VOLES IN LOVE:

Neural Foundations of Love

by DOUG HIDLAY

Love has long been regarded a truly human emotion – something that separates us from the animals. We fall in love as a function of the greater brain and emotional capacity we have been endowed with by evolution. Animals have less brain mass than humans do, particularly in the cortex, the region associated with higher-level thought processes, so it seems only logical that they would be unable to generate abstractions such as "feelings." And yet, the research done with *Michrotus ochragaster,* a monogamous species of vole, challenges the traditional understanding of how the feelings associated with love, trust, and simple companionship are generated by animals. In fact, the study of these species of vole suggests that genes predispose some to an innate tendency towards a concept as culturally engrained as monogamy.

Michrotus ochragaster, the prairie vole, first noted as a possible source of information regarding pair-bonding, shows significant fidelity and duration of typical pair-bonding to the extent that as many as 70% of widowed voles do not form a new pair-bond later in life[1]. This social bond is catalyzed specifically by two neurotransmitters: arginine vasopressin (AVP) and oxytocin (OT). In males, AVP is thought to be the predominant chemical responsible for their ability to pair bond, while OT shows a similar importance in females[2].

Neurotransmitters and their Activity in Voles

This marked response that AVP generates in the male prairie vole has been shown to correlate with a higher density of the corresponding receptors (V1aR) in the ventral pallidum, a feature not shared in its closely-related polygamous cousin species of vole, the montane vole[2]. Neural firing in the ventral pallidum is associated with "hedonistic" impulses in organisms, suggesting that AVP's increased effect leads to higher activity in the brain's "reward" pathways[3]. And since AVP is released as a result of the sensory input from sexual interaction in male prairie voles, the animal's mate becomes a stimulus triggering these reward sensations in the male, increasing his social cueing towards his partner, and forming a more concrete pair-bond. The resulting cueing is not simple mate preference but also increases in mate guarding and similar protective actsaggressive behaviors traditionally associated with AVP. The key difference is that typical AVP increases lead to general increases in aggression, while these changes are directly correlated to interactions between a male and his mate[2].

Despite this association, strong pair bonding itself is largely due to reward circuitry, but the ventral pallidum and its activity are not considered the primary reward pathway; the dopaminergic pathways located largely within the mesolimbic system have instead been found to be highly-correlated to reward and positive reinforcement[4]. Studies show that activation of D2 receptors in the ventral tegmental area and their neuronal projections into the nucleus accumbens, as well as other parts of the brain, are critical to the sense of pleasure and conditioned reward association and are naturally stimulated by processes such as eating and mating[4].

The overlap between the dopaminergic pathways and those of AVP exists on two levels: the mating act itself and the integrated neural circuitry. The act of mating results not only in increased AVP levels, but also in a sharp increase in dopamine (DA) levels. But, as shown by studies in polygamous rats, increasing DA levels alone does not generate monogamous behavior[3]. This implies that the high V1aR density in voles modulates the dopaminergic pathways and correlates the increased reward sensations with mate preference, leading to pair-bonding in males[5].

But even beyond these changes, the DA-modulated pathways are further altered by mating. The D1 receptors in the mesolimbic system are inhibitory and have been shown to block reward stimulus and be an effective opposing force to D2 receptors, and, after male prairie voles mate and form their pair-bond, a massive up-regulation of D1 receptors takes place[3]. One might logically conclude that this prevents the pair-bonding act, but it is believed to actually reinforce social cueing by stopping any further pair-bonding with voles other than the male's mate. Though this occurrence has not been as fully explored, studies have made very strong suggestions towards this explanation, and the reader should be aware of its existence.

Paralleling the studies done in males, research in females has shown that the key element to female vole social cueing lies not with AVP, but OT and its high receptor presence in the nucleus accumbens[6]. The prairie vole shows distinct changes in density and distribution of its OT receptors, similar to the changes in AVP receptors, from its cousin the montane vole and this is believed to increase the female's social recognition of its mate, as OT-release occurs concurrently with AVP during the mating process[5]. As previously mentioned, activity in the nucleus accumbens has been associated with reward pathways and OT activity likely stimulates very similar pathways as AVP does in males.

The specific function of OT seems to be "social memory," or the female's level of companionship with its mate, stimulated by increased reward sensations similar to what AVP generates in males. This function was discovered by showing that the intracerebral introduction of an OT antagonist results in "social amnesia" in female prairie voles, and afterwards no preference of company between a previous mate and a new one[7]. Where AVP causes males to show preference by protective behavior towards its mate, OT instills a female with a "trust" towards its mate, shown by increased contact and time with its partner.

At this stage though, the quantity of research done on OT pathways in prairie voles is significantly less than that of AVP studies; what occurs underlying pair-bonding in females remains less clear, despite the theories, because the research performed has shown less clear-cut data regarding female voles than those examining males. This result is likely due to the minimal differences in OT receptor distribution between male and female voles and the relatively unknown effects of non-DA neurotransmitters in the nucleus accumbens shell and core[8]. The problem at this stage is a matter of discerning why OT seems to have little effect on males and such a profound one on females despite no significant, identifiable difference in physiology, as described above.

The Underlying Genetics of Voles

In any case, the establishment of both AVP and OT as essential in vole pair bonding has lead to the logical next step: genetic analysis of the coding regions associated with the receptors of these neurotransmitters. In comparative studies with montane voles, both types of receptors are nearly functionally, structurally, and genetically identical between species of vole and yet, they seem to almost single-handedly change a species of vole from monogamous to polygamous, or the other way around[6]. The difference then must lie in the promoter and enhancer regions associated with AVP and OT receptor genes and in the locations of activity of these two sequences.

Through analysis of the V1aR gene in male prairie voles, a simple microsatellite polymorphism was found that is not shared with the montane vole, and the result is a sizable difference in the length of this region just 5' of the V1aR gene. This promoter stretch is conserved across prairie voles and is almost 3 orders of magnitude greater than that of its cousin[9]. Studies then confirmed that this stretch of DNA can be artificially lengthened to lead to prairie-vole-like behavior in montane voles or shortened to lead to montane-vole-like behavior in prairie voles[8]. The differences were not limited to the ability of voles to pair bond: longer-repeat prairie voles groomed their partners more and spent more time with their young than shorter-repeat voles did[9].

Visible confirmation of the genetic differences was obtained by autoradiograph of prairie voles with varying sizes of these microsatellite polymorphisms. Correspondingly, a direct increase in V1aR density could be seen as the DNA in this promoter region increased, and the autoradiographed prairie voles showed increased social activity and pair bonding potential in accordance with expectations[9]. The remarkable fact here is that a single promoter for a single gene was able to change one species to an almost identical behavioral twin of another that shares next to none of the same complex social traits.

Attempts have been made to similarly identify promoter regions unique to prairie voles that control OT receptor density and distribution, but no *cis*-acting elements like the V1aR repeat polymorphism have been isolated[8]. In its overall distribution and purpose, OT is a complex molecule of action in males but even more so in females, for the role it plays in inducing labor and proper maternal care[10]. As such, the genetic basis for OT's effects on pair-boding remains mostly theoretical at this stage, and more research is required to isolate the important regions needed to generate the high density of OT receptors found in the nucleus accumbens of prairie voles.

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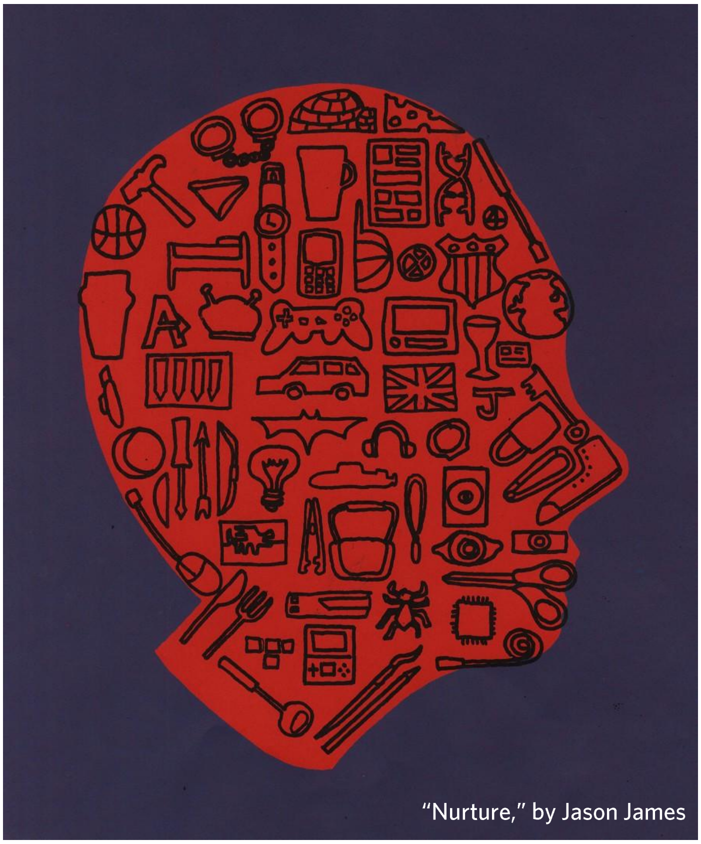
What may be most revolutionary about the study of monogamy through prairie voles is the simplicity of the model. Biologists always search for the simplest organism that can be reasonably used to identify, isolate, and alter a given pathway within an organism's overall physiology. The problem with studying a phenomenon like monogamy is the complexity of such a social behavior, which means that the best model for its study cannot be as "simple" as other traditional biological models. Organisms simple enough to control every aspect of besides the one under study, such as the standard for study of developmental biology, *Caenorhabditis elegans*, do not have the biological complexity necessary for this kind of social interaction. Accepting this fact, the prairie vole is about as ideal a model as possible. While the mechanisms underlying female pair bonding are far from clear, the male



“Nurture,” by Jason James

model is concise and relatively easy to work with. Alteration of a single DNA microsatellite leads to a relatively consolidated and identifiable change in brain chemistry and the results can easily be quantified and studied in-depth. The test of the prairie vole’s importance to the typical person though lies with the ability to translate studies of vole behavior to studies of human behavior, though humans are significantly more complex and the distinction between neurological hard-wiring and cultural practice is difficult to identify.

Neurotransmitters and their Activity in Humans

Studies on the activity of AVP in humans have indeed shown similar effects to that of AVP in voles regarding its general release and overall importance to the act of mating in males. As in voles, AVP has been demonstrated to be released after mating and work as a social cueing mechanism in preparation for reproductive interactions, but unlike in voles, this increase has not shown the same kind of specificty in its pattern of release or location of action in mating or otherwise. Instead, AVP release in humans stimulates general adrenergic pathways and glucocorticoid release that are used to mate as well as cause further cascades of hormones in the male body.

Ancestrally, AVP was strictly an anti-diuretic hormone, but it has been derived to signal the reproductive act in males; vasopressin’s effects can be traced to both blood vessel dilation and increases in blood pressure, brought on in part by its original function to maximize water retention as well as the actions of the other hormones it triggers[11]. Another effect is a general increase in aggression, though not directed solely towards mate protection, which correlates to adrenergic and glucocorticoidal stimulation[12]. As a result of the wider diversity of its actions, the direct influences of AVP alone on male or female behavior have not been identified in detail, but the basic principles of action are thought to be understood since much of the distribution and theorized pathways of AVP receptors appear to be shared between voles and humans.

The original evolutionary effects of OT in females are related to mostly to parturition. This function has been shown to extend to pair bonding in voles as previously mentioned, but in humans it has typically shown correlation only to more general affectionate care, such as grooming; management of nociception - the processing of pain signals; and anxiety[13]. Whereas AVP has been significantly derived from its original role modulating renal function, OT has been more conserved in its activity, allowing for an easier study of its effects. And though these neurotransmitters’ locations of action within the brain are more varied than that of voles, experimental evidence has shown that much of collected data have application to humans[13].

Since oxytocin has shown few toxic effects when administered intranasally, its effects have been well-studied in humans; research has found its activity to be a large factor in interpersonal trust and general social cueing[14]. Higher levels of OT in humans have shown correspondence with higher levels of trusting behavior in laboratory studies and, based on the understanding of OT's high release during the mating act, the data in humans supports a hypothesis that central OT signaling is influential in pair-bonding. Given the data at hand, OT's activity in humans seems more analogous to its rodent counterpart than is AVP's. The consistency of increased grooming, social cueing, and overall trust seen in human female with female voles points towards a higher conservation of OT's functions across female mammals than AVP's or other neurotransmitters' actions in male mammals[13]. As such, further studies on OT will likely reveal increasing similarities of action and concretely show the importance to human female pair bonding behavior.

Since the basic physiological relationships between AVP and OT in voles and humans have been examined, the next step is to compare the genetics of the two organisms and examine relevant similarities and differences in the the AVP and OT receptor genes as well as their related promoters, enhancers, etc. The easiest target for study is that of the AVPR1A gene in humans, a direct homolog to the V1aR in prairie voles. Based on the overwhelming evidence of the power of the 5' microsatellite in voles, the surrounding polymorphisms of the gene have been thoroughly examined for correlations with monogamy. Despite the difficulty of accurately examining human neurochemistry, a relationship has been found between the presence of two copies of the RS3 allele 334 polymorphism and the reported happiness by both the male and his partner in a monogamous relationship[15].

The lack of this allele versus the presence of a single copy has shown only small changes in reported contentment in relationships, but the presence of two of these alleles has been found to correspond to increased fighting, marital troubles, and likelihood of cohabitation of partners instead of marriage. The obvious suggestion is that two copies of this polymorphism is similar to shortening the microsatellite promoter region in male voles; the allele seems to reduce affinity for transcription and production of AVP receptors, decreasing the predisposition towards monogamy[15].

The evolutionary basis for having this kind of regulation of AVP receptors is quite explicable. For one, decreased sensitivity to AVP may reduce spontaneous aggression and some of the debilitating effects of stress on the human brain. This may in turn help maintain organization of the natural social hierarchy of human groupings despite the somewhat counterproductive effect of destabilizing mating interactions. In any case, the data from this study points towards an innate difference in some males' tendency towards monogamy, a fact that may leads to biological questions as well as a number of social ones. Some may point this study and conclude that some men are just "not meant to be" in monogamous relationships, but that statement is hardly answerable as will be discussed.

The genetic basis of OT receptor distribution in humans has yet to be concretely elucidated with regards to social organization, largely due to similarities between OT genes in human males and females and a lack of differentiation in activity except in cases of pregnancy and, theoretically, maternal care[16]. Still, the remarkable consistency in the results between experiments in voles and those in humans suggests a high conservation of overall action of OT. The major dilemma in studying any neurotransmitter in humans is the delicacy of the system that is infinitely more complex than that of the model, and even the model organism here does not demonstrate a simple system for OT. As a result, the expectation of a clear cause-effect model for OT is likely out of reach until it can first be isolated in prairie voles and studied conclusively there.

Ultimately, we must ask what all this data means and how definite these studies of genetics and neurobiology have been. The data at hand is solidly conclusive with regards to AVP and its roles in voles and is even very convincing when discussing OT's overall effects, if not its mechanism and location of action. What will concern the majority of readers though are the social questions many will feel this model of pair-bonding raises.

Simply put, we are not voles. The pressures on human society prior to civilization and the effective end of evolution are factors not shared with the prairie vole. Psychologists, philosophers, non-academics, and even some biologists might disregard the presented information as part coincidence and part scientific attack on cultural institutions, but those reactions are simple forms of paranoia in the face of rational attempts at understanding complex behaviors. When earlier studies examining biological differences in homosexual men[17] or links between genetics and one's spirituality[18] were released, many called the research into question on the basis of religious or personal beliefs and failed to even examine the underlying science. The correct manner to tackle provocative research with is objectivity and an open-mind; the discoveries at hand may be ones that will shape history in the future.

And though research has found genes related to spirituality, sexuality, even antisocial tendencies, these have always been general relationships, not concrete ones. When one considers the possible effects of something as incredibly powerful as the human cerebral cortex, it is clear that few social behaviors are pure hard-wiring; rather, genetics provide a physiological canvas, mapping out how cells will function during development, but the nature of the human brain coupled with the uniqueness of any individual's post-natal experience are likely just as critical to any patterns of complex behavior. In fact, any article claiming to have found the gene responsible for "X", where "X" is anything behaviorally complex, must be read with a measure of cynicism and a sense of the power of one's cerebral cortex. Pigeonholing a single cause to a large effect is scientifically irresponsible.

The examined studies of prairie voles provide conclusive evidence, showing that AVP and OT, through their interactions with reward pathways during the mating act, can almost single-handedly shape the voles' ability to pair-bond and be monogamous. Higher AVP receptor density leads to stronger pair-bonding in males, and higher OT release leads to stronger pair-bonding in females, with little overlap between the two. Experimentally decreasing AVP receptor sensitivity and using OT antagonists have confirmed these simple relationships through the resultant forms of social behavior radically inconsistent with the natural prairie vole model. The V1aR microsatellite in male voles can almost be singly traced to the inter- and intra-specific variations in monogamous behavior. The strength of these studies lies in their definite results and simplicity.

Still, scientists are nowhere near the complete understanding of mating systems in voles, let alone humans, but the studies in voles have noticeably altered the scientific perspective on how social interactions take place and pair-bonding forms in any mammal. The mediation of dopaminergic pathways by AVP and OT emphasizes the incredible complexity of the brain's evolution. Though the logical leap from the original functions of AVP and OT to their current derived ones is not great, the high conservation of purpose these two chemicals show across mammals is somewhat astounding and reinforces the validity of the prairie vole model for future understanding of human mating systems.

In light of this data, monogamy likely has an important place in human society as more than just a cultural institution. While the human cerebrum is incredibly powerful, it is still ruled at some level by natural human instincts such as pair-bonding and protection of mates and offspring. Treating monogamy as an artificial construct ignores the consistency of overall human behavior with other mammals and disregards the fundamental principles that lead us to use animal models of behavior in the first place. We are mildly sexually dimorphic creatures; men are typically larger and hairier, have increased muscle mass, and show different patterns of behavior from women. As a general rule for mammals, the more sexually dimorphic an animal is, the more likely it is not strictly monogamous. In the case of humans, we are by no means significantly different between genders on the scale, and there is a large pool of data for and against monogamy as a natural practice.

The simple answer at this stage in our overall understanding of human sociobiological drives is that model studies can only provide a basic framework for what occurs in humans. Evolution is a frugal creature and works to conserve as many useful biological tools as it can. As such, there are sound theoretical backings for why we see "human" traits and behaviors in more primative mammals, and we should look to them as a first resource for the study of our own actions. Still, completely understanding complex human behavior is as difficult a task as studying the evolutionary processes that got us to this stage. The proper response to these academic hurdles, though, is to continue our self study through the appropriate biological models and dedicate ourselves to unraveling the fundamental principles that govern complex behaviors.

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