Brain Mechanisms Theoretically Underlying Extremes of Social Behaviors: The Best and the Worst

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Summary

The best, most pleasant forms of social behaviors amongst humans are characterized by a degree of altruism, sometimes reciprocal altruism, that has been encouraged universally by institutions that promote civil behavior. Here we review a surprisingly parsimonious neuroscientific theory of how humans manage to behave according to the "golden rule." This theory, while allowing the understanding of pro-social behavior, also leads to a consideration of the neural mechanisms underlying aggression and abnormal social behavior, such as autistic behavior. Here we theorize that damagingly high levels of inputs from ascending CNS arousal systems to the amygdala heighten social anxiety in a manner that increases the chance of autistic behavior.

Introduction

Among scientific theories, the most elegant are those that make very few initial assumptions and do not plead special conditions or abilities. To quote Albert Einstein: "A theory should be as simple as possible but not simpler." Below we propose a means of understanding how people behave in a reciprocally altruistic fashion (when they do). The theory is not predicated on special abilities of the human forebrain; rather, it depends on a *loss* of information, the easiest kind of neural and behavioral transformation to achieve.

Equally important, especially from the points of view of behavioral medicine and public health, are the disorders of social behavior. Knowing that the amygdala is involved in the generation of fear, and observing the behavior of autistic children, we believe that social anxiety may be involved in autism. High levels of arousal-related transmitters being released in the amygdala could account for an avoidance of normal social contact.

Implications of Loss of Social Information in Cortical Circuits

Evolutionary biologists have long considered the origins of reciprocal altruism, where an altruistic act is defined as one that benefits the recipient while having negative

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Pfaff et al.
Hormones and Social Behavior

consequences on the fitness of the performer (reviewed in Lehmann and Keller 2006). Among humans, it appears that shibboleths associated with every religious system we have read (examples in Pfaff 2007) include a norm frequently referred to as the "golden rule" – I should behave toward you as I would have you behave toward me – and one of its consequences could be manifest as reciprocal altruism. The broad appearance of this ethical dictum among human societies encourages a search for its neurobiological underpinnings. Further, a mechanistic analysis is encouraged by the success of Axelrod and Hamilton (1981) in programming computers to display mutual cooperation. In their computer games, mutual cooperation got started spontaneously, thrived and resisted opposition. Axelrod's and Hamilton's success, taken together with the ubiquity of reciprocally altruistic behaviors amongst non-human primates, led us to theorize about mechanisms that could produce such behaviors.

A Theory in Four Steps

First, consider one person's, M's, action toward another, N. Before this act occurs, it is represented in M's brain, as every act must be. Motor acts being represented in one's own brain, so-called "corollary discharges," were conceived first in "reafferenz theory" (a neurophysiological theory that shows how the stability of the visual world is maintained during eye movements) and supported by a large body of experimental data (Held and Freedman 1963). Action representation to one's own brain remains of current interest in neuroscience (Cullen 2004; Sylvestre and Cullen 2006; Quiroga et al. 2006) and biophysics (Poulet and Hedwig 2006; McKinstry et al. 2006).

Second, this act will have consequences for N that M can predict and envision. Then comes the crucial step.

Third, to achieve a feeling consistent with Golden Rule behavior, then M blurs the difference between the other individual and himself to an abstract intermediate image. For example, in terms of face recognition, neurons (Gross et al. 1972) and inferotemporal cortical regions (Kanwisher et al. 1997) specialized for that function are well documented. Mechanisms for blurring, besides simply reducing cortical neuron reliability, include adding noise to the mechanism or altering temporal phases of inputs (Kanwisher N., personal communication). For example, simply reducing the efficiency of GABA-ergic inhibitory neurotransmission or increasing the efficiency of gap junction transmission would raise the overall level of cortical excitability to the point where noise could obscure the signals comprising facial or other images. As a result, instead of seeing the consequences of his act solely for the other individual, M sees them for himself. As an example posed for absolute clarity, if M had been planning on knifing N in the stomach, he loses the difference between N's body and his own. This loss of information is easy to posit because any one of the many steps required for the neurobiology of fear would provide the loss of information this theory supposes. As a result, the knifing is less likely to occur because he shares the other person's fear.

Additionally, the mirror neuron system (Rizzolatti and Craighero 2004) in the cerebral cortex may provide still another mechanism that permits a blurring of the difference between the person beginning an act and the target of that act.

Fourth, if the consequences of M's intended act are good for N, he does it; if the consequences for N are bad, then M does not do it. This decision rests not only upon

fear mechanisms, as mentioned above, but also on positive, affiliative motivations, the bauplan of which is sex behavior, whose mechanisms are relatively well understood (chapters in Pfaff et al. 2002).

This explanation of an ethical decision by the would-be knifer has an attractive feature. Usually we have to recognize and remember differences between ourselves and others. However, the explanation of an ethical decision given here involves only the loss of information, not its acquisition or storage. The learning of complex information and its storage in memory are very hard to understand. However, the loss of information is easy to understand, because it only requires the breakdown of any single part of the complex memory-storage processes, whether it be an intricate biochemical adaptation, subtle synaptic modification or precise temporal pattern of electrical activity. Thus, dampening any one of the many mechanisms involved in memory can explain the blurring of identity required by this explanation of Golden Rule-related behavior. Leaving out any one of the mechanisms involved in social recognition or memory allows us to identify with the person toward whom we are about to act. Moreover, among the theoretical mechanisms described above, the individual mechanism left out could differ from species to species and from person to person and from occasion to occasion. In mechanistic terms, therefore, it is incredibly easy to achieve a sense of shared fate with another.

By extension, this parsimonious theory of how people can behave toward others as they would like themselves to be treated also predicts that, when the "blurring" does not occur, anti-social behaviors would be expressed. This theory thus leads to a consideration of the neurobiological bases of violence in the world, as well as a variety of CNS disorders that lead to pathologies of social behavior. Regarding aggression, comprehensive reviews have covered what we know about the neural, hormonal, genetic and environmental influence on agonistic behaviors in animals and people (Nelson 2006). Among the abnormalities of social behavior, we will treat CNS influences on the development of autism in the next section.

CNS Arousal Mechanisms Leading to Social Anxiety Leading to Autism

In humans, the proper processing and recognition of facial cues is crucial to the expression of normal social behavior. One of the hallmarks of autism and related disorders is an impairment of processing and recognition of facial expressions. Patients with Asperger's disorder and socio-emotional disorder are at increased risk of prosopagnosia, that is, the failure to recognize familiar faces (Barton et al. 2004). Furthermore, when faced with a face recognition task, adults with autism spectrum disorder utilize different face-scanning strategies (i.e., they look at the eyes and other inner features of faces less often than normal individuals) and fail to show proper activation of the fusiform face area and regions of the social brain, including the mirror neuron system and the amygdala. The degree of hypoactivation of these areas correlates with social symptoms of autism (Hadjikhani et al. 2007). When they do look at the eyes during facial discrimination tasks, autistic individuals show greater activation of the amygdala, suggesting increased emotional responses associated with gaze fixation (Dalton et al. 2005). Furthermore, when asked to identify the expression of feelings in photos of

eyes, autistic patients' lower performance was associated with lower or no activation of the superior temporal gyrus and the amygdala (Davidson and Slagter 2000). It seems, thus, that autistic individuals' impaired social recognition is associated with impaired proper processing of social emotions by the amygdala. Also autistics appear not to obtain any rewarding or pleasurable responses from these human contacts.

Consistent with the non-human animal literature (Choleris et al. 2006), it appears that social recognition in humans is under the control of estrogens and their cognate receptors, estrogen receptors (ERs) alpha and beta. In this regard, there is a female advantage in facial processing and the recognition of emotional expressions (Hampson et al. 2006; Montagne et al. 2005) that is modulated by testosterone (van Honk and Schutter 2007). Augmented testosterone (and possibly reduced estradiol) reduces facial recognition and processing. This sex difference in facial recognition and processing has interesting parallels and implications for ERs and sex differences in autism.

A neuropeptide that has been involved in all of the estrogen-dependent social behaviors described above is the nonapeptide, oxytocin (OT). OT is produced in the hypothalamus and released in various areas of the brain as well as in the blood stream, thus exerting its effects both in the CNS and in the periphery (Gimpl and Fahrenholz 2001). Its release from dendrites as well as axons has been studied in some detail (reviewed in Landgraf and Neumann 2004). In particular OT is known to foster pro-social behaviors. including social recognition (Choleris et al. 2003, 2006, 2007; Fergusson et al. 2000, 2001), social learning (Popik and van Ree 1993), maternal (Pedersen et al. 1994; Young et al. 1997; Cho et al. 1999; Insel and Hulihan 1995; Razzoli et al. 2003) and sexual behaviors (Bancroft 2005; Carter 1992). OT is involved in social bonds – romantic and maternal love – even in humans (Bartel and Zeki 2004). Aggression, in contrast, is inhibited by OT administration (McCarthy 1990; Ferris 2005) and increased by blocking OT action (Lubin et al. 2003; Giovenardi et al. 1998). Mice whose gene for oxytocin has been rendered non-functional [oxytocin "knockout" (OTKO) mice] are more aggressive in both home cage (Winslow et al. 2000) and semi-natural environment testing conditions (Ragnauth et al. 2005).

OT and estrogens act in a linked manner, with OT activity being regulated by estrogens at two levels. First, production of OT is under the control of estrogens, as indicated by several pieces of evidence. Plasma OT levels and OT receptor (OTR) mRNA fluctuate with the estrous cycle in a manner consistent with fluctuations in circulating levels of estrogens (Bale et al. 1995; Sarkar et al. 1992; Ho and Lee 1992). More direct evidence shows that estrogen administration heightens the electrical excitability of OT-producing neurons in the paraventricular nucleus (PVN) of the hypothalamus. Second, the transcription of the gene for OTR is under estrogen control, with estrogen administration increasing the rate of transcription from the OTR gene (Quinones-Jenab et al. 1997). This effect is pronounced in the amygdala, which is relevant for the focus of this review, as highlighted below.

A Functional Genomic Network Supporting Social Recognition

The evidence that the risk of developing an autism spectrum disorder carries important genetic influences is overwhelming (Freitag 2007; Losh and Piven 2007; Hoekstra et al. 2007; Szatmari et al. 2007). Our concern is to use our and others' functional ge-

nomic evidence to look into the identification of specific genes contributing to autism's component functions: social recognition and the related function, social anxiety.

In this story, OT and OTR will play major parts, while vasopressin (VP) and its receptors will also provide interesting points. The release of oxytocin in the CNS – not only from synaptic endings but also from dendrites – in the hypothalamus and in the amygdala is thought to be of major importance for a variety of biologically adaptive social behaviors (Landgraf and Neumann 2004).

OT produced within neurons of PVN can be transported along axons into the amygdala, where significant levels of OTR are to be found (Elands et al. 1988; Yoshimura et al. 1993). There, both OT and VP affect neuronal excitability, with the two neuropeptides acting on distinct populations of cells (Huber et al. 2005; Terenzi and Ingram 2005). We have integrated OT actions in the amygdala with estrogenic effects there and its known neuroanatomy to formulate a 4-gene micronet theory that explains certain changes in social recognition in mice.

The involvement of OT in social recognition was initially demonstrated through pharmacological manipulations showing that administration of low levels of OT facilitates social recognition, whereas OT antagonists block it (Popik and Vetulani 1991; Popik et al. 1992, 1996). Later, studies with genetically modified mice showed that both male (Ferguson 2000) and female (Choleris et al. 2003) OTKO mice have a complete deficit in social recognition, even when tested with the more sensitive choice test paradigm (Choleris et al. 2006). OTRKO mice, too, are impaired in social recognition, further confirming the critical involvement of this system (Takayanagi et al. 2005). Further studies then pointed at the medial amygdala as the site of action of OT and OTR in the regulation of social recognition. The deficit of the OTKO male mice can be rescued by infusion of OT in the medial amygdala, whereas infusion of an OT antagonist inhibits social recognition in wild-type males (Ferguson 2001). Similarly, wild-type females that receive an antisense oligonucleotide targeting the mRNA of the OTR gene in the medial amygdala become completely impaired in social recognition (Choleris et al. 2007). The link with estrogens became apparent when it turned out that both ERα and ERβ knockout (α-ERKO and β-ERKO) mice were also impaired in social recognition (Choleris et al. 2003). When assessed with a more sensitive social discrimination test, this impairment was complete in the α-ERKO and only partial in the β-ERKO mice (Choleris et al. 2006). As in the α-ERKO and β-ERKO mice, OTKO mice showed impaired social recognition, as reflected in impaired ability to recognize and avoid parasitized conspecifics. The OTKO mice are also impaired in utilizing other mice as a source of information in mate choices and parasite avoidance.

OT involvement in social disorders has been demonstrated. Low OT plasma levels are observed in autistic patient populations (Modhal et al. 1998; Green et al. 2001), where altered oxytocin production from its prohormone precursor is shown (Green et al. 2001). Furthermore, in initial clinical trials, intravenous infusion of oxytocin ameliorated behavioral symptoms of autism in adult patients (Hollander et al. 2003). Alterations in the OT system are observed also in individuals affected with schizophrenia (Bernstein et al. 1998; Feifel and Reza 1999; Mai et al. 1993) and depression (Bernstein et al. 1998; Uvnäs-Moberg et al. 1999).

The specific impairment in social recognition of the α-ERKO, β-ERKO and OTKO mice prompted the proposal of a 4-gene micronet model to explain the action of estrogens on the oxytocinergic system in the regulation of this behavior. In this model,

ERβ regulates the production of OT in the PVN, whereas ERα controls the transcription of the gene for OTR in the medial amygdala which, in turn, receives and processes olfactory input of social relevance from the main and accessory olfactory systems (Dulac and Torello 2003; Johnston 2003). This model is supported by molecular biology studies and fully explains the behavior of the KO mice. First, ER-β is highly expressed in the mouse PVN, where ER-α is almost absent (Mitra et al. 2003), and directly regulates the production of OT (Patisaul et al. 2003). Accordingly, estrogen regulation of OT is inhibited in β-ERKO mice (Nomura et al. 2002b). Second, ERα is highly expressed in the amygdala (Mitra et al. 2003), where it is necessary for the induction of OTR (Young et al. 1998).

This model explains the behavioral results of the α-ERKO and β-ERKO mice in the more sensitive choice test paradigm (Choleris et al. 2006). The essentiality of ERα for OTR production in the amygdala (Young et al. 1998) explains the complete impairment of the α-ERKO mice, whereas the partial impairment of the β-ERKO mice (Choleris et al. 2006) can be explained by an ERβ-mediated upregulation of existing baseline production of OT in the PVN (Mitra et al. 2003). Accordingly, baseline OT levels and mRNA of the OT gene in the PVN of β-ERKO mice are normal, but they fail to respond to stimulation by estrogens (Nomura et al. 2002b). The baseline levels of OT likely allow for a certain degree of social discrimination in β-ERKO mice, which in normal mice can be enhanced following estrogens/ER-β mediated increase in OT production.

McCarthy and her colleagues (1996) have reported that oxytocin has anxiolytic properties if and only if estrogens are circulating in an adequately high concentration. This requirement for estrogens presumably is due to the strong influence of estrogens on oxytocin receptor gene transcription (Young et al. 1998). In fact, in females, blocking OT receptor activity in the brain increases anxiety-like behaviors in a manner that depends on the hormonal state of the female (Neumann et al. 2000a, 2000b). In the male, testosterone-dependent sexual activity can be followed by the reduction of anxiety due, at least in part, to the release of OT within the brain (Waldherr and Neumann, 2007).

Generalized CNS Arousal Mechanisms Related to Fear

It has been hypothesized that large numbers of ascending and descending neuronal systems involving the expression of more than 120 genes are involved in the adaptive regulation of CNS arousal (Pfaff 2006). Some of the initial need states leading to arousal, such as hunger, are quite specific. However, based on results of a meta-analysis using the mathematical statistical technique of principal components analysis, we have argued that there is a generalized arousal component, an "urarousal," that can account for as much as one-third of arousal-related behaviors (Garey et al. 2003). Of special interest for the present discussion are the effects of generalized arousal neurotransmitters in the amygdala.

Inputs to the amygdala from ascending systems that drive generalized arousal might be important for social anxiety, related to the recognition mechanisms just reviewed above, because this same brain region implicated in social recognition, the amygdala, is crucial for producing the emotion of fear. If signals from conditioned stimuli for fear do not reach the amygdala, then conditioned fearful responses do not occur (reviewed in LeDoux 2000; Rodrigues et al. 2004; Schafe et al. 2005). Likewise, if outputs from the amygdala are suppressed, for example under the influence of the

prefrontal cortex), then fear is reduced. In fact, neuropharmacological approaches to the suppression of amygdaloid facilitation of fear are important not only for syndromes such as post-traumatic stress disorder but also, according to our theorizing below, to reduce the social anxiety of autism (Davis 2005; Ressler et al. 2004). The importance of the amygdala for fear, established in laboratory rodents, holds true for higher primates, including humans (Paton et al. 2006; Kalin et al. 2004; Phelps and LeDoux 2005). What are the relationships of these mechanisms to generalized arousal?

Frightening emotions and emotional memories will not operate correctly to raise fear in a biologically adaptive fashion if the entire CNS has not been aroused. James McGaugh and his colleagues have reported (Roozendaal et al. 2004; McIntyre and McGaugh 2005) that the proper operation of amygdaloid mechanisms related to fear depends on synaptic inputs releasing the arousal-related transmitters, norepinephrine and dopamine. For example, the laboratory of James McGaugh, at University of California at Irvine, reported that they trained rats in a task in which the animals had to avoid returning to a place where their feet had been shocked. Infusing a dopamine receptor antagonist into the lateral amygdala prevented peak performance of fear learning. Conversely, infusing dopamine itself or, for that matter, norepinephrine, into the amygdala enhanced retention of the learned fear response. Even additional shocks between training and testing – which would arouse the animal – increased subsequent fear responses. Thus, animals with low levels of generalized arousal are less likely to show high levels of learned fear responses.

Another arousal-supporting neurotransmitter, serotonin, is involved in the production of anxiety and fear. Serotonin-containing fibers reach the amygdala through long axonal projections from the median and dorsal raphe nuclei of the midbrain. Some of the most exciting work on genetic contributions to fear and anxiety has dealt with the serotonin transporter (5-HTT), the molecule responsible for the reuptake of serotonin from its synaptic cleft. It is now widely recognized that the gene encoding 5-HTT contains a 44 base-pair sequence that in some individuals is inserted, producing a long allele that has high transcriptional activity, whereas in other individuals it is deleted, producing a short allele that has less transcriptional activity. In cell cultures, this translates into a twofold greater rate of reuptake when the long allele is present. What does this mean for anxiety and fear and the amygdala. Three lines of evidence gathered so far show its importance. First, human subjects with one or two copies of the short allele exhibit greater amygdala neuronal activity, as assessed by functional magnetic resonance imaging (fMRI) responses to pictures of frightened or angry faces (Hariri et al. 2002). Second, subjects with a short allele show stronger coupling between amygdala and prefrontal cortex fMRI responses to aversive pictures (Heinz et al. 2005). Since this part of the cortex can act to suppress amygdaloid output, their increased correlation is of undoubted significance and the mechanism remains to be discovered. Third, as expected, patients with one or two copies of the short allele actually showed increased levels of anxiety-related traits, state anxiety and enhanced activation in the right amygdala to anxiety provocation (Furmark et al. 2004).

Hyperarousal Fostering Social Anxiety

There is little doubt that prolonged high levels of arousal are aversive. The Yerkes-Dodson law, supported by a century of research, states that task performance will

consequently be reduced. This would be expected to include "social tasks" in which appropriate behavior with another individual is required.

There are at least three levels of mechanisms to discuss in dealing with the connection between hyperarousal and social anxiety. First, it is easy to think of long-lasting high levels of activity in the ascending arousal systems, including those mentioned above, as causing a socially anxious state. Second and more complex are the possible roles of the neuropeptides oxytocin and vasopressin themselves. They both affect the autonomic nervous systems, are both connected with the regulation of fluid balance in the body and are both involved in the regulation of smooth muscle contraction. The simplest formulation is to state that OT is more concerned with autonomic responses associated with reproduction in safe situations (lactation, delivery of babies), whereas VP is more important with emergency responses to threatening situations (dehydration, hemorrhage). Both of these physiological levels of hypothesis will benefit from comparisons among high-anxiety and low-anxiety lines of rats (Landgraf and Wigger 2002, 2003). Third is the most psychological level of exploration. It considers a "mismatch hypothesis" that social anxiety results in part from a feeling of lack of preparation for the social encounter. If we feel adequately prepared and if OT and VP levels are optimal, then we feel supported and social anxiety does not occur. If instead we are not adequately prepared and/or if OT and VP levels are not optimal, then we certainly will be hyperaroused and the anticipation of the social event, whatever it may be, will be anxiogenic.

Social Anxiety Fostering Autism

We theorize that imbalances among the levels of expression of certain genes in neurons within the amygdala or among expression of genes in CNS arousal pathways lead to the appearance of autism spectrum disorders. Already, the notion of strong amygdaloid involvement receives strong support from the literature. Ralph Adolphs and his colleagues (Spezio et al. 2007) have found that substantial damage to the amygdala reduces eye contact during conversations, following up earlier work (Adolphs et al. 2005) during which destruction of the amygdala in a human was found to have damaged the ability to respond to fearful expressions of others in a normal way. Conversely, scientists working with Andreas Meyer-Lindenberg (Kirsch et al. 2005) reported that human amygdaloid function is modulated by oxytocin, in that fear-inducing visual stimuli did not activate the amygdala in human subjects given intranasal applications of oxytocin. Thus we hypothesize that, in the amygdala, oxytocin action will reduce the potential for autism, whereas excess stimulation from ascending arousal pathways – typical perhaps with Asperberger's patients – will increase the likelihood of autism. Consistently, autistic children have enlarged amygdalar volumes (Schumann et al. 2004).

The possible role of ascending arousal systems, such as dopamine, norepinephrine and serotonin, in influencing the amygdala in such a manner as to increase social anxiety has received some support. All three of these neurotransmitters are imbalanced in autism (Penn et al. 2006). Likewise, there are a few studies showing opioid dysfunction in autistics, also summarized by Penn et al. (2006).

Outlook

In summary, we have presented parsimonious theories of brain mechanisms underlying some of the best forms of social behaviors and some of the worst: altruism and autism. Research to test the "image blurring" component of the hypothesis for reciprocal altruism could involve, for example, purposefully adding noise to the relevant sensory systems by blocking GABA inhibitory transmission. Experiments to test the arousal component leading to social anxiety might well include pharmacologic manipulation of the amygdala with respect to its noradrenergic, dopaminergic and serotonergic inputs. In both cases, laboratory neuroscience is speaking to matters of great public concern.

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