively short period of time, because *u*OR desensitization occurs once downregulation of physiological arousal is achieved, even while endogenous opiates are still present in the internal environment (Stefano et al. 2000). This timely recovery of neural processes involved with opiate actions provides for a successful mechanism to ensure survival.

Physiological quiescence in the consummatory phase may also be promoted by serotonin, which, for example, when released into the anterior lateral hypothalamus during the postejaculatory interval in male rats, directly decreases the preejaculatory increase in NAS DA via disinhibition of inhibitory efferents from the lateral hypothalamus to the NAS (Lorrain et al. 1999), an inhibitory effect that may extend to other appetitive behaviors facilitated by NAS DA, such as feeding (Aoyagi et al. 1992; Schwartz et al. 1989). Serotonergic-induced decreases in autonomic arousal via raphe input to the arousal integration zone in the lateral hypothalamus (Depue & Spoont 1986; Spoont 1992) may also promote calm, prosocial interactions, such as allogrooming in vervet monkeys and positive social interaction in young adult humans, both of which are positively associated with increased serotonin activity (Insel & Winslow 1998).

In sum, as illustrated in Figure 3, distal affiliative cues (e.g., friendly smiles and gestures, sexual features) serve as incentive stimuli that activate DA-facilitated incentive-reward motivation, desire, wanting, and approach to affiliative objects. As these objects are reached, more proximal affiliative stimuli (e.g., pleasant touch) strongly activate *u*-opiate release, which promotes an intense state of pleasant reward, warmth, affection, and physiological quiescence, and brings approach behavior to a gratifying conclusion. These two different types of reward processes are critical to the acquisition and maintenance of learned associations between the context accompanying the approach to and consummation of affiliative objects, or put differently, of affiliative memories. It is to the neurobiology of this formation of social memories that we now turn.

6.2. Formation of affiliative memories

In addition to the processes of reward, we have proposed that affiliation involves the formation of affiliative memories, wherein contexts predictive of affiliative reward are associated with that reward. Although highly complex, the manner in which context is bound to reward processes in appetitive and consummatory phases of reward to form memories is beginning to be elucidated in the animal neurobiology literature. We address this issue in detail in section 6.2.1. To illustrate these processes, it is necessary first to understand the brain structures that process the contextual elements that comprise an affiliative memory, and these are briefly outlined in sections 6.2.1.1–6.2.1.4, wherein special attention is devoted to the integrative nature of the nucleus accumbens in the ventral striatum. The manner in which these brain regions form an organized network is equally important and is reviewed in section 6.2.1.5. With that background, the discussion then focuses on: (a) the specific manner in which the contextual elements associated with reward are bound together to form a contextual ensemble, and (b) how that ensemble is encoded for in-

centive salience. These points are reviewed in section 6.2.1.6, wherein the critical roles of dopamine and glutamate are described. Because of the complexity of the discussion in section 6, a summary of the major points is outlined in section 6.2.1.7. Finally, in section 6.2.1.8, evidence supporting the necessary role of dopamine in the formation of *affiliative* memories, in particular, is reviewed.

6.2.1. Dopamine's role in acquiring environmental context-incentive motivational ensembles. The critical role of the VTA DA-NAS pathway in the facilitation of incentive motivation suggests that the NAS is a site of integration of incentive information. The caudomedial shell region of the NAS (NASshell) is a major point of convergence of motivational information from many corticolimbic structures (Deutch et al. 1993; Heimer et al. 1993; Kalivas et al. 1993; Wilson & Kawaguchi 1996; Wright et al. 1996). Whereas NAS cells decrease firing during periods of focused attention and consummatory events, they increase firing to primary and conditioned signals of reward and novelty, during intervals when reward is expected, and during engagement in rewarding social activity (Apicella et al. 1991; Henriksen & Giacchino 1993; Le Moal & Simon 1991; Schultz et al. 1992; Schultz et al. 1995a). Responses of NAS neurons to salient contextual stimuli are due to afferent excitatory stimulation arising from at least four main sources, all of which are interconnected (Kalivas et al. 1993), but each provides different information about the salient incentive context.

6.2.1.1. Basolateral complex of the amygdala. The basolateral amygdala (i.e., the basal, accessory basal, mediobasal, and lateral nuclei) of the rat (Wright et al. 1996) and monkey (Heimer et al. 1993) provides massive, topographically organized, compartmentally bounded innervation of the NASshell. In both monkeys and humans, the basolateral amygdala plays a critical role in classical stimulus-reinforcement conditioning, the process whereby neutral cues acquire positive and negative incentive status and emotional meaning (Aggleton 2000; Bechara et al. 1995; Cahill & McGaugh 1990; 1998; Emery & Amaral 2000; Everitt & Robbins 1992; Gaffan 1992; LeDoux et al. 1990; Selden et al. 1991). Although the basolateral amygdala has often been viewed as associating negative emotions with reinforcement, recent evidence supports a role for the amygdala in processing positive emotions as well as negative ones, including the learning of stimulus-reward associations (Baxter & Murray 2002; Gottfried et al. 2003). Bilateral basolateral amygdala lesions specifically impair the association of *discrete, explicit* stimuli with reinforcement (as opposed to nonexplicit, contextual stimuli – see sect. 6.2.1.2), whereas the *motivational efficacy* or incentive magnitude of food rewards or of DA injections in the NAS remains intact (Aggleton 1992; Everitt & Robbins 1992; Gaffan 1992). The basolateral amygdala can enhance DA release in the NAS, but this release is under inhibitory control from prefrontal efferents to the NAS (Jackson & Moghaddam 2001). The amygdala provides associative processes for *affiliative* stimuli, because complete amygdala lesions in primates cause a decline in affiliative behavior, social communication, and emotional responses to other animals, which is thought to result from an inability to emotionally interpret complex affiliative stimuli (i.e., to associate them with affective meaning) (Emery & Amaral 2000; Steklis & Kling 1985). More specifically, lesions of the basolateral amygdala prevent induction of conditioned place preference in environments that have been paired with rat pups, and also impair postpartum maternal behaviors to such stimuli (Fleming et al. 1999). And female rats develop increased activity in the basolateral amygdala with increasing exposure to their pups (Fleming et al. 1999).

6.2.1.2. Extended amygdala. Basolateral and olfactory amygdala complexes send massive projections to a group of structures collectively referred to as the extended amygdala, which represents a macrostructure that is characterized by two divisions, central and medial (Heimer 2003; Heimer et al. 1993; Martin et al. 1991; McGinty 1999). Originating from the central and medial nuclei of the amygdala and traversing through the sublenticular area and bed nucleus of the stria terminalis (BNST), the central and medial divisions merge specifically with the caudomedial region of the NASshell (see Fig. 5). Many intrinsic connections occur along these divisions, particularly in the central division, suggesting that high-level integration occurs within the extended amygdala (Heimer 2003; Heimer et al. 1993; Koob & Le Moal 1997; LeDoux 1998). Pharmacological and lesion manipulations of all central extended amygdala structures modify incentive motivation to work for rewards and initiation of locomotor activity as a means of obtaining rewards (Heimer et al. 1993; Kalivas et al. 1993; Koob 1992; Koob et al. 1993). Similar to the outputs from the central nucleus of the amygdala, most structures of the central division of the extended amygdala can transmit this motivationally relevant information to some or all hypothalamic and brainstem structures related to emotional expression (Heimer 2003; Heimer et al. 1993; Holstege 1991; 1992). Whereas the basolateral complex of the amygdala is involved in pairing reinforcement with stimuli that are discrete and explicit and that have been analyzed for their specific characteristics, at least the central division of the extended amygdala appears to associate *general contextual features and nonexplicit, nondiscrete* conditioned and unconditioned stimuli with reinforcement (e.g., light conditions, physical features, spatial relations) (Davis et al. 1997; Davis & Shi 1999; Koob et al. 1993; McDonald et al. 1999). Thus, two emotional learning systems may have evolved: (1) the basolateral amygdala to associate reinforcement with explicit, specific characteristics of objects (a property of the ventral visual stream and auditory feature analysis), and (2) the BNST to associate reinforcement with nonexplicit spatial and contextual stimulus aspects (as in the dorsal visual stream and spatial location of auditory stimuli) (Karnath 2001).

6.2.1.3. Hippocampus. The hippocampus topographically innervates the NASshell (Groenewegen et al. 1991), but lesions of the fimbria-fornix or ventral hippocampus do not impair the association of *discrete* stimuli with reinforcement (Bechara et al. 1995; Gaffan 1992). Rather, hippocampal, but not basolateral amygdala, lesions disrupt Pavlovian associations formed between the *spatial and contextual interrelations* of environmental stimuli and reinforcement (Annett et al. 1989; Davis & Shi 1999; Davis et al. 1997; Selden et al. 1991; Sutherland & McDonald 1990; Winocur 1997). In part, this may be the result of inputs carrying spatial and contextual information from the hippocampus and parahippocampal cortex to the BNST (Davis

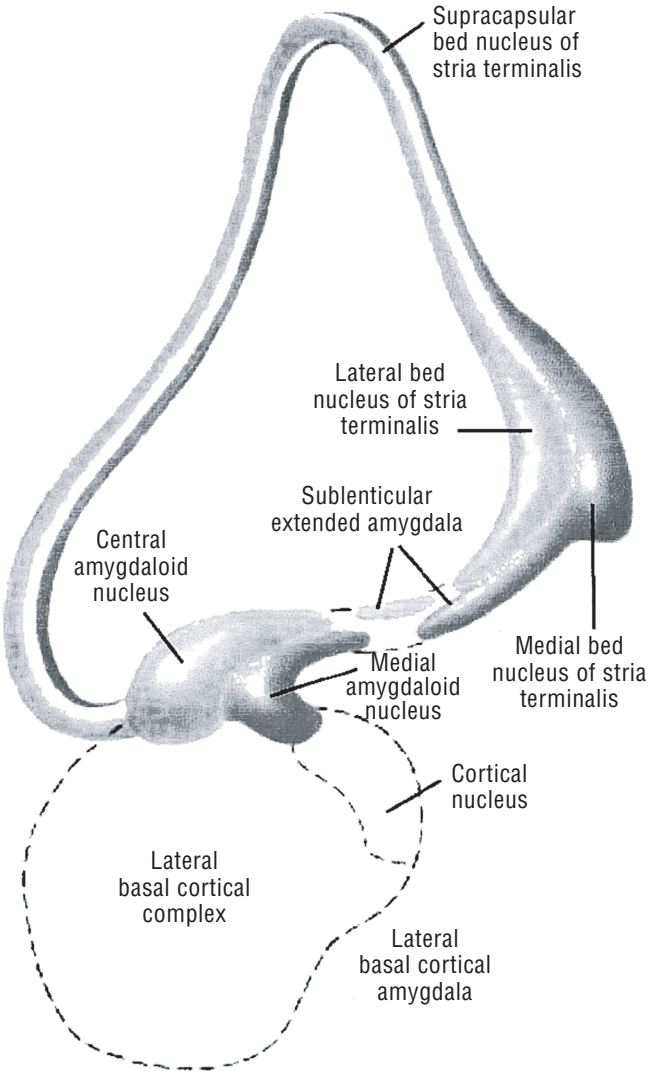

Figure 5. The central and medial divisions of the extended amygdala, shown in isolation from the rest of the brain. From Heimer 2003.

& Shi 1999; Davis et al. 1997). NAS lesions, on the other hand, can produce behavioral deficits closely related to those following impairment of hippocampal functions (Annett et al. 1989). Thus, doubly dissociable limbic-striatal functions (amygdala-NAS vs. hippocampal-NAS) may correspond to the compartmentalization of the NAS (Everitt & Robbins 1992; Gaffan 1992).

6.2.1.4. Prefrontal cortex. The orbital frontal cortex, particularly Brodmann's posterior medial orbital prefrontal cortical area 13 (MOC 13), integrates the most complex level of associations of reinforcement with both stimuli and responses (Adolphs 2003; Bechara et al. 1997; Gottfried et al. 2003; Rolls 2000; Schnider 2003; Thorpe et al. 1983). Via connections with more laterally located orbital cortical circuits, MOC 13 has strong connectivity with regions that process all sensory modalities of contemporaneous and stored information, as well as topographically organized efferents that densely innervate the NASshell (Barbas 1995; Deutch et al. 1993; Goldman-Rakic 1987; Kalivas et al. 1993; Ongur & Price 2000; Price 1999). Through its dense reciprocal connections with the basolateral, central, and extended amygdala regions, MOC 13 has access to emotional and reinforcement associations of contemporaneous and recalled sensory events (Carmichael & Price 1995; Drevets 2001; Elliott et al. 1997; Gallagher et al. 1999; Goldman-Rakic 1987; Hikosaka & Watanabe 2000; O'Doherty et al. 2001; Rolls 1999; 2000; Schnider et al. 2000; Tremblay & Schultz 1999). MOC 13 forms higher-level conditional representations of sensory events by associating them with existing or newly developing response-reinforcement contingencies; or more simply, MOC 13 may abstract an integrated structure of appetitive and aversive behavioral contingencies from the environment (Frey & Petrides 2000; O'Doherty et al. 2001; Rogers et al. 1999; Rolls 2000; Schnider 2003; Thorpe et al. 1983). When behavioral responses evoke unexpected reinforcement outcomes, MOC 13, in collaboration with the basolateral amygdala (Everitt & Robbins 1992; Gottfried et al. 2003) and hippocampus (Gray et al. 1991), encodes the new contingencies that are relevant to the modification of response programs (O'Doherty et al. 2001; Rolls 2000; Schnider 2003; Thorpe et al. 1983). MOC 13 may be capable of holding such representations of behavioral-reinforcement contingencies in working memory as motor strategies are selected over time (Damasio 1999; Goldman-Rakic 1987; O'Doherty et al. 2001; Rolls 1999; 2000; Scalaidhe et al. 1997). This capacity would allow a comparison of the valence and magnitude of outcome expectancies associated with several possible response strategies, and then an updating of contingencies as circumstances unfold during the temporal duration of the selected response strategy (Depue & Collins 1999; Houk et al. 1995).

Because our focus is on affiliation, it is worth noting that the basolateral amygdala, BNST, and MOC 13 receive neural input from cortical regions associated particularly with the processing of faces and biological motion. Such information is relevant to judgments about others emotions, attractiveness, intentionality, friendliness and approachableness, and interpersonal personality traits. These cortical regions would include: (a) the fusiform gyrus in processing the structural, static properties of faces, and (b) more anterior and dorsal regions in the temporal lobe (e.g., the superior temporal gyrus and sulcus) involved in processing the changeable configurations of faces (e.g., facial expressions) and biological motion of the whole body and body parts (gaze shifts and arm, hand, and mouth movements) (Adolphs 2003). Additionally, neural input about light, pleasant touch, and autonomic status from the insular cortex is also substantial to these areas. Thus, areas that encode the incentive salience of contextual stimuli have access to a range of cues relevant to affiliative interactions.

6.2.1.5. Neural organization of incentive-facilitated behavior in a medial orbital network. Together, these brain regions just discussed provide a wealth of contextual information to the NASshell that must be integrated. Many complex motor, cognitive, and motivational processes are integrated via networks of brain regions that have a directed flow of information from cortical areas through striatal, pallidal, and thalamic regions back to one of the originating cortical areas, typically within the prefrontal cortex (Alexander et al. 1990). The purpose of these networks (or reentrant circuits) is to develop a neural ensemble, derived from thousands of elements, that serves as an integrated representation of movement, cognition, or motivation (Graybiel 1997;

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1998), a representation that may be stored in memory as a network of interconnected nodes (Graybiel 1995; Jog et al. 1999; Kelley 1999a; McGaugh 2000; O'Donnell 1999; O'Donnell et al. 1999; Schacter 1996).

Kalivas et al. (1993) proposed that incentive context and reward associations, which are integrated in the basolateral and extended amygdala and MOC, are translated into an incentive motivational state within a *motive circuit* (Kalivas et al. 1993). The circuit includes the NASshell, ventromedial subterritory of the ventral pallidum (VPm), and VTA DA ascending projections (see lower half of Fig. 6). All three regions are strongly, reciprocally, and preferentially connected with each other, as compared to other subregions of the striatum and pallidum (Deutch et al. 1993; Heimer et al. 1993). Functionally, these regions are interdependent in that the rewarding self-administration of electrical stimulation and stimulant drugs, as well as the initiation of locomotor activity, can be elicited from all three regions (Kalivas et al. 1993; Klitenick et al. 1992; Koob et al. 1993).

One major function of the integration of information in the NASshell is to encode the motivational *intensity* or *salience* of incentive stimuli (Kalivas et al. 1993; Robinson & Berridge 1993). As shown in Figure 6, this current motivational code established in the motive circuit can be transmitted from VPm to MOC 13 via the mediodorsal (MD) nucleus of the thalamus (Deutch et al. 1993; Groenewegen 1988; Groenewegen et al. 1999a; 1999b). Presumably, this code is merged with the most current representation of behavioral-reinforcement contingencies held in working memory by MOC 13, perhaps invoking a reintegration that reflects a change in motivational state (Damasio 1999; Depue & Collins 1999; Houk et al. 1995). The result of this processing would be a continual iterative updating, not only of incentive motivational intensity as integrated in the motive circuit, but also of reinforcement priorities and behavioral outcome expectations constructed in MOC 13.

Thus, a broad network of distributed neural structures is implicated in the modulatory influence of incentive motivation on appetitive behavior. Extending the ideas of others (Deutch et al. 1993; Groenewegen et al. 1990; 1991; 1999a; 1999b; Heimer 2003; Heimer et al. 1993; Kalivas et al. 1993), we proposed an MOC network illustrated in Figure 6 (Depue & Collins 1999). In keeping with the structure of other network models (Alexander et al. 1990; Goldman-Rakic 1987; Groenewegen et al. 1990; 1991; 1999a; 1999b; Mesulam 1990), the origin and termination site of this network lies within the prefrontal cortex, specifically MOC 13. Connections among all components of the network are topographically organized (Groenewegen et al. 1990; 1991; 1999a; 1999b), indicating that the basal ganglia-thalamocortical circuits of the ventral forebrain are congruent with the structure of more dorsally located cortical circuits outlined by Alexander et al. (1990). The MOC network incor-

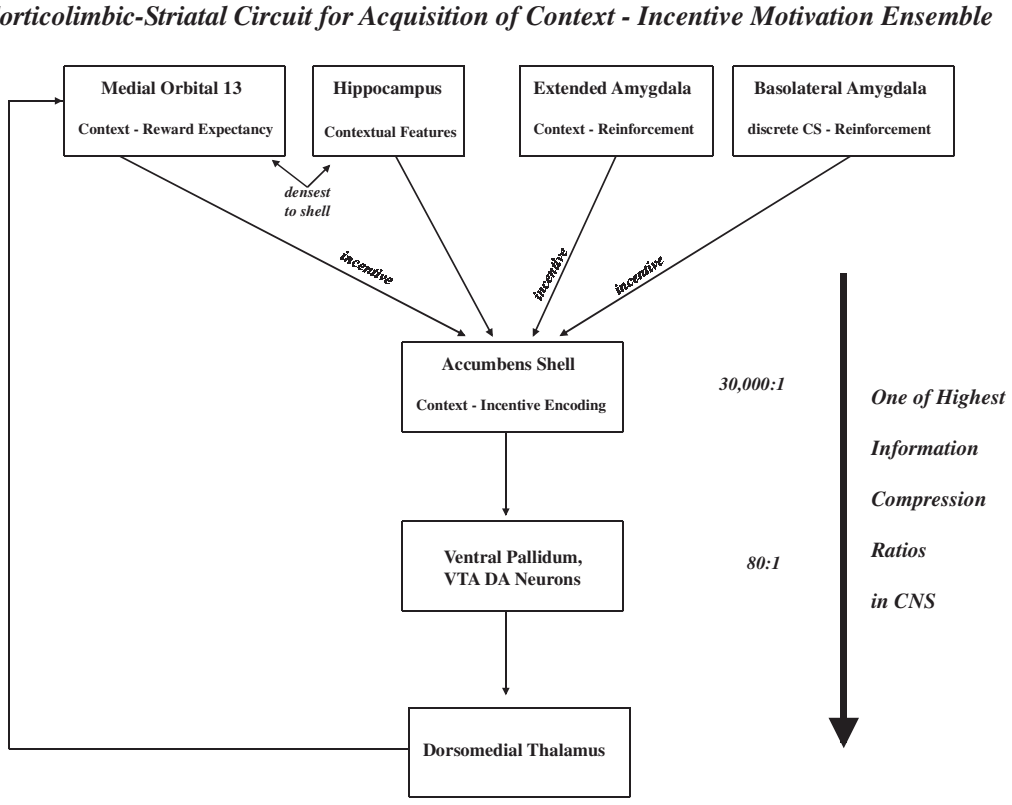

Figure 6. A schematic illustration of a medial orbital prefrontal cortical (MOC) network. Corticolimbic regions convey various types of contextual information to the NASshell in a ratio of 30,000:1 (there are 30,000 corticolimbic inputs to each NASshell spiny neuron dendrite), where information is bound into a contextual ensemble and encoded for incentive salience or value. There is a further compression of the ensemble as it is transferred from the NAS to the ventral pallidum in a ratio of 80:1. The ensemble is transmitted via the dorsomedial thalamus to the ventral prefrontal region of Brodmann's medial orbital 13, where it is merged with the highest representation of environmental reward contingencies and used to regulate incentive-motivational modulation of goal-directed behavior. See text for details. (Abbreviations: VTA = ventral tegmental area; DA = dopamine).

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porates three basic components: (1) a motive circuit, which integrates, maintains, and updates information to form an intensity-encoded incentive motivational state, (2) the VTA DA projection system, which facilitates the neural integration occurring in the motive circuit, as well as within network interactions more generally (Depue & Collins 1999), and (3) MOC 13, which performs higher-order regulation of network processes, which is consistent with similar proposals regarding the rat ventral prefrontal cortex (Deutch et al. 1993; Kalivas et al. 1993; Thorpe et al. 1983; Watanabe 1990).

6.2.1.6. Formation of a contextual ensemble in the MOC network: DA–glutamate interactions. The MOC network provides incentive-related contextual information that needs to be integrated (Heimer 2003). As shown in Figure 6, in one of the highest information compression ratios in the central nervous system (CNS) (Graybiel 1998; O'Donnell 1999), corticolimbic regions in the MOC network send approximately 30,000 afferents to each medium spiny neuron in the NASshell (more densely to the NASshell than to any other striatal region; Groenewegen et al. 1999a; 1999b), thereby binding that information into neural ensembles encoded for incentive magnitude or salience (Graybiel 1998; Jog et al. 1999; Kelley 1999a; 1999b; O'Donnell 1999; O'Donnell et al. 1999). Further compression occurs in the flow of information from the NAS to the ventral pallidum (in an 80:1 ratio) and then to the dorsomedial thalamus. The final contextual ensemble is transmitted to MOC 13, where it is represented at its highest level in association with reward expectancies (Goldman-Rakic 1987; Kalivas et al. 1999; O' Donnell 1999; O'Donnell et al. 1999; Schoenbaum et al. 1998; Thorpe et al. 1983; Watanabe 1990).

But just how is a contextual ensemble formed? The acquisition of contextual ensembles is strongly dependent on DA facilitation in the NASshell (Aosaki et al. 1994; Depue & Collins 1999; Everitt et al. 1999; Graybiel 1998; Jog et al. 1999; Meredith & Totterdell 1999; O'Donnell 1999; White 1997; Wickens et al. 1996). Brain regions carrying contextual information (right side of Figure 7) innervate the heads of dendritic spines of NASshell projection neurons using glutamate as a transmitter, and most of these efferents are excitatory to NAS function and are reciprocated (Calabresi et al. 1996; Christie et al. 1987; Davis 1992; Dudai 1989; Fuller et al. 1987; Goldman-Rakic 1987; Gronewegen et al. 1990; 1999a; 1999b; Groves et al. 1995; Houk et al. 1995; Kalivas et al. 1993; 1995; McGinty 1999; Meredith et al. 1993; Pierce et al. 1996; Schultz et al. 1995b; Sesack & Pickel 1990; 1992; Takagishi & Chiba 1991; Wickens & Kotter 1995). In addition, approximately 8,000 VTA DA projections also innervate the dendritic shaft or spinal necks of each NAS spiny neuron (Groves et al. 1995; Grace 1991; Meredith et al. 1993; O'Donnell 1999; O'Donnell et al. 1999; Schultz et al. 1995b; Sesack & Pickel 1990; 1992). As illustrated in detail only at the proximal level of the dendrite for basolateral amygdala input (but occurring at all other input levels as well), glutamate and DA can substantially increase release of each other via *N*-methyl-D-asparate (NMDA) and D1 receptors, respectively, located on terminals (Berretta & Jones 1996; Calabresi et al. 1996; 1997; Chowdhury & Fillenz 1991; Gracy & Pickel 1996; Groenewegen et al. 1999a; 1999b; Kalivas 1995; Krebs et al. 1991; Liste et al. 1995; Lu et al. 1997; McGinty 1999; Nestler & Aghajanian 1997; Pierce & Kalivas 1995; 1996; Sesack et al. 1994; Shi et al. 1999; Wickens et al. 1996; Zamanillo et al. 1999; Zhang et al. 1997).

As shown in Figure 7, a DA–glutamate interaction takes place via intracellular cascades in NAS spiny neurons, and facilitates the development of long-term potentiation (LTP) (Kelley 1999b; McGinty 1999). Indeed, such DA facilitation of glutamate release has been shown to be critical for the efficacy of glutamate via NMDA receptors to trigger LTP of amygdala and hippocampal afferents to the NAS (Bissiere et al. 2003; Groenewegen et al. 1999a; 1999b; Li et al. 2003; Malenka & Nicoll 1999; O'Donnell 1999; O'Donnell et al. 1999). This suggests that DA can affect the efficacy of corticostriatal transmission with long-term consequences that could affect striatum-based learning and memory (Graybiel 1998). Moreover, the DA–glutamate interaction at *basolateral* amygdala–NASshell synapses not only triggers LTP at those synapses, but also, because the dendritic location of the amygdala afferents is in close proximity to the soma (Groenewegen et al. 1999a; 1999b), it may have a strong depolarizing effect on the soma and proximal dendrite (see bottom part of Figure 7). This, in turn, increases the voltage-dependent effects of glutamate on NMDA receptors at more distal synapses on the dendrite arising from other contextual inputs (e.g., from MOC 13 and extended amygdala), thereby facilitating the strength of *coherently* activated input to the dendrite (associativity effects) (McGaugh 2000; Meredith & Totterdell 1999; O'Donnell 1999; O'Donnell et al. 1999). In this way, in conjunction with DA input, reward magnitude of *discrete, explicit* contextual stimuli carried by basolateral amygdala afferents to the NAS can facilitate the triggering of LTP in other contextual afferents to the NASshell (Gallagher & Holland 1994; McGaugh 2000).

Importantly, the facilitatory effect of DA on strengthening synaptic connections in the NASshell is dependent on the strength of the contextual afferent input. Lesions of the glutamatergic afferents representing contextual inputs to VTA DA or NAS regions prevent incentive-motivated responding, despite the fact that the intact VTA DA and NAS neurons are activated by a DA agonist (Dahlin et al. 1994; Kalivas 1995; Kalivas & Stewart 1991; Pert et al. 1992; Yoshikawa et al. 1991). As shown in Figure 8, DA's variation of effect as a function of strength of afferent input leads to an increased contrast between inputs (Begg et al. 1993; Houk et al. 1995; O'Donnell 1999; Schultz et al. 1995b; 1997; Wickens & Kotter 1995), and in this way appears to play an important role in selective strengthening of the corticolimbic antecedents associated with reward and with previously successful responses (Houk et al. 1995; Kalivas 1995; Pierce et al. 1996; Schultz et al. 1995b; 1997; Toshihiko et al. 1994; Wickens & Kotter 1995). Presumably, the more DA that is released in the NAS, (a) the greater the strengthening of contextual afferents on NAS dendrites, and (b) the greater the number of afferents facilitated. Hence, variation in DA input to the NAS will modulate the strength of the contextual ensemble, and hence the capacity of the ensemble to elicit incentive motivation, positive affect, and approach behavior. *This then represents the encoding by DA of incentive salience of contextual ensembles*.

The next obvious question, then, is what exactly activates DA release in the NAS so that the formation of a contextual ensemble can be facilitated? As illustrated in Figure 9, the same brain areas that provide contextual information to the NAS also provide afferent input to the VTA DA neurons,

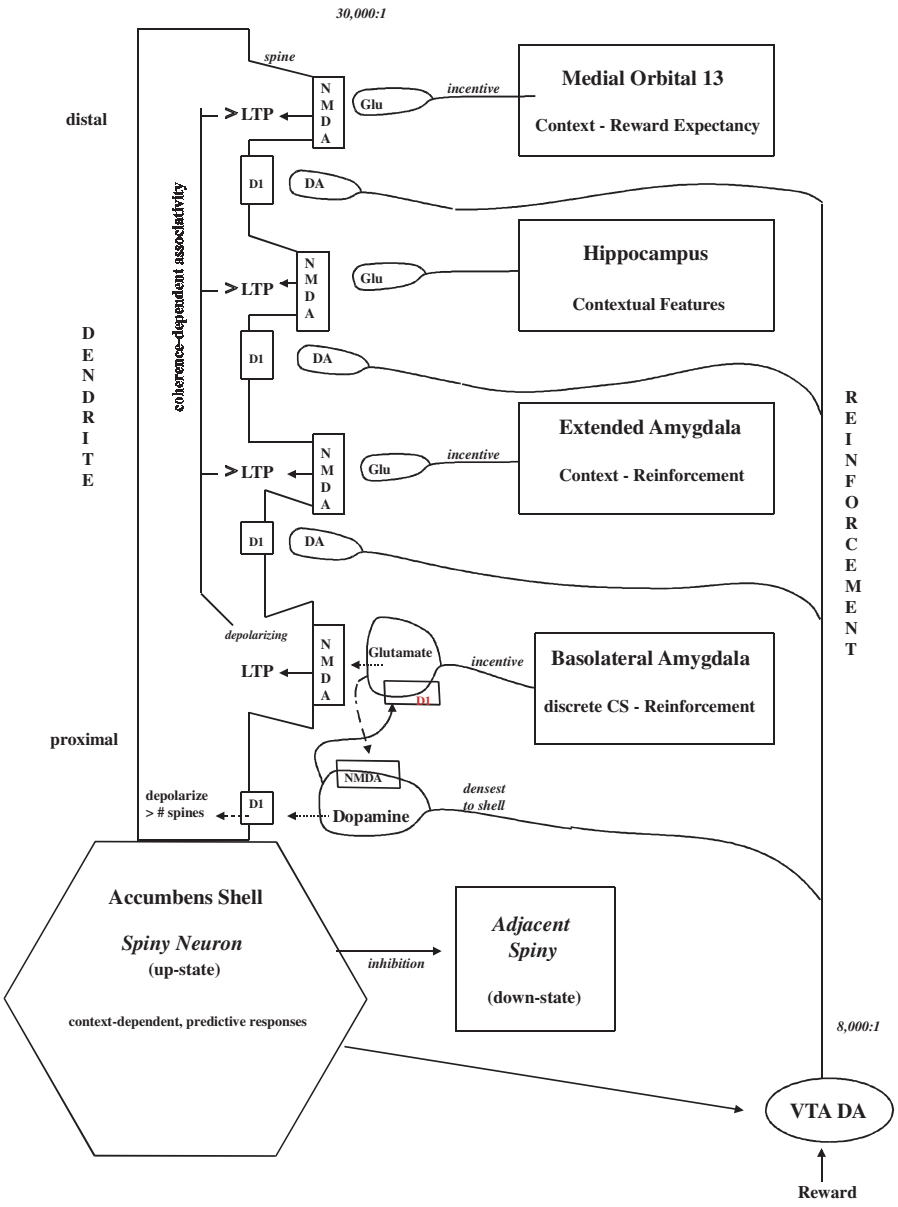

Figure 7. Binding of salient context with incentive motivation in the NASshell. The acquisition of contextual ensembles is strongly dependent on DA facilitation in the NASshell (Aosaki et al. 1994; Depue & Collins 1999; Everitt et al. 1999; Graybiel 1998; Jog et al. 1999; Meredith & Totterdell 1999; O'Donnell 1999; White 1997; Wickens et al. 1996). Corticolimbic brain regions carrying contextual information (right side of figure) innervate the heads of dendritic spines of NASshell projection neurons using glutamate as a transmitter; most of these efferents are excitatory to NAS function and are reciprocated. In addition, approximately 8,000 VTA DA projections also innervate the dendritic shaft or spinal necks of each NAS spiny neuron. As illustrated in detail only at the proximal level of the dendrite for basolateral amygdala input (but occurring at all other input levels, as well), glutamate and DA can substantially increase release of each other via NMDA and D1 receptors, respectively, located on terminals. In this way, DA is thought to strengthen the connections between inputs of the salient incentive context predictive of reward and incentive processes integrated in the NASshell. See text for details. (Abbreviations as in Figure 6, except Glu = glutamate; NMDA = N-methyl-D-aspartate glutamate receptor; LTP = long-term potentiation; D1 = D1 dopamine receptor).

thereby activating DA release in the NAS as a function of salient context. Also, direct projections from superior colliculus to midbrain DA neurons, activated by unpredicted, biologically salient stimuli, activate those DA neurons (Comoli et al. 2003). The optimal stimuli for activating VTA DA neurons are phasically occuring unpredicted unconditioned rewards, whereas fully predicted stimuli are ineffective (Schultz et al. 1995b). This can be seen during an experiment's progression: VTA DA neurons show (a) increased activity in the presence of neutral stimuli that consistently predict reward (an activation produced by corticolimbic contextual inputs to the VTA DA neurons), and (b) a concurrent decrease in activity to the unconditioned rewards, until DA responding has transferred completely to the con-

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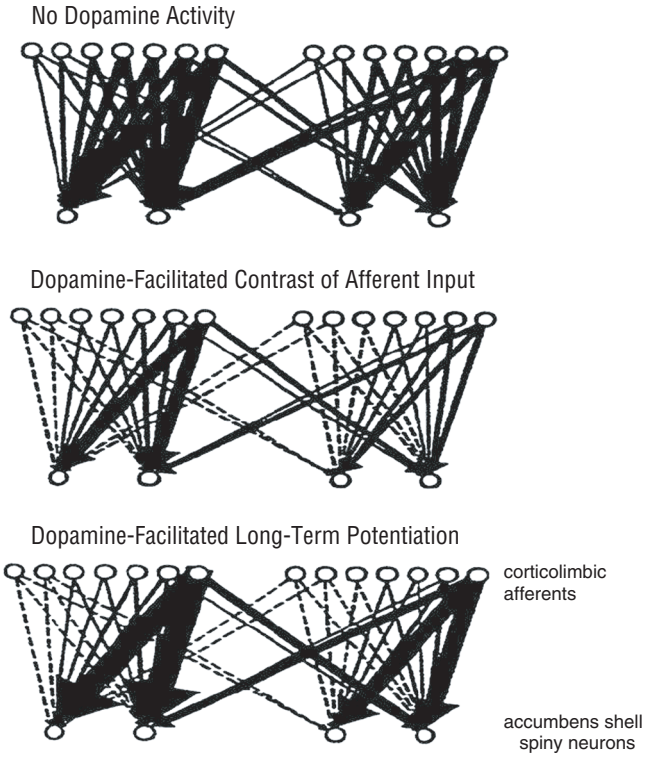

Figure 8. Progressive, differential effects of dopamine release on weak (depressing) and strong (facilitating) cortical and limbic inputs to NAS spiny neurons. At the bottom of the figure, the salient corticolimbic inputs to the NASshell have been enduringly strengthened by dopamine release via a process thought to be similar to long-lasting long-term potentiation. Adapted from Schultz et al. 1995b.

ditioned incentive stimuli (Schultz et al. 1995b; 1997). Importantly, the *orbital area* provides *the major source* of activation of VTA DA neurons (Carr & Sesack 2000; Taber et al. 1995), which increases the activity of VTA DA cells that project to the NASshell, central and basolateral amygdala, and VPm (Groenewegen et al. 1990; 1991; 1999a; 1999b). MOC input strongly regulates burst firing of VTA DA cells, which is associated with a doubling of DA release per action potential in the NAS (Gonon 1988; Johnson et al. 1992; Suaud-Chagny et al. 1992). Because DA release in the NASshell gates motivational information arriving from the amygdala and hippocampus (Mogenson et al. 1993), MOC regulation of VTA DA–NASshell projections has a significant impact on contextual ensemble formation. As also shown in Figure 9, orbital and other corticolimbic contextual afferent activation of VTA DA neurons is also part of the memory network of an ensemble, in that DA–glutamate interactions at synapses of these afferents on VTA DA neurons trigger NMDA-mediated L-LTP (Graybiel 1998; Kalivas & Alesdatter 1993; O'Donnell 1999; O'Donnell et al. 1999). As shown in Figure 9, this process is enhanced by the facilitatory action of somatodendritically released DA from VTA neurons onto D1 receptors on glutamate axonal terminals.

6.2.1.7. Summary. The complexity of the discussion in section 6 can be illuminated by presenting the essential elements in outline form. First, there are numerous corticolimbic brain regions, including the MOC, basolateral amygdala, extended amygdala and BNST, and hippocampus, that serve as depositories of contextual sensory information which is processed in various brain pathways. The corticolimbic regions associate the contextual information with reinforcement and established memories, and transmit that information via glutamatergic afferents to two neural sites: (a) DA neurons in the VTA, and (b) the dendrites of spiny neurons in the NASshell.

Second, the glutamatergic corticolimbic afferents carrying contextual information, if of sufficient salience, establish an interaction with DA long-lasting, long-term potentiated connections with VTA DA neurons. It is this associative connectivity that allows contexts predictive of reward to activate VTA DA neurons to release DA into the NASshell whenever those contexts occur in the future, thereby facilitating incentive–reward motivation, desire, and approach to rewarding objects.

Third, the same corticolimbic regions that activate VTA DA neurons also send afferents to NASshell dendrites, in a ratio of approximately 30,000 inputs to each NASshell dendrite. This input is accompanied by VTA DA neuron afferents that terminate on these same NASshell dendrites. DA release in the NASshell via corticolimbic activation of VTA DA neurons facilitates connection of corticolimbic contextual inputs to NAS dendrites, where again a DA–glutamate interaction can establish long-lasting, long-term potentiation of these connections if the corticolimbic inputs are sufficiently strong. The purpose of this anatomical convergence of corticolimbic and VTA DA afferents on NASshell dendrites is to bind the thousands of elements comprising the context together to form a contextual ensemble that is predictive of reward.

Importantly, the degree of corticolimbic activation of VTA DA neurons, and hence of DA release in the NASshell, is a function of the magnitude of reward associated with the current context. Thus, magnitude of reward is encoded in each contextual ensemble by the magnitude of DA release in the NASshell. Incentive-encoded contextual ensembles provide predictive information about the probability and magnitude of reward, and, in turn, modulate affective and behavioral responses via *proportional* activation of DA functioning. Indeed, in rats DA-agonist-induced NAS DA reactivity and behavioral responding are enhanced in diffuse contexts previously associated with reward (as in place preference) (Ahmed et al. 1993; 1995; Jodogne et al. 1994; Le Moal & Simon 1991). Thus, context can substantially modulate the unconditioned response to DA agonists.

Fourth, the importance of these processes is that each context in which reward occurs is represented by a memory network that is the incentive-encoded contextual ensemble. Therefore, when multiple contexts occur either externally or as central representations in working memory (e.g., simultaneous occurrence of several affiliative objects or their central representations), the NAS operates, together with VTA DA facilitation, as a selective mechanism, allowing expression of the ensemble with the greatest incentive salience. The selected contextual ensemble (associated with one of the affiliative objects) will thus gain passage around the MOC network – from the NASshell to the ventral pallidum, mediodorsal thalamus, to the MOC 13 region. MOC 13 then uses that ensemble information to construct the most current, highest-order representation of context-behavioral outcome expectations, and accordingly activates (or releases) behavior via several pathways. As behavioral approach to the goal (one of the affiliative objects)

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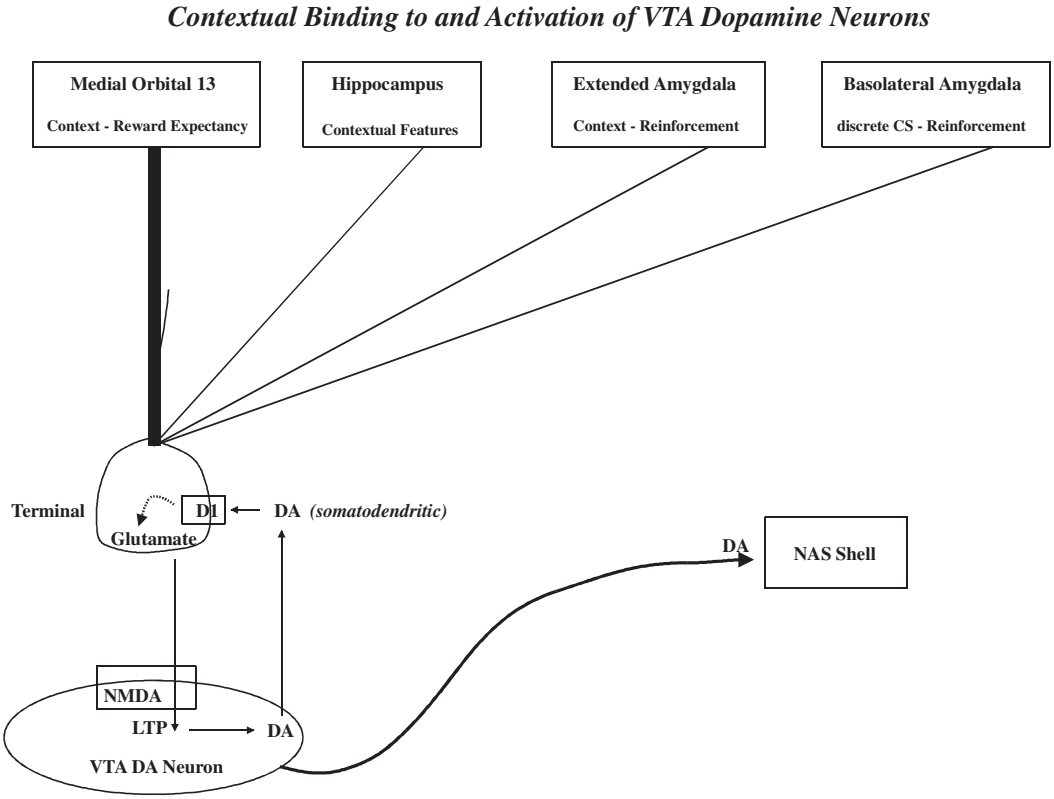

Figure 9. Contextual binding to and activation of VTA DA neurons. The same brain areas that provide contextual information to the NAS also provide afferent input to the VTA DA neurons, thereby activating DA release in the NAS as a function of context. The thicker line from Medial Orbital 13 indicates that the orbital area provides *the major source* of activation of VTA DA neurons, which increases the activity of VTA DA cells that project to the NASshell, central and basolateral amygdala, and VPm. Orbital regulation of VTA DA–NASshell projections has a significant impact on contextual ensemble formation. Orbital and other corticolimbic afferent activation of VTA DA neurons is also part of the memory network of an ensemble, in that DA–glutamate interactions at synapses of these afferents on VTA DA neurons trigger NMDA-mediated L-LTP, a process enhanced by the facilitatory action of somatodendritically-released DA from VTA neurons onto D1 receptors on glutamate axonal terminals. See text for details. (Abbreviations as in Figures 6 and 7, except NASshell = nucleus accumbens shell subterritory).

proceeds, the corticolimbic-striatal-thalamic-prefrontal circuit provides a means to update the contextual ensemble that currently has the highest incentive salience (which may be the same ensemble or not), and transmits that information to MOC 13, which then constructs an updated representation of context-outcome expectations.

Fifth, during approach to the goal, VTA DA release in the NASshell provides an incentive salience code for the ensemble, creates subjective feelings of incentive, desire, and reward, and facilitates forward locomotion. As the goal (affiliative object) is reached, μ-opiate release: (a) creates a state of consummatory reward that ensures incorporation of proximal contextual stimuli in the contextual ensemble, (b) helps encode the reward value of the entire contextual ensemble, and (c) creates a pleasurable state of liking and physiological quiescence, thereby bringing incentive-motivated approach to a gratifying conclusion. The outcome of this process is the acquisition and maintenance of a reward-encoded contextual ensemble that promotes approach to and interaction with the rewarding goal. When the goal is an affiliative object, such as a mate, a partner preference is established and maintained.

6.2.1.8. Dopamine and affiliative memories. The relevance of acquisition of contextual ensembles to the development of affiliative memories, in particular, is supported by several recent studies on the role of DA in partner preference and memory formation and consolidation. Sex serves as a potent reward in rats (Pfaff 1999; Sheffield et al. 1955), and male and female rats display mating-induced place preferences (Everitt 1990; Oldenburger et al. 1992). Interestingly, the act of mating, or even exposure to sensory stimuli from a male rat, strongly activates DA release particularly in the NAS in female and male rats and hamsters, an increase that can persist during the entire period of exposure to a male or female (Damsma et al. 1992; Lorrain et al. 1999; Meisel et al. 1993; Mermelstein & Becker 1995; Pfaff 1999; Pfaus et al. 1995; Vathy & Etgen 1989; Wenkstern et al. 1993). Mating in female prairie voles also leads to a partner preference, but the formation of the preference is time- and experience-dependent, requiring at least 14 hours of male exposure with 10–20 bouts of copulation during this interval (Insel & Hulihan 1995; Wang, Z. et al. 1999). In female prairie voles, increases of 50% in extracellular DA occurred in the NAS within 15 minutes of mating and continued to be high (by 30%) for 3 hours, and smaller increases (17% and 8%, respectively) were evident in nonestrus females simply exposed to a male, indicating that DA activation may occur as a result of both mating and social stimulus activation (Gingrich et al. 2000). In prairie voles, however, DA

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does not affect the ability of males and females to perform specific mating behaviors (Wang, Z. et al. 1999). Rather, even in the absence of mating, DA agonists injected into the NAS dose-dependently facilitated the development of partner preference in female prairie voles, mimicking the effects of mating (Gingrich et al. 2000). Conversely, DA antagonists administered specifically in the NAS directly before or immediately after mating did not affect mating behavior per se, but did block the development of partner preference if administered bilaterally and if active drug levels endured for approximately 24 hours in the NAS (Gingrich et al. 2000; Insel et al. 1995; Wang, Z. et al. 1999). The need for prolonged DA antagonism is consistent with the findings of a surge of DA release with repeated mating after 12 hours of mating (Wang, Z. et al. 1999). Moreover, the fact that administration of a DA antagonist 24 hours after mating, but directly prior to the preference test, did not block partner preference suggests that DA blockade is affecting the formation and/or consolidation of the mate-reward associative memory during the first 24 hours of mating, rather than olfactory or other discrimination thresholds (Wang, Z. et al. 1999) or memory retrieval (McGaugh 2000; Schacter 1996). Together, these results suggest that DA plays a necessary role in the formation and consolidation of a mating-induced partner preference in female rodents of several species, although the results are most clear with respect to the prairie vole, in which a D2 receptor mechanism is supported (Gingrich et al. 2000; Wang, Z. et al. 1999).

Exactly which processes are being facilitated by DA during and after mating is not empirically known. One possibility is a direct effect on more basic sensory detection, which would affect affiliative recognition processes. A partner preference in female prairie voles requires olfactory detection of social cues (Williams et al. 1992), and thus DA enhancement of such sensory information may influence mate recognition processes and thereby associative phases of mate-reward assoication. DA plays an important role in such processes. Stimulation of the accessory olfactory system causes release of DA in the NAS (Mitchell & Gratton 1992b), and NAS DA is important for affiliative identity in male rats (Ploeger et al. 1991). In addition, D2 agonists decrease (Doty & Rissler 1989) and D1 agonists increase (Doty et al. 1998) olfactory sensitivity. However, as noted in section 6.2.1.8, the fact that administration of a DA antagonist 24 hours after mating, but directly prior to the preference test, did not block partner preference suggests that DA blockade is not affecting these more basic sensory processes per se. Rather, DA may be affecting the incorporation of the sensory information in the formation and/or consolidation of the mate-reward associative memory during the first 24 hours of mating. Thus, DA may act directly on processes involved in formation and/or consolidation of mate-reward associations comprising part of a contextual ensemble in a fashion identical to the well-established role of NAS DA in the formation of conditioned place preference (Le Moal & Simon 1991). Indeed, mating, which increases NAS DA, can induce place preference in male and female rats and in female hamsters, an effect that can be blocked by DA antagonists (Agmo & Gomez 1993; Meisel & Joppa 1994; Meisel et al. 1993; Oldenburger et al. 1992; Paredes & Alonso 1997). In sum, these studies suggest that DA plays a facilitatory role in the acquisition of mate-reward associations that is concordant with DA's role in the formation and incentive encoding of contextual ensembles in general.

6.3. Enhancing the incorporation of affiliative stimuli in contextual ensembles

The above discussion on the formation of contextual ensembles that predict reward is a generalized case. What seems important to understand, however, is the manner in which specific contextual stimuli that are selected for inclusion in an ensemble are weighted or enhanced as a function of the target class of stimuli that currently define the behavioral goal. In a sociosexual context, it is advantageous, relative to other sensory cues, to weight affiliative stimuli as particularly salient elements of the total context, as a means of ensuring their incorporation in contextual ensembles. We review several mechanisms that may provide the means for enhancing affiliative stimuli in contextual ensembles. These include: (1) a network of brain regions that appear to integrate affiliative stimuli and transfer their representation to the nucleus accumbens (the medial extended amygdala in sect. 6.3.1.), (2) the role of opiates, presumably carrying *affiliative* information, in facilitating DA and glutamate functioning in the nucleus accumbens (sect. 6.3.2), and (3) the functional roles of gonadal steroids, oxytocin, and vasopressin in perception and memory formation in the presence of affiliative stimuli (sect. 6.3.3).

6.3.1. Contribution of the medial extended amygdala. An interconnected network of brain regions integrates affiliation-relevant exteroceptive and interoceptive sensory information that modulates the expression of a host of affiliative behaviors. These regions include nuclear groups in the *medial* division of the extended amygdala (MXA, see Fig. 5), the lateral septum, mPOA, the anterior hypothalamus, the ventromedial nucleus and adjacent ventrolateral hypothalamus, and the PAG. All regions are reciprocally interconnected, have neurons that contain gonadal hormone receptors, and modulate more than one type of affiliative behavior (De Olmos & Heimer 1999; Ferguson et al. 2001; Larsson & Ahlenius 1999; McDonald et al. 1999; Newman 1999; Panksepp 1998; Pfaff 1999; Rolls 1999). Modulatory rather than strict mediating action of this network is suggested by the fact that so many affiliative behaviors are influenced by manipulations of regions in the network, including male and female courtship and sexual behaviors (sniffing, mounting, lordosis, copulation, ejaculation), maternal behavior, nest building, grooming, territorial marking, territorial aggression, mate guarding, and maternal and paternal aggression (Larsson & Ahlenius 1999; Newman 1999; Panksepp 1998; Rolls 1999). Corticolimbic regions in the network (e.g., structures of the MXA) may serve to integrate various sensory inputs for the purpose of modulating regions that integrate sociosexually-relevant neuroendocrine and autonomic functions (e.g., the mPOA-anterior hypothalamic continuum, the nuclei of the medial and lateral hypothalamus, and pituitary function), and, in turn, influence a host of social behavior patterns mediated by PAG circuits (Bandler & Keay 1996; de Olmos & Heimer 1999; Larsson & Ahlenius 1999; McDonald et al. 1999). The MXA may be particularly important in integrating contextual affiliative stimuli, and providing that representation to the NAS for integration into a comprehensive contextual ensemble related to reward. As shown in Figure 10, the MXA includes the medial amygdaloid nucleus and the medial bed nucleus of the stria terminalis, in addition to cell columns between these two structures, both within the stria

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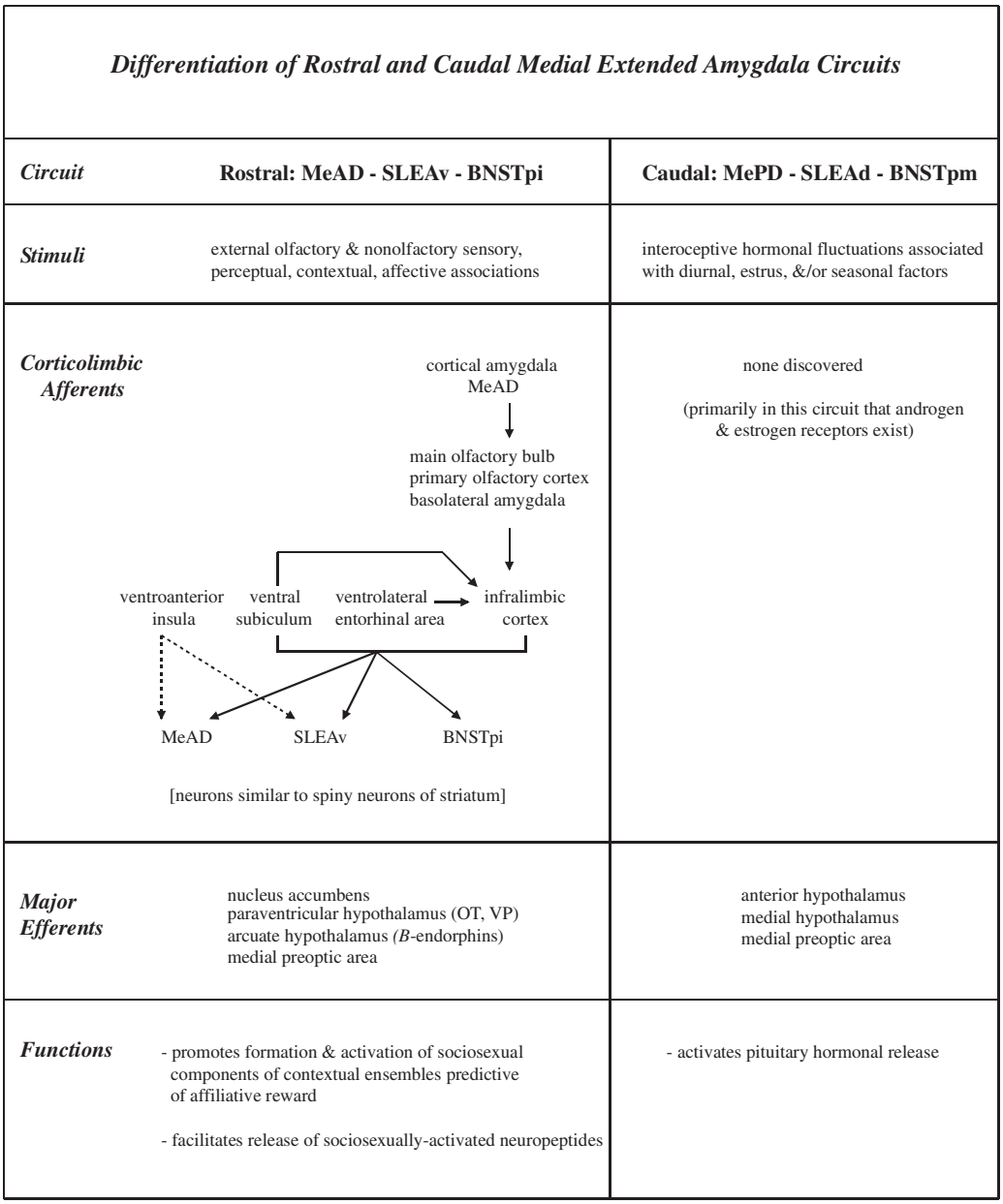

Figure 10. Differentiation of rostral and caudal medial extended amygdala circuits. See text for details and abbreviations.

terminalis and in the subpallidal or ventral sublenticular area, whereas the cortical and basolateral nuclei of the amygdala are not included (de Olmos & Heimer 1999).

There are two subdivisions within the MXA (see Fig. 10; Newman 1999): a *rostral* circuit, extending from the anterior dorsal subregion of the medial nucleus of the amygdala to the posterior intermediate BNST, including ventral aspects of the sublenticular area (MeAD–SLEAv–BNSTpi); and a *caudal* circuit, extending from the posterior dorsal subregion of the medial nucleus of the amygdala to the posterior medial BNST (MePD–SLEAd–BNSTpm). Structures in the *rostral* circuit show increased Fos protein expression in response to mating – as well as aggressive encounters in both male and female hamsters after tail pinching in rats, which enhances affiliative behaviors – but not to nonsocial motor and sensory activity alone. Lesions of the *caudal* circuit completely abolish mating (mounting, ejaculation) and chemosensory investigation in rodents, and the behavior cannot be restored by injections of testosterone or estradiol. Therefore, this appears to be an essential circuit for the activation of various sociosexual behaviors. Also, structures in the *caudal* circuit show increased Fos protein expression specifically to chemosensory investigation or ejaculation during mating sequences, and lesions of these structures modify only the temporal pattern of mating behavior rather than the performance of the behaviors themselves. Moreover, it is primarily in the *caudal* circuit that androgen and estrogen receptors are localized, and in which testosterone or estradiol injections restore the temporal patterning of mating behaviors. Therefore, the *caudal* circuit may be strongly modulated by hormonal fluctuations associated with diurnal, estrus, and/or seasonal factors.

As summarized in Figure 10, of significance with respect to the formation of contextual ensembles, *only* the *rostral*

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circuit structures receive corticolimbic projections, and may have cells similar to the spiny neurons of the striatum (see review by McDonald et al. 1999). Corticolimbic projections originate from the ventral subiculum and ventrolateral entorhinal area (projecting to all three areas of the circuit), the ventroanterior insular cortex (projecting to MeAD and SLEAv), and the infralimbic cortex (projecting to all three circuit areas). The rat infralimbic cortex, which is homologous to the primate medial orbital cortex (Depue & Collins 1999), is a particularly important integration region as a source of contextual input to the *rostral* circuit. The infralimbic cortex receives: (a) an array of nonolfactory sensory, perceptual, and relational contextual input from the ventral subiculum, ventrolateral entorhinal cortex, and basolateral complex of the amygdala; and (b) similar to the anterior insular cortex, olfactory contextual input directly from the primary olfactory cortex, the main olfactory bulb, and indirectly from the latter via the cortical nucleus of the amygdala and the MeAD. Furthermore, the infralimbic cortex is also a major source of information to the central division of the extended amygdala, thereby having the capacity to strongly influence activity in both divisions of the extended amygdala.

On the basis of these differential patterns of corticolimbic afferentation to the two subdivisions of the MXA, McDonald et al. (1999) concluded that, in response to mainly interoceptive hormonal signals, the *caudal* circuit is mainly involved in regulating pituitary hormonal release during sociosexual interactions via projections to the anterior and medial hypothalamus and mPOA. In contrast, the *rostral* circuit is proposed to be involved in regulating sociosexual behavior by external affiliative stimuli. We would add the possibility that such affiliative stimulus input is integrated in the structures of the *rostral* circuit, and that integrated information may then modulate circuit projections to the NASshell and to regions controlling release of sociosexually-activated neuropeptides, such as to the paraventricular nucleus of the hypothalamus, as a means of activating oxytocin and vasopressin release, as well as to to the β-endorphin neurons in the arcuate nucleus and mPOA (McDonald et al. 1999). An example of how this integrated system might operate is instructive: Male rats exposed to a receptive female manifest an increase in DA release selectively in the NAS, *but only in sexually naive animals* (Larsson & Ahlenius 1999). Sexually naive animals will need to acquire a contextual ensemble that encodes sensory features of receptivity with incentive salience. According to McDonald et al.'s (1999) findings, sensory features of the receptive female are likely integrated in the *rostral* circuit, and the known projections from this circuit to the NAS may influence DA neurotransmission in the NAS, *thereby facilitating the formation of a contextual ensemble informed by affiliative stimuli* (de Olmos & Heimer 1999).

6.3.2. Contribution of opiates. We reviewed in section 6.1.2 that *u*ORs are activated strongly by affiliative stimuli, may mediate affiliative reward, and provide an unconditioned reward for establishing conditioned place and mate preferences. Facilitation of associative processes between affiliative stimuli and reward in corticolimbic structures would be critical to the process whereby stimulus characteristics of others take on positive valence. Indeed, opiate release is highly conditionable (Nelson & Panksepp 1998; Shippenberg & Elmer 1998), and this conditioned release of opiates can be induced by stress, a finding with implications for relapse in opiate addicts (Shaham et al. 2000). For example, merely the anticipation of daily cocaine self-administration sessions resulted in increased opioid receptor occupancy in the NAS, thereby indirectly indicating increased release of opiates in the NAS (Gerrits et al. 1999). Also, in a brain imaging study of heroin-addicts (Sell et al. 1999), both heroin (unconditioned stimulus) and salient conditioned cues (video of drug paraphenalia) activated the same midbrain areas centered in the VTA DA region and PAG, both of which are rich in ORs (Koob 1992; Legradi et al. 1996). Similar brain regions were activated in opiate addicts in response to monetary reward (Martin-Soelch et al. 2001) and in normal humans when a previously neutral visual cue acquired behavioral salience (Morris et al. 1997). Moreover, the μOR-agonist morphine versus *u*OR-antagonist naltrexone promotes or blocks, respectively, the establishment of odor–mother and male–female recognition associations (Byrnes & Bridges 2000; Leyton & Stewart 1992; Nelson & Panksepp 1998; Panksepp 1998). Such conditioning can take place very early in development, when brain levels of opiates at birth in normal human infants are 100 times greater than those at older ages (Waterhouse et al. 1996). That opiates may provide the reward involved in mother–infant conditioning is suggested by the fact that pairing of a novel odor or taste with morphine induced a conditioned preference in 4-day-old rats, and naltrexone blocked this preference if it preceded morphine at conditioning or if it was given at test (Blass 1992; Kehoe & Boylan 1994). Similar processes appear to operate in human newborns, suggesting that newborns can extract from caretaker interactions certain features that regularly predict the delivery of a substance that causes release of endogenous opiates, and that loss of this predictive quality is disturbing, as judged by crying (Blass 1992). Thus, these *u*OR-dependent processes may play a significant role in not only the *establishment* but also the *maintenance* of long-term affiliative bonds via the facilitation of affiliative contextual ensembles. Therefore, it is an important question as to how opiates might accomplish this facilitation.

B-endorphin neurons in the medial basal arcuate nucleus have access to many corticolimbic sites that are involved in processing contextual stimuli, and their neurons are activated by the MXA, which is involved in binding sociosexual contextual stimuli (de Olmos & Heimer 1999; Larsson & Ahlenius 1999; McDonald et al. 1999). As illustrated in Figure 11, there are at least three specific ways in which opiates may act via *u*ORs to facilitate acquisition of affiliative contextual ensembles and affiliative memories. First, as shown in Figure 11a, in the NASshell and its small-celled islands, *u*ORs are localized mainly to dendrites or dendritic spines that also express type 1 NMDA receptors (NMDAR1) (Gracy & Pickel 1996; Gracy et al. 1997; Svingos et al. 1996; Voorn et al. 1996). When *u*ORs are activated by *B*-endorphin or other agonists, postsynaptic NMDA-induced currents to glutamate are potentiated, which represents the main action of *u*ORs in the NASshell (Martin et al. 1997). In the NAS and other brain regions, this form of potentiation appears to be a result of the ability of *u*OR ligands to increase postsynaptic responses to NMDA receptor stimulation through activation of both protein kinase C (PKC) and of calcium/calmodulin-dependent (CaM) kinase, and at least in the trigeminal nucleus, the enhanced responses last as long as 60 minutes after agonist washout (Chen &

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Huang 1991; Kitamura et al. 1993; Mao et al. 1994; 1995; Martin et al. 1997). This effect is believed to depend on the ability of PKC to remove the Mg^{2+} block from the NMDA receptor, allowing the influx of Ca^{2+} as a trigger for the development of LTP (Chen & Huang 1991; Malenka & Nicoll 1999; McGaugh 2000). Thus, at least one population of spiny neurons in the NASshell is subject to dual modulation by *u*OR and NMDAR ligands. Because *B*-endorphin neurons are activated by affiliative stimuli, *u*OR activation in the NASshell may potentiate affiliative corticolimbic contextual inputs mediated by glutamate release on NMDAR in the NAS (Jaskiw et al. 1991).

Second, as illustrated in Figure 11b, again in the NASshell, most spiny neuron dendrites that express *u*ORs without colocalized NMDAR1 receive input from axons that (a) express NMDAR1, and (b) have morphological features typical of DA afferents (Bouyer et al. 1984; Freund et al. 1984; Sesack et al. 1994). Consistent with the axonal terminals being DA afferents is that DA terminals in the NASshell do express NMDAR1 (Gracy & Pickel 1996). Moreover, DA D_1 and D_2 agonists injected into the NAS increase μOR mRNA expression (Azaryan et al. 1996), an effect that may be a result of either (i) postsynaptic DA receptor activation-induced potentiation of *u*OR response to ligands, and/or (ii) activation of presynaptic DA receptors localized on opiate afferents (see Fig. 11b) (Curran & Watson 1995). Alternatively, μOR agonists (morphine) administered in the NAS increase NAS DA release, support conditioned place preference, and sensitize DA receptor reactivity to DA agonists in the NAS (Cunningham & Kelley 1992; Spanagel et al. 1991). This DA-opiate interaction in the NAS would thereby represent a DA-mediated potentiation of the effects of opiates on NAS dendritic *u*ORs (Azaryan et al. 1996; Sharp et al. 1995). Consistent with this interaction, opiate antagonists reduce the effect of estrus female olfactory cues on DA release in the NAS (Mitchell & Gratton 1991). Thus, because *B*-endorphin neurons are activated by affiliative stimuli, reciprocal enhancement between *u*-opiate and DA afferents to NASshell dendrites would increase the probability that affiliative inputs to the dendrite become part of the contextual ensemble.

Third, as shown in Figure 11c, activation of *u*ORs and *d*ORs localized on GABA-A interneurons in the VTA dose-dependently inhibits the GABA-induced inhibition of DA neurons – a net disinhibition of VTA DA neuron firing (Bals-Kubik et al. 1993; Johnson & North 1992; Shippenberg & Elmer 1998). This enhances VTA AMPA receptors and hence DA neuron sensitivity to glutamate, particularly VTA DA neurons projecting to the NAS, and this is a necessary component of conditioning of opiate-mediated reward (Carlezon et al. 1997; 2000; Leone et al. 1991; Zhang et al. 1997). For example, injections of morphine or the selective *u*OR agonist DAMGO into the VTA, particularly its rostral zone (Carlezon et al. 2000), induce a conditioned place preference, whereas injections that are dorsal or lateral to the VTA or are placed in the amygdala, medial prefrontal cortex, lateral hypothalamus, caudate-putamen, ventral pallidum, or substantia nigra do not (Bals-Kubik et al. 1993; Shippenberg & Elmer 1998). The importance of VTA *u*ORs for conditioned place preference was underscored by the prevention of morphine-induced conditioned place preference when VTA *u*ORs were blocked. In any case, *u*-opiate-induced enhancement of VTA DA neuron reactivity to salient stimuli could have two effects related to

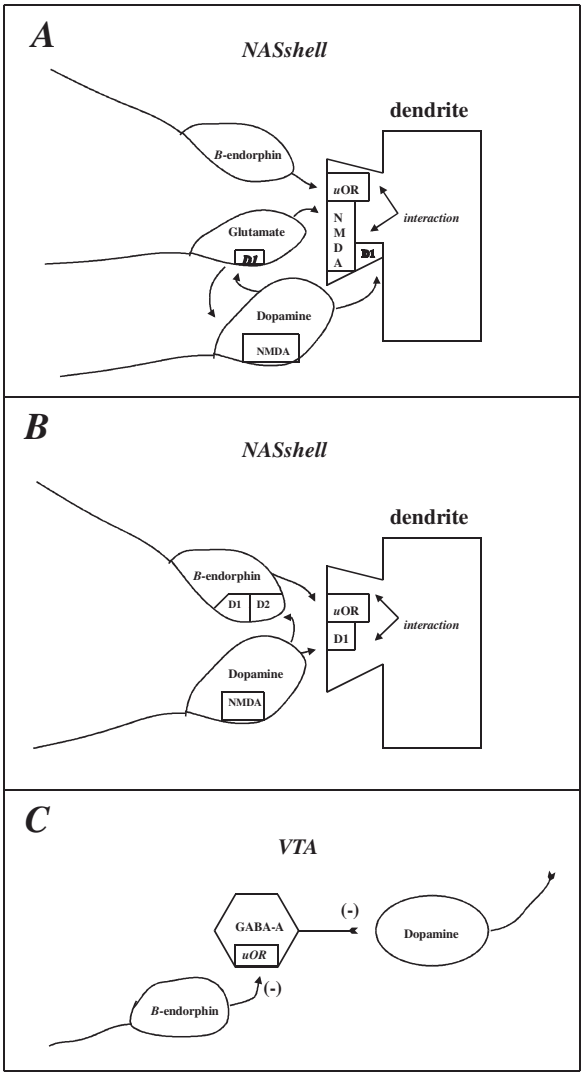

Figure 11. Dopamine and opiate interactions in the NAS and VTA. Three types of interaction are shown. Part A = in the NASshell μORs are localized mainly to dendrites or dendritic spines that also express type 1 NMDA receptors (NMDAR1). When μORs are activated by β-endorphin or other agonists, postsynaptic NMDA-induced currents to glutamate are potentiated, which represents the main action of μORs in the NASshell. In the NAS and other brain regions, this form of potentiation appears to be a result of the ability of μOR ligands to increase postsynaptic responses to NMDA receptor stimulation; Part B = in the NASshell, most spiny neuron dendrites that express μORs without colocalized NMDAR1 receive input from axons that: (a) express NMDAR1, and (b) DA afferents. DA D1 and D2 agonists injected into the NAS increase μOR mRNA expression. Alternatively, μOR agonists (morphine) administered in the NAS increase NAS DA release. This DA-opiate interaction in the NAS would thereby represent a DA-mediated potentiation of the effects of opiates on NAS dendritic μORs; Part C = activation of μORs localized on GABA-A interneurons in the VTA dose-dependently inhibits the GABA-induced inhibition of DA neurons – a net disinhibition of VTA DA neuron firing. This enhances VTA AMPA receptors, and hence DA neuron sensitivity to glutamate, particularly VTA DA neurons projecting to the NAS. See text for details. (Abbreviations as in Figures 5–8, except μOR = mu-opiate receptor; GABA-A = gamma-amino-butyric acid type A receptor).

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formation of affiliative memories: (1) enhanced somatodendritic DA release at the level of the VTA would facilitate the heterosynaptic plasticity that connects corticolimbic afferents carrying salient context to VTA DA neurons, as illustrated in Figure 9; and (2) enhanced VTA DA-NAS neurotransmission would facilitate corticolimbic afferents carrying salient context to NASshell spiny neuron dendrites (Carlezon & Wise 1996; Jaeger & van der Kooy 1996; Kuribara 1996; Leyton & Stewart 1992 Sora et al. 1997). Because β-endorphin neurons are activated by affiliative stimuli, *u*-opiate enhancement of VTA DA-NAS release would strengthen affiliative stimulus input to the NAS, in particular. *In all of these cases, opiate potentiation of glutamate and DA processes in the VTA and/or NASshell may facilitate specifically the incorporation of sociosexual and affiliative stimuli into a developing ensemble that represents the salient context of reward.*

6.3.3. Contribution of gonadal steroids, oxytocin, and vasopressin

6.3.3.1. Gonadal steroids. In many mammalian species, acute or prolonged internally- or sociosexually-induced gonadal steroid (estrogen, progesterone, testosterone) secretion temporally sets the occasion for most types of sociosexual interaction and the sensititivity to affiliative stimuli. It also can play a permissive role in the action of other sociosexually-related neuropeptides in a regionally specific manner, such as for oxytocin (OT), vasopressin (VP), and opiates. For example, depending on species but including humans, peripheral and central OT synthesis rate, release, and receptor proliferation, density and affinity; OT-induced sexual and maternal behaviors and reduction in autonomic arousal; mating-, grooming-, and stress-induced OT release; VP-induced aggression in male rodents; increased functioning and dendritic processes of OT and VP neurons; and opiate functioning can all be dependent, *at least in initial phases* of sociosexual interactions on gonadal steroid levels (Argiolas & Gessa 1991; Bale & Dorsa 1995a; 1995b; Bridges & Ronsheim 1987; Caldwell et al. 1989; 1994; Carter et al. 1995; 1997; de Kloet et al. 1986; Gorzalka & Lester 1987; Insel 1992; 1997; Insel et al. 1993; 1997; Jezova et al. 1996; Jirkowski et al. 1989; Johnson 1992; Keverne 1996; McCarthy 1995; McCarthy & Altemus 1997; Ostrowski 1998; Pedersen 1997; Petraglia et al. 1985; Sinchak & Micevych 2001; Wang & Devries 1993; Witt 1995; 1997; Young et al. 1998).

In addition to the effects of steroid hormones on the activity of neurons that express steroid receptors (Fleming et al. 1999; Hull et al. 1995), as illustrated in the left half of Figure 3, the internal hormonal milieu provided by gonadal steroids may play permissive and/or facilitatory roles in sensitizing sensory, perceptual, and attentional processes involved in detecting and transmitting external affiliative stimuli as a function of developmental period, circadian and circannual rhythms, reproductive cycle, and affiliative experience. For example, concerning permissive hormonal effects, male faces and odors evoke robust neurochemical release in the mediobasal hypothalamus of the ewe during, but not outside of, estrus (Fabre-Nys et al. 1997). Similarly, odors of lambs do not influence release of neurotransmitters or neuronal activity in adult sheep before giving birth, but they do after birth because of plastic changes in the olfactory bulb (Kendrick et al. 1992; 1997; Levy et al. 1992). In a similar vein, virgin rats are repelled by pup odors but lactating females are not (Agren et al. 1997), and maternal recognition of rat offspring depends on both gonadal hormones and pup sensory cues (Calamandrei & Keverne 1994). And Ostrowski (1998) cites evidence that hormonal priming of the brain during pregnancy facilitates expression of human maternal behavior. But, in general, in primates and humans sexual and parental functions are much more loosely linked to gonadal steroid levels (Keverne 1996), indicating that neurobiological organization of sociosexual processes may vary in these species, and that the role of gonadal steroids may in these cases be more modulatory than permissive.

Perceptual preferences for certain affiliative cues may also rely in part on internal hormonal milieu. For example, human children show a preference for adult faces before puberty, whereas after puberty they prefer infantile faces that possess neotenous features (Fullard & Reiling 1976). After puberty, individuals prefer cues of potential sexual partners that may be viewed as exerting permissive or facilitatory effects on mate selection. Besides the permissive effects of physical cues related to apparent youth, health, and hence fertility (Buss 1989), human females are attracted to males, as measured by odor preference, who have major histocompatibility complex factors (e.g., human leukocyte antigen or HLA) different but complementary to their own, which may benefit their offspring's immune function by protecting against pathogens or may function as a mechanism to avoid inbreeding (Wedekind et al. 1995). But this effect is also dependent on hormonal variation related to the menstrual cycle. Women on oral contraceptives preferred the odors of males who had *similar* HLA to themselves (Wedekind et al. 1995). Likewise, recognition and bonding in mother–infant pairs is facilitated by HLA-influenced odor (Beauchamp & Yamazaki 1997). Furthermore, when perception of three categories of visual stimuli (nude men, babies, and stimuli related to body care) was measured in women across the menstrual cycle, it was found that, relative to other phases, during the preovulatory phase the ability to recognize sex stimuli was improved and stimuli were incorrectly labeled as sex stimuli (Krug et al. 1994). Thus, gonadal steroids may permit or facilitate the perception of sociosexual stimuli and the activation of sociosexually relevant neuropeptides, thereby enhancing their inclusion in contextual ensembles.

6.3.3.2. Oxytocin and vasopressin. OT and VP play a significant role in many sociosexual interactions, and they both are activated by projections arising from the MXA (de Olmos & Heimer 1999; Larsson & Ahlenius 1999; McDonald et al. 1999; Newman 1999). From a phylogenetic point of view, OT and VP, which are found only in mammals (Insel 1997), are nevertheless two of the most highly conserved hormones (Argiolas & Gessa 1991), and across mammalian phylogeny, the limbic structures that manifest OT and VP receptors are largely unchanged (Insel 1997; LeDoux 1987; 1998), indicating that human sociosexual processes are likely influenced by these neuropeptides. Most neuroanatomical and behavioral data on OT and VP, however, relate to rodents, and significant differences occur within rodent species in receptor distributions of OT and VP, and among practically every other mammalian species (Carter et al. 1995; 1997; Richard et al. 1991; Russell & Leng 1998). Indeed, there are important species differences between

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rodents and anthropoid primates in the hormonal mechanisms mediating sexual behavior (Dixson 1998). Therefore, extension to human behavior requires empirical study.

In rodents and humans, a host of unconditioned *and* conditioned sociosexual stimuli elicit OT neuron activity, including vaginocervical stimulation at birth, genital and breast stimulation and copulation, olfactory stimuli, and suckling (Argiolas & Gessa 1991; Carter 1992; Carter et al. 1995; Forsling 1986; Insel 1992; 1997; Insel & Shapiro 1992; Keverne 1996; Keverne et al. 1983; McCarthy & Altemus 1997; Nissen et al. 1998; Richard et al. 1991; Witt 1995; 1997; Young et al. 1998). Nonsexual stimuli such as grooming, nongenital touch or light pressure, massage, hair stroking, pleasant vocalizations, warmth, and rat pup and lamb exposure can also induce OT release and OT dendritic arborization (Carter 1992; Carter et al. 1995; 1997; Insel 1992; Modney & Hatton 1991 Nelson & Panksepp 1996; Nissen et al. 1998; Uvnas-Moberg 1997). Such stimuli can also induce synaptic modifications in OT neurons of the supraoptic nucleus, such as increased dendritic synapses and an enhancement of electrical coupling between OT neurons (Fleming et al. 1999).

In turn, intracranially injected OT or unconditioned or conditioned stimulus-induced OT activity facilitates numerous sociosexual functions in male and female rodents, sheep, and humans, including milk ejection, uterine contractions, parturition, lordosis, copulation and ejaculation, rat maternal behaviors of retrieval and grouping of pups, licking of pups, nest building, and crouching, as well as affiliation patterns of mother–infant interaction, partner preference, offspring preference in sheep, and nonsexual social contact (Argiolas & Gessa 1991; Carter 1992; Carter et al. 1995; 1997; Englemann et al. 1998; Gorzalka & Lester 1987; Insel 1997; Insel & Hulihan 1995; Insel & Shapiro 1992; Insel et al. 1997; Kehoe & Blass 1989; Kendrick 2000; Kendrick et al. 1992; Keverne & Kendrick 1994; McCarthy & Altemus 1997; McCarthy et al. 1992; Meaney 2001; Nishimori et al. 1996; Nissen et al. 1998; Richard et al. 1991; Uvnas-Moberg 1997; Williams et al. 1994; Winslow & Insel 1991a; Winslow et al. 1993; Witt 1997; Witt & Insel 1991; Witt et al. 1990; 1992; Young et al. 1998). At least in female prairie voles, central administration of OT appears to be a critical component in the development of a partner preference even in the absence of mating (see below in this section on DA effects) (Insel & Hulihan 1995).

Less is known about VP, but in male prairie voles, mating is associated with an increase in VP mRNA in neurons that project to the lateral septum, and therefore, an increase in VP synthesis and release (Young et al. 1998). Also in male prairie voles, VP and VP antagonists promote or block, respectively, aggressive territorial mate protection, partner preference even without mating, paternal care, and perhaps social recognition memory (e.g., gustatory preference); and in human males VP levels peak during sexual arousal (Carter et al. 1995; 1997; Insel 1997; Popik & van Ree 1993; Wang et al. 1994; Winslow et al. 1993; Young et al. 1998). In juvenile rats, social recognition of conspecifics is VP-dependent in males in the lateral septum but not in the mPOA; in female rats, social recognition is VP-independent in the lateral septum, but is OT-dependent in the mPOA (Engelmann et al. 1996). Placement of the vasopressin V1a receptor gene from the affiliative prairie vole into nonaffiliative mice resulted in enhanced affiliative behaviors in the mice, and experimentally increasing the V1a receptor gene using viral vector gene transfer in the ventral pallidum enhanced affiliation and pair bonding (Young et al. 1999). Although OT (female) and VP (male) *functions* are gender-dependent in some rodents, the fact that both neuropeptides are found in both sexes in rodents and humans indicates that their role in each gender requires further specification (Argiolas & Gessa 1991; Strand 1999). In prairie voles, VP receptors are very dense in the ventral pallidum and OT receptors are very dense in the NAS in both males and females, indicating that this receptor distribution is not related to "male" or "female" behaviors specifically.

Four points concerning the possible functional role of OT and VP can be suggested. First, neither OT nor VP appears to mediate reward, although OT can facilitate it (Sarnyai & Kovacs 1993). For example, self-administration of heroin is facilitated by an OT analogue, whereas a VP analogue inhibited it (van Ree & De Wied 1977). Second, in view of their diverse physiological targets and sociosexual functions, the role of these neuropeptides may be more generally one of facilitative modulation than mediation (Carter et al. 1997). For example, genetically engineered knockout mice that have a deficiency of OT everywhere, including in the main brain sites of central OT synthesis [paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus], are viable and fertile (Nishimori et al. 1996; Young et al. 1999). Both males and females of such mice have no fertility, reproductive, or parenting behavioral or functional deficits except a female inability to nurse (eject milk). These effects were not a result of altered receptor distribution or abundance. Also, reductions of up to 60% of the normal birth-induced OT increase did not affect maternal behavior of sheep, other than a reduced peak in low-pitched bleats and lamb sniffing (da Costa et al. 1999). On the other hand, OT may be more necessary to reproductive and maternal behavior in rats. Significantly, rats are maternal only after parturition (Brown et al. 2000), whereas mice and most primates exhibit maternal behavior independent of parturition. Therefore, species with more general activation of maternal behavior may be less dependent on the facilitatory effects of OT and permissive effects of gonadal steroids on maternal behavior, but more dependent on neurobiological networks and neurotransmitters that are more generally active and responsive to affiliative stimuli (Insel & Winslow 1998).

Third, the importance of OT and VP may be more predominant in the *initiation* (or appetitive phase) than in the *maintenance* of sociosexual functions (Carter et al. 1997; Insel & Shapiro 1992; Keverne 1996; Nelson & Panksepp 1998). For instance, OT antagonists or PVN lesions that eliminate OT and VP neurons (and possibly receptors) disrupt initiation of nurturant, maternal, and reproductive behaviors, but have no effect once maternal behavior is established (Ostrowski 1998). Also, both procedures interfere with the formation of partner preferences, which develop in the initial mating bouts in prairie voles (Carter et al. 1995; Insel & Shapiro 1992; Williams et al. 1994). Similarly, OT knockout mice are deficient in forming social recognition memories that would be necessary in acquiring mate preferences (Ferguson et al. 2000; Nishimori et al. 1996; Winslow & Insel 2002). Also, sexual interaction increases OT plasma levels in sexually naive male rats, but not in sexually experienced rats, suggesting that OT is activated mainly under novel circumstances involving acquisition phases of learning and memory compared to circumstances

when learning has already occured (Hillegaart et al. 1998). Moreover, whereas *acute* sexual activity in rodents promotes OT and VP release, mating behaviors, and social memories, the decreased copulatory frequency, increased social (nonsexual) contact, prolonged reduction in sympathetic autonomic and neuroendocrine activation, increased vagal tone, and calm sedation that is associated with *repeated* sexual activity over several days is blocked by opiate, but not OT, antagonists (Carter et al. 1997).

Fourth, *peripheral* versus *central* OT and VP systems in rodents and humans can differ in their functional effects, receptor regulation and distribution, and stimulus-elicitors (Carter et al. 1995; 1997; Insel 1992; 1997; Keverne 1996; Strand 1999; Uvnas-Moberg 1997). They are therefore potentially dissociable. The peripheral system involves OT and VP *magnocellular* neurons in the PVN and SON that activate OT and VP secretion from the neurohypophysis. In turn, OT and VP traverse the blood stream locally to the anterior pituitary, as well as more broadly to effect many peripheral functions, such as uterine contractions and milk ejection. In contrast, the central system involves OT and VP *parvocellular* neurons in the PVN that project to many corticolimbic regions, such as the amygdala, BNST, NAS, and prelimbic cortex (Carter 1992; Carter et al. 1995; 1997; Hulting et al. 1996; Insel 1992; 1997; Insel et al. 1997; Insel & Shapiro 1992; Ivell & Russell 1996; McCarthy & Altemus 1997; Richard et al. 1991; Strand 1999; Uvnas-Moberg et al. 1990; Witt 1995; 1997). Thus, whereas the peripheral system seems well positioned to facilitate basic bodily processes related to sociosexual functions, the broad central corticolimbic distribution may correspond to an increased capacity to guide sociosexual interactions by more general motivational processes and by social memories. Therefore, central OT and VP may play a critical role in facilitating limbic-based memory and motivational processes that either: (a) enhance recognition of mate sensory stimuli, and/or (b) associate mate and offspring stimuli with reward (Carter et al. 1997; Insel 1992; Insel & Shapiro 1992; Winslow & Insel 2002).

In support of point (a), the modulatory role of OT on the maternal behavior of rats, which is expressed only after parturition, is strongly exerted at the level of incoming sensory stimuli. For example, OT antagonist administration in the olfactory bulbs reduces maternal behavior of rats (Yu et al. 1997, and prepartum destruction of noradrenergic input to the rat olfactory bulb, which interacts with OT receptors in the bulb, also impairs maternal behavior (Insel et al. 1993). Vaginocervical stimulation enhances oxytocin receptor (OTR) sensitivity in the olfactory bulb, but this stimulation only potentiates lamb olfactory memory formation or consolidation when it is applied in the presence of the offspring, indicating that OT is potentiating olfactory stimulus processing (Keverne et al. 1997; Popik & van Ree 1991; 1993; Popik et al. 1992). Such sensory potentiation may be important in humans, wherein sociosexual behavior is less tightly linked to gonadal steroids and neuropeptides, but is significantly influenced by affiliative stimuli (Keverne 1996).

In support of point (b), OT activation facilitates association of the odor of a mate with copulation in male prairie voles, thereby promoting partner preference (Young et al. 1998), and similar effects have been found for OT and VP in rats (Dantzer et al. 1987; 1988; Popik et al. 1992; Renelli et al. 1995). OT also appears to facilitate olfactory-based memory acquisition that maternal sheep form of their offspring in the 2 to 4 hour post-parturition bonding window (Kendrick et al. 1992). Also, OT knockout mice are deficient in forming social recognition memories (Ferguson et al. 2000; Nishimori et al. 1996; Winslow & Insel 2002), an effect that may be a result of the lack of OT, and hence, of OT receptor activation, in the medial nucleus of the amygdala and in the BNST, where olfactory and contextual cues, respectively, are associated with reinforcement. For example, OT knockout mice fail to recognize familiar conspecifics after repeated social encounters; however, central OT administration into the amygdala restores social recognition (Winslow & Insel 2002).

There are several ways in which OT may modulate affiliative memories in addition to enhancing sensory processing. First, OT improves the establishment of long-lasting long-term potentiation in the acquisition of hippocampal-dependent spatial learning and memory (Tomizawa et al. 2003). Interestingly, this effect is particularly strong during motherhood in mice, suggesting an interaction with gonadal steroid status.

Second, in the human brain OTRs are densely expressed by the basal forebrain acetycholine (ACh) neurons in the nucleus basalis of Meynert and the diagonal band of Broca (Insel 1997; McCarthy & Altemus 1997). The nucleus basalis sends projections to the amygdala, hippocampus, thalamus, olfactory bulbs, and brainstem, whereas the diagonal band densely innervates the hippocampus (Kandel et al. 1991; Nauta & Feirtag 1986). Moreover, both neuron regions send diffuse projections that release ACh in the neocortex (Nauta & Feirtag 1986). Taken together, these ACh afferents are known to modulate memory systems in the amygdala, hippocampus, and neocortex, indicating that OT may modulate memory formation or consolidation through its influence on ACh function (McGaugh 2000).

Third, OT neurons in the PVN projecting to β-endorphin neurons in the arcuate nucleus can increase opiate release by 300% (Csiffary et al. 1992). Thus, OT may facilitate the rewarding effects of opiates, which, in turn, would promote reward-mediated associations. In contrast, many peripheral OT functions can be inhibited presynaptically by direct β-endorphin projections to magnocellular PVN OT neurons, wherein OT synthesis and release from OT terminals is inhibited (Cassidy 1999). Moreover, in rats, opiates inhibit OT release peripherally, and opiate antagonists result in enhancement of OT neurons centrally (Keverne & Kendrick 1991). Similarly, during labor in female humans, exogenous opiates inhibit OT secretion (Lindow et al. 1993). All of these results indicate that the effects of opiates in bringing affiliative interactions to a gratifying *conclusion* may involve suppressing the OT-facilitated *initiation* of affiliative behavior (Brown et al. 2000).

Fourth, OT interacts with DA in the NAS and VTA, thereby potentially modulating DA facilitation of the acquisition of affiliative contextual ensembles. DA D3 receptors also mediate increases in the release of OT (Uvnas-Moberg et al. 1995). OT interaction with NAS DA may increase sensory processing or memory processes (Drago et al. 1986; Kovacs et al. 1990; Sarnyai et al. 1990). Because both OT and DA are involved in facilitating partner preference in female prairie voles, their interaction in the NAS and VTA may play an important role in such memory formation (Gingrich et al. 2000; Insel & Hulihan 1995; Wang, H. et al. 1999; Williams et al. 1994). The affiliative male and female prairie voles have a dense concentration of OT receptors in the NAS,

whereas this is not the case in the nonaffiliative montane vole (Insel & Shapiro 1992). Moreover, blockade of NAS OT receptors abolishes partner preference formation in general (Gingrich et al. 2000), as well as the facilitatory effects on partner preference of a DA agonist that was injected intracerebroventricularly (Gingrich et al. 2000). In addition, OT neurons in the rostral PVN and dorsolateral POA send afferents to the VTA, which facilitate maternal behavior in the postpartum (Insel 1997). And OT injected intracerebroventricularly induces a robust and enduring increase in the firing rate of VTA DA neruons (Yu et al. 1997). When taken with the fact that the affiliative prairie vole also has a much more dense presence of VP receptors in the ventral pallidum than the nonaffiliative montane vole, and experimentally increasing VP1AR in the ventral pallidum results in enhanced affiliation and pair bonding (Young et al. 1999), perhaps OTRs in the NAS and vasopressin receptors (VPRs) in the DA receptor-rich ventral pallidum play a critical role in enhancing the incorporation of affiliative stimuli in the salient context predictive of affiliative reward.

6.4. Integrative summary

Our discussion indicates that numerous neurobiological variables contribute to affiliative behavior patterns. Rather than explicating all of the many sociosexual functions subserved by these variables, we organized their contribution around the processes of approach and consummatory phases of reward and memory formation, because we believe that these are most critical to the development and maintenance of affiliative bonds. Thus, we suggested that DA in interaction with glutamate within an MOC network encodes the incentive salience of contextual stimuli predictive of reward during the approach phase and, in collaboration with μ-opiate-mediated consummatory reward, encodes the incentive salience of proximal stimuli directly linked to the affiliative object. Whereas it appears that μ-opiates provide an independent contribution to the experience of consummatory reward, their interaction with DA processes in the VTA and NAS are critical for the formation of social memories. The end result of this sequence of processes is an incentive-encoded affiliative memory network that continues to motivate approach toward and interaction with the affiliative object.

Of course, affiliative memory formation and consolidation involve other processes and brain regions. Therefore, we focused on the specialized processes that may ensure that affiliative stimuli are weighted as significant elements in the contextual ensembles representing affiliative memory networks. These specialized processes include: (a) the binding of affiliative stimuli in the MXA and subsequent transmission to the NAS; (b) the construction of a contextual ensemble via affiliative stimulus-induced opiate potentiation of DA processes in the VTA and NAS; and (c) the influence of permissive and/or facilitatory factors, such as gonadal steroids, OT, and VP, on (1) sensory, perceptual, and attentional processing of affiliative stimuli and (2) formation of social memories.

7. Neurodevelopmental sources of individual differences in trait affiliation

A basic challenge in deriving a neurobiological model of a personality trait is to identify the sources of individual differences that occur within the functioning of the network of neural structures and variables associated with the trait. Individual variation in all of the neurobiological variables and processes, discussed in section 6, is likely to contribute to variation in the level of trait affiliation. For us, however, the capacity to experience affiliative reward has a disproportionately high weight in determining the level of trait affiliation, because it influences both: (a) the basic reward sensitivity to affiliative stimuli, and hence (b) variation in the development of associative memory networks that support the maintenance of affiliative preferences and bonds. Therefore, we focus on individual differences in central μ-opiate functioning and on its neurobiological modulators (i.e., DA, OT, VP) as mediators of variation in affiliative reward and trait affiliation. Because individual differences emerge through dynamic developmental processes (Collins & Depue 1992), our discussion of the animal work on individual differences is organized around three neuro-developmental sources of input to the brain: genetic, experience-expectant, and experience-dependent processes (Greenough & Black 1992).

7.1. Genetic variation in μ-opiate properties

Tellegen's measure of trait affiliation, Social Closeness, is subject to significant genetic variation (Tellegen et al. 1988). If *u*-opiates are a major source of variation in this trait, individual differences in opiate functioning would also be expected to exhibit genetic variation. Most animal and human genetic research has focused on *u*OR expressive properties, wherein differences appear to result in large part from variation at the *u*OR gene locus rather than from *u*OR affinities per se (Uhl et al. 1999). Individual differences in humans and rodents have been demonstrated in levels of *u*OR expression and binding that are associated with a preference for *u*-agonists, such as morphine (Belknap et al. 1995; Berrettini et al. 1994a; 1994b; Berrettini et al. 1997; Sora et al. 1997; Uhl et al. 1999; Zubieta et al. 2001). In humans, individual differences in CNS *u*OR densities show a range of up to 75% between the lower and upper thirds of the distribution (Frost et al. 1988; 1989; Pfeiffer et al. 1982; Uhl et al. 1999), differences that appear to be related to variation in the rewarding effects of alcohol in humans and rodents (Berrettini et al. 1997; De Waele et al. 1994; 1995; Gianoulakis 1993; Gianoulakis & De Waele 1994; Gianoulakis et al. 1992; 1996; McCall et al. 2000a; 2000b; Olson et al. 1997). The greatest proportion of variation in *u*OR density in humans appears to be governed by a *single* genetic locus that contains the human *u*OR gene (Berrettini et al. 1997; Wendel & Hoehe 1998). Moreover, broad individual variability in normal human *u*OR binding potential not only has been demonstrated under placebo conditions, but also in the change in binding to a standardized stressful stimulus, indicating that individual differences in the *u*OR system may be observed under resting conditions as well as in the dynamic response to stimuli (Zubieta et al. 2001).

Differences of this magnitude in the *expressive* properties of the *u*OR gene could contribute substantially to individual variation in *u*OR-induced *behavioral* expression via an effect on *B*-endorphin functional potency. For example, one source of this individual variation is different single nucleotide polymorphisms (SNPs) in the *u*OR gene, OPRM1 (Berrettini et al. 1997; Bond et al. 1998; Gelernter et al.

1999). The most prevalent of these is A118G, which is characterized by a substitution of the amino acid Asn by Asp at codon 40, with an allelic frequency of 10% in a mixed sample of former heroin abusers and normal controls (Bond et al. 1998). Although this SNP did not bind all opiate peptides more strongly than other SNPs or the normal nucleotide sequence, it did bind *B*-endorphin three times more tightly than the most common allelic form of the receptor (Bond et al. 1998). Furthermore, *B*-endorphin is three times more effective in agonist-induced activation of G-protein–coupled potassium channels at the A118G variant receptor compared to the most common allelic form (Bond et al. 1998).

Genetic variation in *u*OR properties is related to response to rewarding drugs, such as morphine, alcohol, and cocaine, and to opiate self-administration behavior in animals (Berrettini et al. 1997). For instance, the recombinant inbred mouse strain B6, which has 33% fewer *u*1ORs than six other inbred strains, showed relative insensitivity to opiate agonists. As a means of compensating for the reduced *u*ORs, the B6 strain self-administered four times the amount of opiate agonists as the other strains, and showed an increased resistance to extinction after removal of active drug (Elmer et al. 1995). Furthermore, the B6 strain experiences far greater sensitivity, in terms of locomotor activation, learning/memory, and muscular rigidity, than the D2 strain to most opioid-activating drugs, such as ethanol, morphine, and cocaine (Berrettini 1994b; Mogil et al. 1999a; 1999b; Wendel & Hoehe 1998). In addition, when transgenic insertion was used to increase *u*OR density specifically in mesolimbic areas thought to mediate substance abuse via VTA DA neurons, transgenic mice showed increased self-administration of morphine compared to wild-type mice, even when the amount of behavior required to maintain drug intake increased tenfold (Elmer et al. 1995). Thus, the efficacy of morphine as a reinforcer was substantially enhanced in transgenic mice. Conversely, *u*OR knockout mice do not develop conditioned place preference and physical dependence on morphine, whereas morphine induces both of these behaviors in wild-type mice (Matthes et al. 1996).

Taken together, these studies suggest that genetic variation in *u*OR properties in humans and rodents is: (a) substantial, (b) an essential element in the variation in the rewarding value of opiates, and (c) critical in accounting for variation in the Pavlovian learning that underlies the association between contextual cues and reward, as occurs in partner and place preferences (Elmer et al. 1995; Matthes et al. 1996).

7.2. Genetic variation in modulators of opiate functioning: DA, OT, VP

Opiate effects on affiliation are modulated by the facilitatory effects of OT and perhaps VP, facilitatory or permissive effects of gonadal steroids, and are directly dependent on the interaction with DA in the VTA and NASshell. Such interactive effects of OT, VP, and DA with μ-opiate functioning could influence the expressive qualities of incentive-driven approach to affiliative stimuli, the rewarding qualities of affiliative interactions, and the extent to which neutral cues are associated with affiliative objects and contexts (i.e., acquisition of social memories). As discussed in section 6.3.2, there are direct modulatory effects in the interaction of DA and *u*-opiates in the VTA and NASshell, such that genetically influenced individual differences in either DA or *u*-opiates could modulate the functioning of the other variable. As we and others have reviewed recently, genetic variation in VTA DA and/or NAS DA functioning has powerful effects on a wide range of incentive-motivated behaviors, including affiliation, acquisition of self-administration of DA agonists, and conditioned reinforcement (Depue & Collins 1999; Gelernter et al. 1998; Le Moal & Simon 1991; Piazza & Le Moal 1996; Puglisi-Allegra & Cabib 1997). Such differences could modify DA's influence in the initial, appetitive phases of establishing an affiliative bond via variation in incentive reward encoding and contextual conditioning. Alternatively, genetic variation that influences expression or function of *u*ORs contributes to variation in the neuroadaptive properties of the mesolimbic DA system that can affect affiliative behavior (Smolka et al. 1999).

Individual differences in the facilitatory effects of OT on opiate functioning could influence *the frequency and quality of expression* of opiate-modulated behaviors, and could modulate formation of affiliative memories (e.g., Ferguson et al. 2000). A polymorphism at the human OTR gene has been identified on chromosome 3 (Michelini et al. 1995). The human DNA encodes a 388 amino acid polypeptide with several possible sites for post-translational modifications (Kimura et al. 1992). In the 3' nontranslated region of the human OTR cDNA, there is a stretch of 15 CA dinucleotide repeats (bases 2246–2277) that are often polymorphic (Michelini et al. 1995). The polymorphism contains two alleles, which occur with frequencies of 0.77 and 0.23 in a sample of Caucasian CEPH parents. These mutations in the sequence of the OTR gene could alter the biological effects of OT (Michelini et al. 1995), although it is not yet clear how these polymorphisms relate to behaviors associated with OT functioning in humans. Clearer, is that extreme sociosexual differences between some species appear to be related to variation in OT and VP receptor brain distribution and density rather than in presynaptic features, variation that is likely to be of genetic origin (Insel 1997; Strand 1999; Young et al. 1998). For example, prairie voles show extensive maternal care and extended sexual behavior that promotes social preferences for familiar partners, although intimate social contact is the primary influence on the development of emotional bonds (Mason & Mendoza 1998). In contrast, montane voles live in isolated burrows, do not show selective pair-bonds, show little parental care, and spend little time with other voles (Insel & Shapiro 1992). There is a differential distribution of OT and VP receptors in prairie and montane voles, who are monogamous and polygamous, respectively. Relative to montane voles, prairie voles show much denser OTR and VPR distribution in reward areas, such as the prelimbic cortex, the NAS, and ventral pallidum, which could directly influence the development of partner preference (Young et al. 1998; 1999). Also, Young et al. (1999) demonstrated that placement of the VP gene from the affiliative prairie vole into nonaffiliative mice resulted in enhanced affiliative behaviors in the mice, and that experimentally increasing the vasopressin V1a receptor gene using viral vector gene transfer in the ventral pallidum enhanced affiliation and pair bonding. Importantly, there are significant *within-species* differences in prairie voles in: (a) the vasopressin V1a receptor gene, which appears to manifest great potential for polymor-

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phism (Hammock & Young 2002; Young et al. 1999), and (b) NAS density of OTR (Young 1999; Young et al. 1999), raising the possibility that intraspecies variation in affiliative behavior may also be subject to genetic influence.

7.3. Experiential contribution to individual differences in affiliative behavior

As measured by Tellegen's Social Closeness scale, affiliation not only shows significant genetic influence, but also substantial modification via experiences that occur both within and outside the family (Tellegen et al. 1988). Experiential sources of individual differences derive from two main sources: *experience-expectant* and *experience-dependent* processes (Collins & Depue 1992; Greenough & Black 1992). *Experience-expectant* processes involve widespread cortical synapse overproduction during sensitive periods in brain development when critical stimulation relevant to a specific neural system is likely to occur (Greenough & Black 1992; Rakic et al. 1986). Following overproduction, excess cortical synapses are "pruned back" in response to relevant environmental stimulation. The basic implication of experience-expectant processes for the development of individual differences is that the degree of stimulation-rich environment will be encoded in the number of functional synaptic connections within neural pathways. Moreover, during expectant periods, individual differences in both genotypic processes (e.g., *u*-opiate neuron number or *u*OR density) and environmental experience (e.g., quantity and/or quality of infant–maternal interactions) would be expected to collaborate. The outcomes of such periods therefore might establish different trajectories in the functional development of the *u*-opiate system across individuals, and thus partially specify eventual trait levels of affiliation.

It is unknown whether experience-expectant processes are a significant source of individual differences in OT, VP, or *u*-opiate functioning, but sensitive periods in the postnatal development of the OT and opiate systems do exist. In both rodents and primates, shortly after birth there is overproduction and later pruning of OTR and VPR (around weaning) in limbic areas of the brain, notably in the cingulate cortex, a region that is important in evaluation of emotional significance of sensory stimuli (Carter 1998; Insel 1997; Insel & Winslow 1998). There is also higher OT binding in the cingulate cortex, dorsal subiculum, NAS, and anterior nucleus of the olfactory bulb in the preweaning compared to adult stage in rats, regions that are associated with social memory, reward processes, and infant behaviors directed towards the mother (Shapiro & Insel 1989). Upon pruning of these innervations at weaning, there is a substantial change in social behavior in the infant (Nelson & Panksepp 1996; Nissen et al. 1996). Thus, this overproduction and pruning back of OT innervations appears to be coincident with a sensitive period of nursing and, by association, of affiliative bonding between mother and infant.

OTR expression in female rodents and primates also undergoes changes across the lifespan that are estrogen dependent: expression is high in infancy (unrelated to estrogen), declines in the early years of life, and then increases at puberty, mating, and during parturition and childbirth (Insel & Winslow 1998). At parturition, OTR increase in number in the mPOA, VMN, and BNST of female rats (Nelson & Panksepp 1998; Witt 1995). In human infancy, OTR primarily are distributed in the cingulate cortex, globus pallidus, and the midline nucleus of the thalamus, whereas in the adult, OTR are distributed in the BNST and VMN regions that contain no OT receptors before maturity. These brain areas are important for sexual and nurturant behavior and for associative processes between context and reward that support the acquisition and maintenance of pair bonding (Insel 1992).

*u*OR expression and density also undergo developmental change, increasing rapidly during development in the rat brain (Pintar & Scott 1993). *u*OR densities in the globus pallidus and VTA are high in the immediate postnatal period but then decline to adult levels during the first month, coinciding with the early period when the infant is with the mother most of the time (Pintar & Scott 1993). Interestingly, more precocial species, such as lambs, show *u*OR expression at birth that is more similar to adult expression than that of altricial species, such as rats or mice (Pintar & Scott 1993). Thus, changes in regional expression of OTR and mRNA for OTR, *u*OR, and their projections, from birth through adolescence, mating, parturition, and parenting, suggest that plasticity in these systems allows for rewiring of neural circuits that enable the encoding of environmental experience during critical events of the lifespan (Ostrowski 1998). In this way, species-typical experiences can affect affiliative behavior through the influence of developmental processes on peptide functioning (Ostrowski 1998).

Experience-dependent processes encode experience unique to the individual through interactions of neurotransmitters and neuropeptides that modulate dendritic outgrowth, synaptogenesis, synaptic regression and hence synaptic connectivity, or the intrinsic excitability of neurons within the distributed structures of a particular neural system or network (Colman et al. 1997; Magee & Johnston 1997; Mattson 1988; Zhang & Linden 2003). As discussed in various sections above, OT, VP, *u*-opiate, and DA are capable of undergoing and also of inducing neural plasticity as a function of environmental experience. Repeated exposure can result in sensitization or an *augmented response* to cues, thereby increasing the probability of their being incorporated into contextual ensembles that predict affiliative reward. This is a critical point, because whereas social recognition can occur rapidly and may not involve close contact, the development of social preferences (implying formation of affiliative memories based on reward) primarily is dependent on *repeated intimate social contact* (Insel & Winslow 1998; Mason & Mendoza 1998). For example, mating in female prairie voles leads to a partner preference, but the formation of the preference is time- and experience-dependent, requiring at least 14 hours of male exposure with 10–20 bouts of copulation during this interval (Insel & Hulihan 1995; Wang, Z. et al. 1999). Also, male rats show enhanced response to estrus female rat bedding with repeated noncopulatory olfactory exposure, but not to male or ovariectomized female bedding (Mitchell & Gratton 1991). Additionally, rat pups acquire preference for a maternally associated odor with experience (Nelson & Panksepp 1996), and they are more likely to approach an odor that was paired with maternal reunion on the previous day (Panksepp et al. 1997).

Nurturant behavior can also be enhanced as a result of experience, because it can be induced in nonpregnant female rats and male rats by repeated exposure to pups, which has been interpreted as sensitization to the pups' sen-

sory cues (Cruz & Del Cerro 1998; Rosenblatt 1994). Moreover, rat dams find their pups more rewarding after experience (Fleming et al. 1999), and more frequently press a bar that provides access to pups compared to inexperienced female rats (Lee et al. 1999. After only two exposures, these mothers also favor visual environments that were paired with their pups (Fleming et al. 1994). Deprivation of experience can have the opposite effect. Whereas only 2 hours of interaction between mother and rat pups on the first day after birth is sufficient to permit maternal behaviors toward foster pups 10 days later (Orpen & Fleming 1987), maternal behaviors are diminished over the first week after birth if mothers and offspring are separated (Fleming et al. 1999; Orpen & Fleming 1987). Ewes also appear to develop a transient olfactory memory of their lambs within 1–2 hours postpartum if they have been exposed to olfactory and vaginocervical stimulation, but this is blocked if they are separated from their lambs for 3 hours thereafter. However, with exposure to lambs for 12–24 hours postpartum, the ewe will remember her lamb even after a 6-hour separation, in tandem with extensive reorganization of connections in the olfactory bulb (Keverne et al. 1997).

Human maternal experience itself can prime or sensitize the neurochemical mechanisms that enable mothers to recognize their offspring (Fleming et al. 1999). New mothers show enhanced sensitivity to sensory cues emitted by infants as a result of experience, in that, for example, they can correctly identify the cry of their infant above the din of multiple infant cries after only a brief exposure (Cismaresco & Montagner 1990). Because olfactory stimuli are primary triggers of sexual and maternal behavior in many species, the tight linkage between olfactory cue consolidation and mating behavior that has developed throughout evolution might be present even in humans who have become less dependent on olfaction as a primary sensory modality for recognition of affiliative objects (Englemann et al. 1996). The infant's own interaction between perceptual preferences and behavior may affect memory formation, in that infants prefer the smell of lactating women's breasts compared to the breasts of nonlactating women (Makin & Porter 1989). Furthermore, human infants prefer the smell of their mother's breasts, and their mother's odor can attenuate crying in distressed infants, both findings suggesting that infants form recognition memories based on their mother's odor (Porter 1999; Porter et al. 1991). The sooner human mothers breastfeed after birth and the closer they keep their faces to their infants when holding them, thereby allowing for increased odor exchange, the more appealing they find their infants' body odors and the more accurately they recognize their infants' odors (Corter & Fleming 1995; Fleming et al. 1999). Moreover, women are able to recognize the smell of their infants within hours of giving birth (Keverne et al. 1997), and can identify their infant by the odor of their shirt or by smelling the heads of several infants while blindfolded after a short period of exposure (Kaitz et al. 1987; Russell & Leng 1998). Significantly, the mothers who accurately identified their infants from olfactory cues typically had been exposed to their infants earlier and for a longer period of time, had engaged in closer interactions with their infants, and felt more intense warmth and nurturance than women who were not accurate in their identification (Corter & Fleming 1995; Cruz & Del Cerro 1998). In addition to olfactory exposure, vaginocervical stimulation at birth in human mothers may be an important *initial* experiential variable in forming memories and in bonding with infants. Mothers who gave birth via vaginal delivery versus Caesarean section showed more effective nursing and affiliative behaviors toward their infants in the first few days after birth (Uvnas-Moberg 1997). Of course, human mothers have other, more recently evolved modalities for recognizing their infants, but this might represent an important experiential contributor to bonding with one's offspring.

The significance of these various findings is that maternal behavior, at least in rodents, is a major source of not only offspring neural, endocrine, and genetic development that affects offspring emotional reactivity, but also of maternal behavior of offspring as adults (Meaney 2001). Thus, maternal behavior serves as a major source of intergenerational transmission of behavioral profiles in offspring across the life span. In humans, parental factors also can mediate the effects of environmental adversity on development and offspring behavior, including the effects of poverty on child development (Conger et al. 1994; Eisenberg & Earls 1975; McLloyd 1998), and early stress has deleterious effects on adult attachment behavior (Henry & Wang 1998). Furthermore, other temperament factors that affect the behavior of the mother, such as neuroticism, attachment style, separation anxiety, and rejection sensitivity will likely modify affiliative bonding with offspring.

Thus, the capacity for and regulation of neuroplasticity by these neural systems may be one avenue for *collaboration* among genotypic, experience-expectant, and experience-dependent processes (Collins & Depue 1992; Depue & Collins 1999). By way of example, in the case of a highly nurturing, affectionate mother–infant interaction during nursing, which may in part be a result of genetic influence on the μ-opiate system of the mother as well as the infant, the likely (but not inevitable) outcome of this sensitive, expectant period would be a strong functional capacity in the *u*-opiate system of the infant to respond to unconditioned and conditioned affiliative stimuli. Subsequent experience-dependent processes would likely maintain this capacity, because an enduring predisposition to engage unconditioned and conditioned affiliative stimuli established during experience-expectant development would entail frequent activation of synaptic connections in the terminal fields of *B*-endorphin projections. Thus, early experiential processes may lay the foundation for *trends* in affiliative approach and bonding behavior across the life span by moderating the strength of subsequent experience-dependent processes (such as dendritic arborization or neuropeptide release) involving the functional capacities of *B*-endorphin, OT, and VP projection systems.

8. Modeling behavioral effects of individual differences in *u*-opiate functioning on the acquisition and maintenance of affiliative bonds

Our discussion in section 7, concerning the sources of individual differences in the functioning of variables potentially associated with affiliative behavior, naturally raises the question of how such individual differences contribute or translate to behavioral variation that comprises the phenotype of trait affiliation. In short, how can such psychobio-

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logical individual differences be modeled to better understand variation in affiliative behavior.

As we have argued in section 7.1, research suggests that individual differences in *u*-opiate functioning are associated with variation in the magnitude of gratification experienced from naturally occurring rewards, presumably also from affiliation-elicited reward. We now more specifically, albeit speculatively, model the influence of individual differences in *u*-opiate-mediated affiliative reward on affiliative behavior (sect. 8.1), and discuss the implications of the model for a trait of human affiliation, particularly in terms of acquisition and maintenance of affiliative bonds (sect. 8.2). In so doing, it is worth noting that a major source of individual differences that broadly overlays other sources of indvidual variation is that females appear to have a greater disposition to express attachment-caregiving behavior than males (Taylor et al. 2000). Finally, in section 8.3, we present our preliminary human evidence suggesting that variation in opiate functioning is associated with the trait of affiliation.

8.1. A psychobiological threshold model of affiliative reward

Models of behavioral processes often employ a minimum threshold that represents a central nervous system weighting of the external and internal factors that contribute to initiation of the processes (Depue & Collins 1999; Stricker & Zigmond 1986; White 1986). In the case of affiliative reward, the threshold would be weighted most strongly by the joint function of two main variables: (i) magnitude of affiliative stimulation, which ultimately is mainly a function of the magnitude of reward induced by an unconditioned or conditioned affiliative incentive stimulus, and (ii) level of *u*-opiate postsynaptic receptor activation (e.g., by endogenous *B*-endorphin) (Belknap et al. 1995; Berrettini et al. 1994a; 1994b; Frost et al. 1988; 1989; Gianoulakis 1993 Gianoulakis et al. 1996; Olson et al. 1997; Pfeiffer et al. 1982; Sora et al. 1997; Uhl et al. 1999). The relation between these two variables is represented in Figure 12 as a trade-off function (Grill & Coons 1976; White 1986), where pairs of values (of affiliative stimulus magnitude and *u*-opiate activation) specify a diagonal representing the minimum threshold value for activation of affiliative reward. Findings we reviewed in section 6.1.2 show that agonist-induced *state* changes in *u*OR activation influence the threshold of reward, as indicated by modifications in the efficacy of inherently rewarding stimuli, an effect that may be especially mediated by *u*ORs located in the VTA and NAS (Duvauchelle et al. 1996; Herz 1998; Koob & Le Moal 1997; Schlaepfer et al. 1998; Shippenberg & Elmer 1998). Because the two input variables are interactive, independent variation in either one not only modifies the probability of affiliative reward, but it also simultaneously modifies the value of the other variable that is required to reach a minimum threshold of affiliative reward. Finally, individual variation in variables that significantly interact with *u*-opiate functioning would serve as a source of modulation of the threshold of affiliative reward, and in Figure 12 variation in the modulatory effects of DA, OT, VP, and gonadal steroids is so represented. For example, increased functional activity of these modulators would increase *u*-opiate activity and thereby decrease the threshold for affiliative reward.

8.2. Implications for conceptualizing a trait of affiliation

A threshold model allows behavioral predictions that have implications for conceptualizing trait affiliation. A *trait* di-

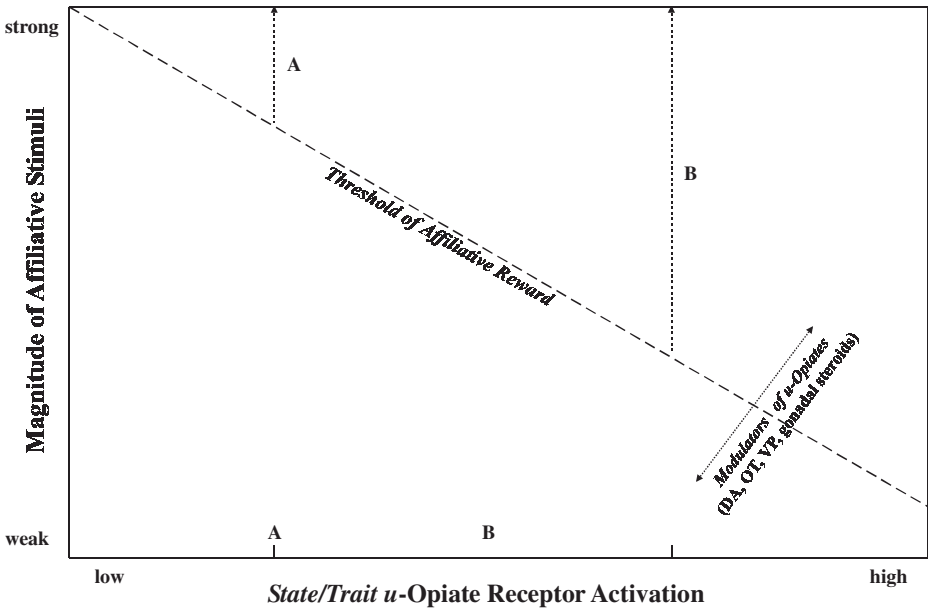

Figure 12. A minimum threshold for affiliative reward is illustrated as a trade-off function between affiliative stimulus magnitude (left vertical axis) and central μ-opiate postsynaptic receptor activation (horizontal axis). Range of effective (reward-facilitating) affiliative stimuli is illustrated on the right vertical axis as a function of level of μ-opiate activation. Two hypothetical individuals with low and high *trait* μ-opiate postsynaptic receptor activation (demarcated on the horizontal axis as *A* and *B*, respectively) are shown to have narrow (*A*) and broad (*B*) ranges of effective affiliative stimuli, respectively. Threshold effects resulting from DA, OT, VP, and gonadal steroid modulation are illustrated, as well. See text for details. (Abbreviations: DA = dopamine; OT = oxytocin; VP = vasopressin).

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mension of μ-opiate postsynaptic receptor activation is represented on the horizontal axis of Figure 12, where two individuals with divergent trait levels are demarcated: *A* (low trait level) and *B* (high trait level). These two divergent individuals may be used to illustrate the effects of trait differences in μ-opiate receptor activation on both acquisition and maintenance of affiliative bonds.

8.2.1. Acquisition of affiliative bonds. As Figure 12 indicates, for any given affiliative stimulus, the degree of *state* (contemporaneous, stimulus-induced) μ-opiate response will, on average, be larger in individual *B* than individual *A*. Our proposal is that this is a major source of the neurobiological basis of the temperamental (i.e., nonexperiential) component of affiliative reward, and hence of variation in the acquisition of affiliative bonds, and ultimately in levels of trait affiliation. Because the degree of state μ-opiate activity is correlated with the magnitude of *subjective emotional experiences* that are naturally elicited by affiliative stimuli (i.e., increased interpersonal warmth, affection and kindness, gratification, pleasure, and peaceful calmness), this emotional experience is also predicted to be more enhanced in *B* versus *A* (Cleeland et al. 1996; Ferrante 1996; Greenwald et al. 1996; Olson et al. 1997; Schlaepfer et al. 1998; Uhl et al. 1999).

This difference between individuals *A* and *B* in magnitude of affiliative stimulus-induced *u*OR activation and accompanying subjective emotional experience may contribute to two important sources of variation in acquisition of affiliative bonds. First, as noted in section 8.1, independent variation in either of the two interactive variables that determine the threshold of affiliative reward (*u*OR activation and magnitude of affiliative stimulus) also, simultaneously, modifies the value of the other variable that is required to reach a minimum threshold of affiliative reward. This suggests that individual *B* will encode contemporaneously the magnitude of affiliative reward for any given affiliative stimulus as greater relative to individual *A*. Importantly, enhanced reward encoding would be expected, in turn, to affect the magnitude of positive affective representations of affiliative objects during subsequent acquisition and consolidation of social memory, thereby increasing incentive-driven approach to and affiliation with these objects (Damasio 1994; LeDoux 1998).

Second, if individual differences in reward encoding apply across the full range of magnitudes of affiliative stimuli, trait differences in *u*OR activation may have marked effects on the *range* of effective (i.e., reward- and behavior-inducing) affiliative stimuli. This is illustrated in Figure 12, where the right vertical axis represents the range of effective affiliative stimuli. Increasing trait levels of *u*OR activation (horizontal axis) are associated with an increasing efficacy of weaker affiliative stimuli and, thus, with an increasing range of effective affiliative stimuli. In Figure 12 individuals *A* and *B* are shown to have a narrow versus broad range, respectively. Significantly, the broader range for individual *B* suggests that, on average, *B* will experience more frequent elicitation of subjective emotional experiences associated with affiliative reward. This means that the probability at any point in time of being in a *u*-opiate-facilitated state for individual *B* is higher than it is for *A*. Therefore, when subsequent affiliative stimuli are encountered, their subjectively evaluated magnitude of affiliative reward will show a stronger positive bias for *B* than *A*. Thus, trait differences in affiliative reward reflecting variation in *u*OR activation may *proactively* influence the reward evaluation and reward encoding of affiliative stimuli, and may not be restricted to *reactive* emotional processes (Bindra 1978).

This raises the possibility of variation in the *dynamics* of affiliative engagement with the environment. A positive relation between *state uOR* activation and affiliative stimulus efficacy suggests that, as an initial affiliative stimulus enhances *u*OR activation, the efficacy of subsequently encountered affiliative stimuli may be increased proportional to the degree of the initial *uOR* activation. Under conditions of strong *u*OR activation, perhaps even previously subthreshold affiliative stimuli may come to elicit affiliative reward for a period of time. This dynamic process of gradually rising affiliative reward might affect the degree of facilitation of affiliative behavior throughout the temporal course of the affiliative engagement, and hence the aggregate reward value encoded for the affiliative goal.

The overall manifestation of these various processes is likely to be more frequent and more affectionate interpersonal contact for individual *B* relative to individual *A*. If this reflects enhanced affiliative reward experienced by indiviudal B, there is one additional effect of importance that involves the interaction of *u*-opiates and DA. As discussed in section 6.1.1, the magnitude of both unconditioned and conditioned rewards is strongly associated with the quantity of DA release in the NAS and with a graded increase in the frequency and duration of VTA DA neuronal activity (Blackburn et al. 1989; Nishino et al. 1987; Schultz 1986; Schultz et al. 1995b; White 1986). Moreover, DA neurons show increased activity in the presence of neutral stimuli that consistently predict reward (Schultz et al. 1995b; 1997). Thus, holding trait DA functioning constant, a broader range of effective affiliative stimuli, each with enhanced *u*OR activation-induced affiliative reward, is expected to produce more robust DA reactivity to affiliative reward in individual *B*. This effect follows from the fact, as discussed in section 6.3.2, that *u*-opiate projections from the arcuate nucleus significantly activate both VTA DA neurons and NAS DA functioning. Accordingly, an enhanced acquisition of a broader array of conditioned stimuli that are predictive of affiliative reward can be expected for individual *B*. Thus, variation in *u*OR activation by affiliative stimuli may not only influence the level of affiliative reward, but also may lead to variation in the strength of DA-facilitated associative processes that link neutral stimuli with affiliative reward, as well as DA-facilitated approach to affiliative objects. *The outcome of these interactions may be the* acquisition *of a more elaborate associative* network *linking reward to affiliative objects (infants, mates) in individual B*.

8.2.2. Maintenance of affiliative bonds. *Longer-term maintenance* of affiliative bonds in species that have a relatively long offspring developmental period, which is extreme in humans, presents complications beyond the mere *acquisition* and *short-term maintenance* of affiliative bonds. Perhaps the most significant development in humans that contributes to maintenance of affiliative bonds between mothers and infants and between mates is the unbinding of both maternal caregiving and sexual activity from the strict hormonal control of reproductive cycles (Keverne et al. 1997). This unbinding liberates affiliative reward mechanisms to operate continuously between mother and offspring and between mates. For example, unbinding permits

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engagement in sexual activity between mates at any time, and hence increases its frequency, and thereby promotes two important factors: (1) prosocial and sexual tactile stimulation, which serves as the most potent source of stimuli that activate affiliative reward; and (2) conditioning of the mate's personal features to affiliative reward, thereby enhancing the establishment of mate preference. These factors would be enhanced, as well, by the human social strategy of monogamy, which increases nonsexual and sexual tactile interactions and other behavioral dependencies required for offspring care and survival of nuclear family members. Furthermore, perhaps in tandem with the release of sex from reproductive hormonal control is the enhancement of the external manifestation of physical sexual attractors in humans, including female breasts and male penis. Additionally, social group living in humans also would increase nonsexual tactile stimulation, and perhaps has extended the utility of an affiliative reward mechanism to create less intense but more enduring bonds between members of a social group as a means of promoting group cohesion.

Individual differences in the maintenance of affiliative bonds in humans may relate to the very factors that promote acquisition of affiliative bonds. As stated in section 6.3.2, variation in *u*OR activation by affiliative stimuli may not only influence the level of affiliative reward, but also may lead to variation in the strength of DA-facilitated associative processes that link neutral stimuli with affiliative reward. The latter would be expected to result in variation in the breadth and strength of the encoded *network* of conditioned positive incentives that represent the general context and specific features associated with affiliative objects. These factors may lead to variation in the long-term encoding of the reward magnitude of affiliative objects in memory, resulting in consistent differences in the intensity of positive affective central representations of affiliative objects (Mishkin 1982). Such differences could have marked effects on the maintenance of affiliative behavior through the operation of cognitive processes of working memory integrated in prefrontal cortical regions. In prefrontal regions, central representations of the salient context, the affiliative object, prior response strategies, and their association with reward can all be held on-line as a means of: (a) "reliving" affiliative interactions and reward, despite gaps in space and time, and (b) motivating approach to the affiliative object via symbolic central representations (Brothers & Ring 1992; Damasio 1999; Goldman-Rakic 1987; Rolls 1999; Waterhouse et al. 1996). Subsequent to approach, repetition of affiliative reward processes would then further reinforce the affiliative bond (Di Chiara & North 1992; Insel & Winslow 1998). This sequence is likely critical to the enduring nature of affiliative bonds in humans, because repeated interactions are vital for their maintenance. For example, prairie voles show a significant preference for a familiar partner up to 8 days of separation, but by 10 days of separation they do not exhibit a significant preference for the partner, and by 2 weeks they treat formerly familiar and preferred voles as strangers (Carter et al. 1995). In humans, *recognition* of the individual is not lost, but the incentive salience of an affiliative bond can be degraded and the relationship threatened after prolonged separation (Dellmann-Jenkins et al. 1994). Thus, individuals *A* and *B* may develop *differences in their capacity to facilitate over time affiliative reward and affiliative approach behavior by central incentive representations of affiliative objects and their contexts*.

Finally, individual *A* is predicted to exhibit less resistance to extinction relative to *B* in situations where affiliative reward is relatively weak, intermittent, or based on delayed gratification. This is because of: (a) weaker contemporaneous encoding of affiliative reward, and (b) a weaker network of conditioned incentives to activate affiliative approach behavior and affiliative reward by central representations. Importantly, such reward conditions represent those that exist at critical times of affiliative bond formation and maintenance, such as in the beginning of bond formation (weaker and/or intermittent reward) and during times of separation from affiliative objects (intermittent reward and delayed gratification). As these various "obstacles" to reward increase, individual *A* is predicted to show earlier extinction of affiliative approach behavior, and hence less frequent intimate contact with the affiliative object than individual *B*, both of which should reduce maintenance of affiliative bonds.

8.3. Preliminary support for opiate involvement in trait affiliation

We have begun to study the association of opiate functioning with a human trait of affiliation. From a sample of 2981 college students who all took Tellegen's MPQ, including the Social Closeness (SC) scale, we randomly selected high SC (top decile) and low SC (bottom decile) females (19–21 years of age; 47–70 kg). Structured interview ruled out DSM-IV psychiatric and medical disorders, smoking, use of birth control pills, and pregnancy. General experimental controls included circadian (subjects were run between noon and 3 PM), menstrual cycle (subjects were run in the mid-follicular phase, days 5–12 after initiation of bleeding), and fasting from midnight the previous night. The general experimental approach involved assessing two dependent variables: (a) *state* affiliation ratings and (b) tolerance to heat, both measured after viewing either a film clip that specifically induces an affiliative subjective experience versus a neutral film clip of a rain forest. In addition, these film-induced changes in the two variables were measured under two drug conditions: placebo and an opiate antagonist.

8.3.1. Dependent variables. We used an affiliation rating scale that was demonstrated to be sensitive to the affiliative film material used here (i.e., showed significant changes after the affiliative film but not after the neutral film), and which correlated significantly with SC but not with any other MPQ scale (Morrone-Strupinsky et al. 2000; Morrone-Strupinsky & Depue 2002). The scale uses the two strongest adjectival markers defining an affiliation factor – *warm* and *affectionnate* – to characterize the emotional nature of the rating scale (Goldberg & Rosolack, 1994). We did not designate adjectives of increasing magnitude as anchors for each point of the rating scale, because a full complement of affiliative adjectives scaled for intensity has not been well differentiated. Instead, on the basis of extensive preliminary work, we devised a 7-point scale entitled Warm and Affectionate, in which each of the 7 points was labeled by a modifier of increasing magnitude, *from not at all* (0) to *completely* (6). Ratings of the Warm and Affectionate scale were current state ratings introduced by "Rate how you currently

feel in comparison to the highest level indicated on the rating scale." Heat tolerance was chosen as a dependent variable because it is a well-established measure of μ-opiate activity in animals, is blocked by naltrexone, and is correlated with reward effects of opiates, although the *u*OR subtype may differ for the two effects (Carlezon et al. 2000; Stefano et al. 2000; Uhl et al. 1999; Wilson et al. 2000). Our interest in assessing pain tolerance also arose from the significant difference ($p < .01$) we previously found between 30 high SC and 30 low SC females in self-reported menstrual pain (assessed on a standard questionnaire as a summed score on six 6-point rating scales, ranging from "none" to "intense, disabling," for muscle stiffness, headache, cramps, backache, fatigue, general aches and pains).

8.3.2. Film material. The 15-minute affiliative film clip portrayed the development of a close mate relationship (without sex scenes) as they encounter struggles and joys while they are expecting their first child and after the birth of their child. A 30-second verbal synopsis of the film's story line (without conveying final events) appended to the beginning of the film clip provided a contextual framework for the clip, and any relevant information on the identity of the main protagonists. In this way, the film's story and characters had immediate specific meaning for subjects. The affiliative film was found to induce strong, significant changes in ratings of warmth and affection, that were specifically and significantly associated with MPQ SC, but not with any other MPQ scale including agentic extraversion (Morrone-Strupinsky & Depue 2004; Morrone et al. 2000). The neutral film was a 10-minute narrated segment of tropical rain forest scenes and had no significant effect on ratings of warmth and affection (Morrone et al. 2000).

8.3.3. Heat tolerance. Heat tolerance estimation involved placing the nondominant hand on a plexiglass plate located over a high-intensity light source. Extensive pilot work guided by pain experimental literature evolved the following method: Every 30 secs, subjects rated their intensity of heat-induced pain on a 7-point scale, for a maximum of 5 minutes to avoid skin damage. Subjects also reported verbally: (a) first detection of "painful," and (b) "stop" with removal of their hand. The first report indicates the time to pain detection, and the second indicates time to tolerance of pain. Of course, it is not possible to separate pure physiologic pain detection and tolerance from psychological factors, because they are essentially nonseparable aspects of pain in self-report under natural conditions (Zubieta et al. 2001).

We have measured Social Desirability via the MPQ, and 20 high and 20 low SC subjects did not differ significantly ($p > .40$), nor did SC correlate with Social Desirability ($n = 2000$, $r = .07$), so it is unlikely the groups differed in degree of self-esteem, diffidence, or wishing to *please* the experimenter. No significant group differences were found in pain detection level (i.e., level of 4 on the rating scale), or in time of reaching that detection level, on the heat feelings rating scale in any condition. Therefore, the results focus on tolerance.

8.3.4. Opiate antagonist. The opiate antagonist naltrexone (NT) was used to demonstrate an opiate relation to the dependent variables. NT (ReVia) is a potent opiate antagonist that has high affinity for μ-opiate receptors (*u*ORs) and has no opiate agonist properties (Carroll et al 2001; Katzen-Perez et al 2001; Kim et al. 2001; McCaul et al 2001; Sathe et al 2001). NT can be administered orally, has no interaction with food or beverages, is not habit-forming, has a benign adverse effect profile no different from placebo at doses below 50 mg/day, does not require nutritional support, and tolerance to NT is not known to occur. NT undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the GI tract. NT plasma levels correlate with NT dose ($r = .88$, $p < .01$). On average, and equally for both males and females, a 25 mg oral dose of NT reaches peak blood concentration in 1 h, the mean elimination half-life value is 3.5 h, and NT reduces positive mood state in normal subjects within 45 min of oral administration. Importantly, in humans NT blocks the rewarding and tension-reducing effects of alcohol, morphine, and sexual orgasm, and the euphoric subjective ef-

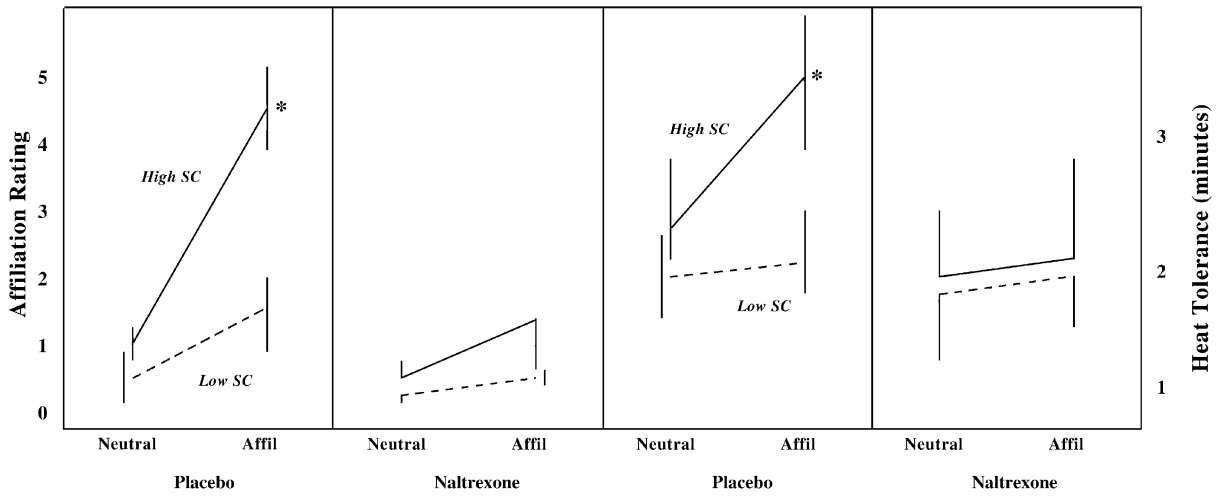

Figure 13. Preliminary data showing that: (a) affiliative film material induces a stronger state of warmth and affection (left half of figure) and heat tolerance (right half of figure) in subjects who are high versus low in trait affiliation on Tellegen's Social Closeness (SC) scale under placebo conditions, and (b) elimination of these differences between groups under administration of the opiate antagonist naltrexone. See text for details. (Abbreviations: Neurtral = neutral film condition; Affil = affiliative film condition).

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fects of opioids, all of which are mediated largely by *u*ORs (Uhl et al 1999). NT also blocks the development of vaginocervically-induced mother–infant bonds in sheep, causes maternal neglect in monkeys (Keverne 1996), blocks a preference for a novel odor or taste paired previously with morphine (Blass 1992), and blocks the establishment of odor–mother and male–female recognition associations in rodents (Leyton & Stewart 1992; Nelson & Panksepp 1998; Panksepp 1998). We used 25-mg oral doses.

Fifteen high SC (top decile) and 15 low SC (bottom decile) females were run in two randomized, cross-over, double-blind drug conditions (separated by a 4-day interval) of placebo (lactose) and 25-mg oral NT (identical gel capsules were used for the two conditions). Both conditions involved watching in counterbalanced order neutral and affiliative film segments (separated by a 10-min interval) in both drug conditions. After each film segment, affect ratings (also measured before each film) and heat tolerance were assessed. The left half of Figure 13 shows the increase in affiliation ratings induced by the affiliative film relative to the neutral film in both drug conditions. A 2 Groups x 2 Films x 2 Drugs ANOVA with repeated measures on the last two factors showed a significant 3-way interaction ($F = 17.4$, $p < .01$). Post-hoc Tukey testing of the *placebo* condition data showed that high SC subjects significantly increased their affiliation ratings to the affiliative film relative to the neutral film ($p < .01$), whereas low SC subjects showed no significant increase in affiliation ratings ($p > .30$). Moreover, the affiliative ratings to the affiliative film were significantly higher in the high SC versus the low SC subjects ($p < .01$), whereas the groups did not differ significantly in ratings to the neutral film ($p > .20$). That opiates may be involved in the film-induced increased affiliation state under placebo conditions in high SC subjects is suggested by the lack of significant increase in ratings by the high SC subjects to the affiliative film relative to the neutral film in the NT condition ($p > 30$). Indeed, in the NT condition, high and low SC groups are statistically indistinguishable for either film.

The right half of Figure 13 shows the increase in heat tolerance (time to "stop") induced by the affiliative film relative to the neutral film in both drug conditions. The significant 3-way interaction ($F = 12.7, p < .05$) mirrors the affiliation rating data: In the *placebo* condition, Tukey testing showed that (a) high SC subjects show significantly greater increases in heat tolerance after the affiliative film relative to the neutral film ($p < .01$), whereas the low SC subjects show no significant rating changes ($p > .30$), and (b) high SC subjects have significantly higher heat tolerance scores after the affiliative film than low SC subjects ($p < .01$), but the groups do not differ after the neutral film ($p > .30$). However, in the NT condition, these various comparisons show no significant differences between high and low SC subjects.

Thus, NT-induced blockade of opiate receptors eliminates the significant effects of affiliative film material on affiliative ratings and heat tolerance on high SC subjects, such that the high and low SC groups become statistically indistinguishable for either film. This suggests that the differences between high and low SC subjects in affiliative stimulus-induced feelings of affection and warmth and heat tolerance are in part a result of variation in opitate functioning. Although differences between the two groups do not appear to be related to social desirability and its correlates (self-esteem, diffidence), other unmeasured factors that might affect affiliative ratings to affiliative film material (e.g., attachment styles, rejection sensitivity, mate experiences) need to be controlled in future research.

9. Concluding remarks

There is a great paucity of *human* neurobiological research on traits that comprise the broad domain of interpersonal behavior, although animal research over the past decade has provided a significant foundation for such work (e.g., Carter et al. 1997) and human social neuroscience is an emerging field (Cacioppo et al. 2002). As a social animal, such human interpersonal traits influence some of the most important aspects of our existence, particularly the social relationships that are crucial to the survival of ourselves and our offspring, such as those between mother and infant, sexual mates, and close friends in small groups. We have argued that an affiliation trait based on an underlying process of *u*-opiate–mediated reward is a critical element in determining variation in affiliative behavior, because *u*-opiates appear to influence both the basic reward sensitivity to affiliative stimuli, and hence variation in the development of associative memory networks that support the acquisition and maintenance of affiliative preferences and bonds.

An important caveat in considering our modeling is that our analysis relies very heavily on literature from rodent studies, mainly because that is where most of the relevant data currently exist. The primate brain and primate social life are substantially more complex than that of the rodent, suggesting that the hypothetical links between animal and human suggested in the analytic strategy in Figure 2 be drawn with great care and eventually with empirical support. It might be asked, for example, what maternal care or partner preference in rodents shares with the concept of affiliation in humans, as assessed for example by the trait of social closeness (Tellegen & Waller, in press). We are not arguing that there is strict isomorphism between animal and human affiliative behavior, or that rodent affiliative behavior directly informs human social closeness as a concept. Rather, we have attempted to use the rodent literature to define more basic associations between affiliative stimuli, neurobiology and neurochemistry, and affiliative behavior including social memories, and then to apply these associations to human affiliation. One example of such a basic association is the relation between affiliative stimuli (e.g., gentle tactile stimulation) and *u*-opiate-mediated reward. It is likely, of course, that there exist more complex influences on these associations by other neurobiological modulators and social behavior in humans, influences that will obviously need to be empirically discovered in subsequent human research. A recent study, however, is supportive of our general strategy: Based in part on associations observed in the rodent neurobehavioral literature, the study demonstrated a similar regulation of human affective responses by similar neuroanatomical brain regions and limbic *u*-opiate mechanisms (Zubieta et al. 2003).

Of course, models of personality traits based on one neurotransmitter or neuropeptide, such as *u*-opiates, are clearly too simplistic, and will require the addition of other modifying factors (Ashby 1996; Depue & Collins 1999). In our model, the central *u*-opiate projection system is only one, albeit predominant, contributor to affiliative reward and bonding, and we attempted to specify the specific roles of DA, OT, vasopressin, gonadal steroids, and the rostral

APPENDIX: *Personality questionnaire traits*[a] *that correspond to the numbered trait abbreviations illustrated in Figure 1*

Study	Numbered trait abbreviation (in numerical order)	Corresponding personality questionnaire trait[a]
Tellegen & Waller (in press)		
	WB1	Tellegen Multidimensional Pers. Q., Well-Being
	Dom2	Tellegen Multidimensional Pers. Q., Social Potency
	Ach3	Tellegen Multidimensional Pers. Q., Achievement
	Affil4	Tellegen Multidimensional Pers. Q., Social Closeness
	Ach5	Personality Research Form, Achievement
	Affil6	Personality Research Form, Affiliation
	Dom7	Personality Research Form, Dominance
	Persis8	Personality Research Form, Endurance
	Affil9	Personality Research Form, Exhibition
	Nurtur10	Personality Research Form, Nurturance
	Play11	Personality Research Form, Play
	Affil12	Personality Research Form, Social Recognition
	Succor13	Personality Research Form, Succorance
Church 1994		
	Affil14	Costa & McCrae NEO, E1 – Warmth
	Affil15	Costa & McCrae NEO, E2 – Gregariousness
	Dom16	Costa & McCrae NEO[b], E3 – Assertiveness
	Act17	Costa & McCrae NEO, E4 – Activity
	Excit18	Costa & McCrae NEO, E5 – Excitement Seeking
	PE19	Costa & McCrae NEO, E6 – Positive Emotions
	Affil20	Costa & McCrae NEO, E7 – Agreeableness
	WB21	Tellegen Multidimensional Pers. Q., Well Being
	Dom22	Tellegen Multidimensional Pers. Q., Social Potency
	Ach23	Tellegen Multidimensional Pers. Q., Achievement
	Affil24	Tellegen Multidimensional Pers. Q., Social Closeness

[a]References for the trait measures may be found in the study that used them.
[b]NEO = Neuroticism–Extraversion–Openness; Pers. Q. = Personality Questionnaire.

circuit of the MXA in affiliative processes. Clearly, though, individual differences in: (a) neurobiological modulators of *u*-opiate functioning (see Fig. 12), (b) nonopiate neurobiological processes associated with other traits of interpersonal behavior (e.g., separation anxiety, agentic extraversion), and (c) social experience (Meaney 2001) will all represent error variance in predicting trait affiliation from *u*-opiate functioning alone. However, we believe that despite the complexity inherent in the neurobiology of temperament and personality, there is good reason to attempt to specify the role of one major neurotransmitter or neuropeptide, explore the details of its relation to other neurobiological variables and to personality traits, and gradually build complexity by adding additional factors one at a time. In this way, neuromodulator models of complex behavior patterns may serve as important building blocks for more comprehensive models of personality traits.

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Open Peer Commentary

Affiliative drive: Could this be disturbed in childhood autism?

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Abstract: Affect mirroring allows infants to distinguish emotional and intentional states of significant others, which – in the pursuit of their own drive satisfaction, including satisfaction of the affiliative drive – become important contextual stimuli predictive of reward. Learning to perceive and manipulate others' attitudes toward oneself in pursuit of affiliative reward may be an important step in social development that is impaired in autism.

Depue & Morrone-Strupinsky (D&M-S) acknowledge that, apart from affiliation, social cooperation involves several motivational processes including social dominance (agency), competitive aggression, and avoidance of social isolation. Social integration emerging from these processes increases the individual's abilities to satisfy a number of basic needs (drives), such as those pertaining to shelter, food, or mates. In social groups, strategies for the satisfaction of a variety of drives do not only involve the physical presence of conspecifics or their coincidental pursuit of similar ac-