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CHAPTER 34

Molecular genetic studies of the arginine vasopressin 1a receptor (*AVPR1a*) and the oxytocin receptor (*OXTR*) in human behaviour: from autism to altruism with some notes in between

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Abstract: Converging evidence from both human and animal studies has highlighted the pervasive role of two neuropeptides, oxytocin (OXT) and arginine vasopressin (AVP), in mammalian social behaviours. Recent molecular genetic studies of the human arginine vasopressin 1a (*AVPR1a*) and oxytocin (*OXTR*) receptors have strengthened the evidence regarding the role of these two neuropeptides in a range of normal and pathological behaviours. Significant association between both *AVPR1a* repeat regions and *OXTR* single nucleotide polymorphisms (SNPs) with risk for autism has been provisionally shown which was mediated by socialization skills in our study. *AVPR1a* has also been linked to eating behaviour in both clinical and non-clinical groups, perhaps reflecting the social and ritualistic side of eating behaviour. Evidence also suggests that repeat variations in *AVPR1a* are associated with two other social domains in *Homo sapiens*: music and altruism. *AVPR1a* was associated with dance and musical cognition which we theorize as reflecting the ancient role of this hormone in social interactions executed by vocalization, ritual movement and dyadic (mother-offspring) and group communication. Finally, we have shown that individual differences in allocation of funds in the dictator game, a laboratory game of pure altruism, is predicted by length of the *AVPR1a* RS3 promoter-region repeat echoing the mechanism of this hormone's action in the vole model of affiliative behaviours and facilitation of positive group interactions. While still in its infancy, the current outlook for molecular genetic investigations of AVP-OXT continues to be fascinating. Future studies should profitably focus on pharmacogenomic and genomic imaging strategies facilitated by the ease and efficacy of manipulating AVP-OXT neurotransmission by intranasal

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administration. Importantly, physiological measures, behavioural paradigms and brain activation can be informed by considering between-group and also within-group individual differences defined by common polymorphisms. Ultimately, investigators should strive to develop a cohesive model explaining how genomic variations are translated into individual and group differences in higher-order social behaviours.

Keywords: arginine vasopressin 1a receptor (*AVPR1a*); oxytocin receptor (*OXTR*); molecular genetics; social behaviour; autism; neuropeptides; music

Introduction

Emerging research on the molecular genetic foundations of arginine vasopressin (AVP) and oxytocin (OXT) mediation of human behaviour has been the fortuitous beneficiary of three proximal research streams: (1) The well-documented role of OXT and AVP receptor genes (*AVPR1a*, *OXTR*) in mammalian behaviour, particularly the vole (Young, 1999), has stamped the molecular genetic signature of these two neuropeptides on affiliative behaviours across species and kindled interest in finding similar mechanisms in their human homologues; (2) association studies of both *AVPR1a* (Kim et al., 2002; Wassink et al., 2004; Yirmiya et al., 2006) and *OXTR* (Wu et al., 2005; Jacob et al., 2007; Lerer et al., 2007) examine their role in autism, a disorder whose core deficits are centred on social interaction and communication. These clinical investigations by studying an extreme phenotype have also underscored the potential importance of these two neuropeptides in normal human social behaviours and (3) a new bag of tools has been provided by the burgeoning field of behavioural neuroeconomics (Adolphs, 2003; Camerer, 2007), emphasizing novel laboratory-based paradigms to assess the neurocognitive architecture of social behaviour. Of particular interest are studies showing that administration of intranasal administration of OXT caused subjects to display a remarkable change in social behaviour and related brain activity, including modulated amygdala responses to facial expressions, a willingness to trust anonymous partners in an economic task and an improved ability to recognize emotions (Kirsch et al., 2005; Kosfeld et al., 2005; Domes et al., 2007a, b). While these studies have helped clear the waters for a general understanding of how OXT and AVP function as social facilitators, the basis for the often significant individual differences in these phenotypes has been left unexplored, providing a unique opportunity for molecular geneticists.

Behavioural effects of AVP and OXT are species-specific with the neuropeptides exerting their actions via binding to specific receptors. Both OXT (Gimpl and Fahrenholz, 2001) and AVP receptors (Thibonnier et al., 2002) have seven transmembrane domains and belong to the class of G-protein-coupled receptors. In humans, at least three vasopressin receptor types (V_1R/V1a, V_2R and V_3R/V1b) have been identified (Thibonnier et al., 2002; Streefkerk and van Zwieten, 2006). Of special relevance for human behavioural studies is *AVPR1a* (chr 12q14-15) because regional brain-expression patterns of the V1a receptor gene determine marked intra- and interspecies variation in social and reproductive behaviour in the vole model (Hammock and Young, 2002, 2004, 2005, 2006; Hammock et al., 2005). Therefore, research in human social behaviour has perforce focused on the *AVPR1a* receptor. However, the $V_{1b}R$ (V_3R) receptor type is also of interest because some studies have linked it to anxiety and depression (Ring, 2005).

AVPR1a

The species-specific pattern of *AVPR1a* brain expression is determined by repeat elements (microsatellites) in the upstream receptor promoter region (Hammock and Young, 2002, 2004, 2005, 2006; Hammock et al., 2005). In a remarkable series of investigations, the longer length of the repeat in the prairie vole was shown to explain its gregarious nature and affiliative behaviours. Individual

differences in prairie vole behaviours are also explained by within-species microsatellite variation that determines gene expression (Hammock and Young, 2005). Intriguingly, our research group also showed that upstream promoter-region microsatellite length appears to modulate a spectrum of *human* social behaviours including some that resonate with similar phenotypes observed in lower mammals (Bachner-Melman et al., 2004, 2005a, c, 2007; Knafo et al., 2008).

Located on chromosome 12q14-15, *AVPR1a* is distinguished by three microsatellites in the 5′ flanking region and a fourth in the single intron (Thibonnier et al., 2000; Thibonnier, 2004). Following the vole studies, attention has been primarily focused on two microsatellites in the promoter region, RS1 and RS3, which are highly polymorphic (many repeat alleles of varied lengths are represented in the population) and which have been the mainspring of research to date; see Fig. 1 for a schematic. Most importantly, as shown in Fig. 2, the first findings using human postmortem hippocampal samples showed that long *AVPR1a*. RS3 repeats (>325 bp) were associated with higher *AVPR1a* mRNA levels than short repeats, revealing a functional molecular genetic basis for the differences in social behaviour (Knafo et al., 2008) and as discussed later on in this chapter.

OXTR

The human *OXTR* is a 389-amino acid polypeptide located on chromosome 3p25 spanning approximately 19 kbp and containing three introns and four exons (Inoue et al., 1994). Approximately 30 single nucleotide polymorphisms (SNPs) are known in the *OXTR* gene region. An intelligent SNP marker selection scheme has been developed which is aimed at increasing the chances that at least one typed SNP would be in linkage disequilibrium (LD) with the disease/phenotype causative variant, while at the same time controlling the cost of the study in terms of the number of markers genotyped and samples. Empirical studies reporting block-like segments in the genome with high LD and low haplotype diversity have motivated a marker selection strategy whereby subsets of SNPs that 'tag' the common haplotypes (htSNPs) of a region are selected for genotyping, avoiding typing redundant SNPs (Halldorsson et al., 2004).

Following this strategy of cost-effective and efficient SNP selection, we used HapMap data http://www.hapmap.org/ and the Haploview programme (Barrett et al., 2005) to identify 18 tagging htSNPs across the *OXTR* gene region. As discussed below, we genotyped these tagging SNPs and tested association with autism (Lerer et al., 2007). The location of these htSNPs along the

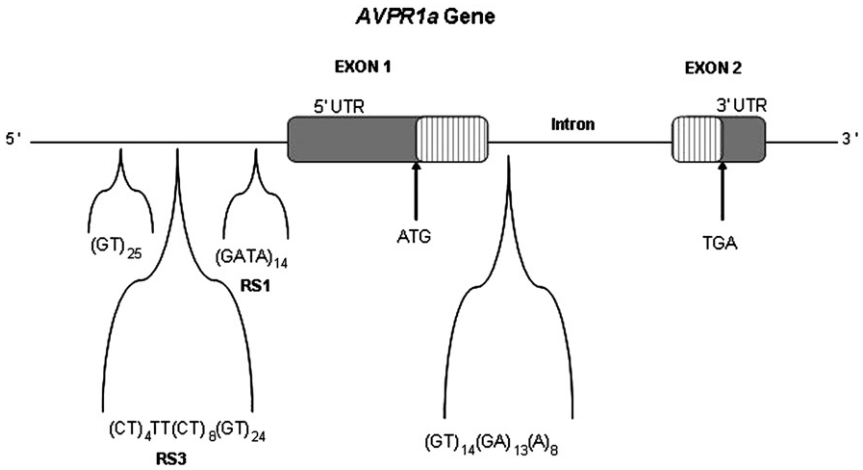

Fig. 1. Location of *AVPR1a* microsatellite repeats (Thibonnier et al., 2000). The start site of protein synthesis is represented by ATG.

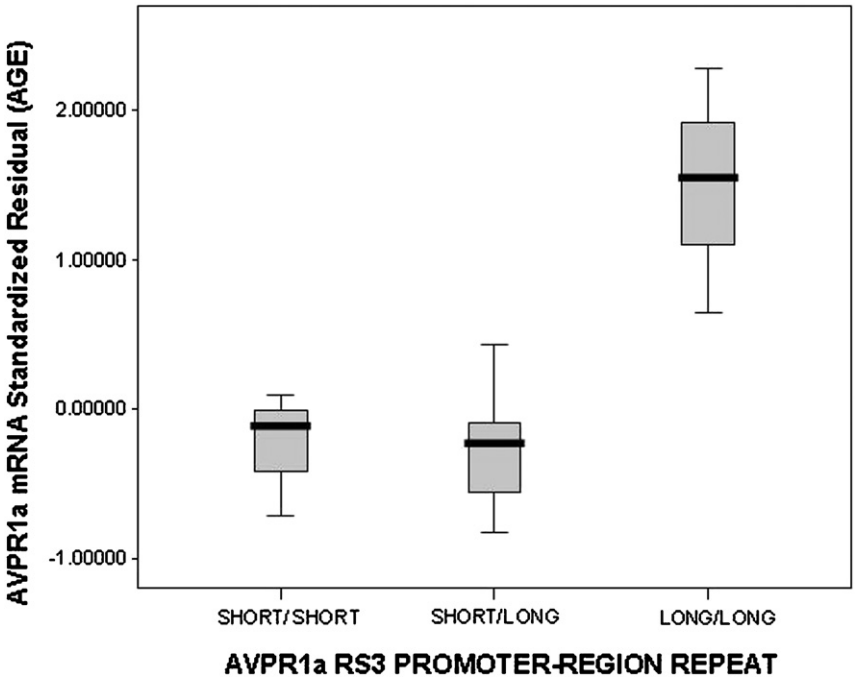

Fig. 2. Hippocampal *AVPR1a* mRNA levels grouped by *AVPR1a* RS3 promoter-region repeat by genotype length. The data is presented as a SPSS box plot. Control subjects had no contact with any psychiatric service prior to death, had not received antipsychotic medication, had not died by suicide nor had any neurological disorder. Age: 46.6 years $\pm$ 15.2 (S.D.); sex: 4F/11M, post-mortem interval (PMI): 42.0 h $\pm$ 16.4 (S.D.) and pH of brain tissue: 6.3 $\pm$ 0.22 (S.D.). Post-mortem mRNA levels correlated only with age. We also analysed the data using the non-parametric Kruskal Wallis statistic (chi-square = 6.8, 2 DF, $p = 0.033$).

OXTR genomic region and their relationship to the exon/intron boundaries are displayed in Fig. 3.

Genetic studies

Clinical studies: autism

Mediation of social behaviours by AVP and OXT in animal models led a number of investigators to postulate that variants in these two neuropeptides could potentially contribute risk to human behavioural disorders, especially autism spectrum disorders (ASD) (Insel et al., 1999; Lim et al., 2005; Carter, 2007; Hammock and Young, 2006). ASD, which is no longer uncommon (Newschaffer et al., 2007), is a pervasive neuropsychiatric disorder marked by a triad of impairments including deficits in social interaction and communication, and repetitive and restrictive behaviours and interests.

Kim et al. (2002) first demonstrated an association between *AVPR1a*.RS3 microsatellites and autism. Two later studies by Wassink et al. (Wassink et al., 2004) and our group (Yirmiya et al., 2006) provided independent replications of this first finding. Wassink et al. (2004) found modest evidence for LD in both the RS1 and the RS3. We (Yirmiya et al., 2006) demonstrated that the association between autism and *AVPR1a* is partly mediated by deficits in socialization skills. The demonstration that the risk conferred by *AVPR1a* for autism is partially mediated by socialization skills strengthens the link between the well-characterized role of this social hormone in other mammals and humans. Moreover, these results suggest the somewhat remarkable notion that during the long course of vertebrate evolution including *Homo sapiens*, these two neuropeptides have a conserved role in enabling social and affiliative behaviours.

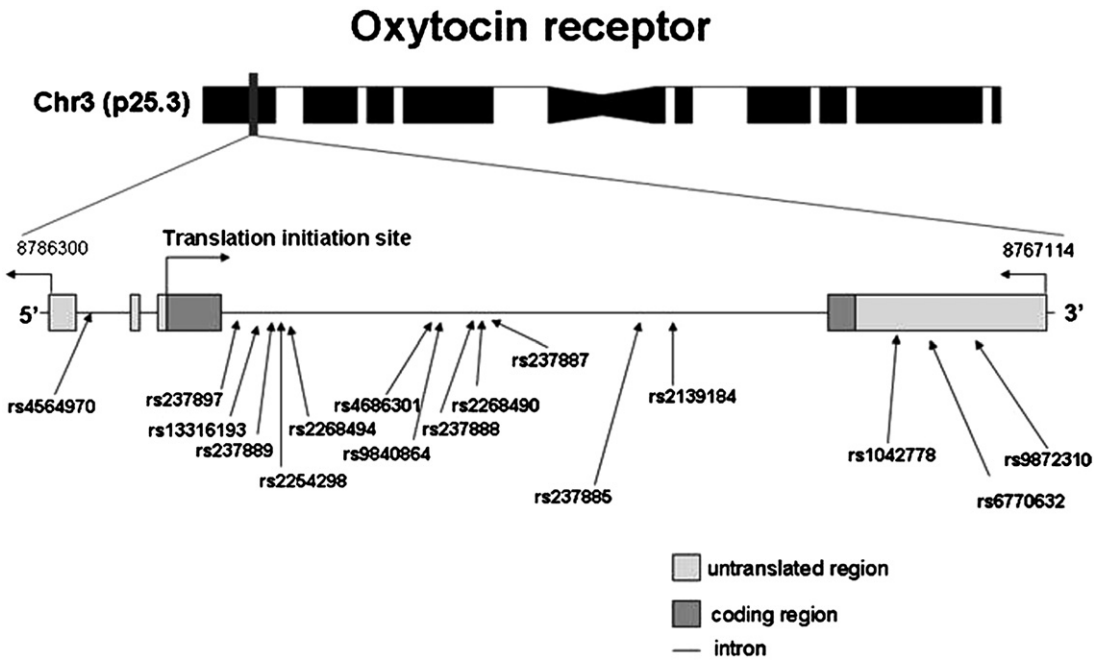

Fig. 3. Position of tagged SNPs sites and their relationship to the exon–intron boundaries of the *OXTR* gene.

Recently, Wu et al. (2005) genotyped four SNPs in *OXTR* in 195 Chinese Han trios and demonstrated association with ASD with both individual SNPs and haplotypes. A second study by Jacob et al. (2007) genotyped two *OXTR* SNPs and observed a significant association with a single SNP (rs2254298) in Caucasian children and adolescents with autism. We undertook a comprehensive study of all 18 tagged SNPs across the entire *OXTR* gene region (Fig. 3). Altogether 152 subjects diagnosed with autism spectrum disorders (ASD, i.e. DSM IV autistic disorder or pervasive developmental disorder — NOS) from 133 families were genotyped (parents and affected siblings). Both individual SNPs and haplotypes were tested for association using family-based association tests as provided in the UNPHASED set of programmes (Koeleman et al., 2000; Dudbridge, 2003). Significant association with single SNPs and haplotypes (global p values <0.05, following permutation test adjustment) were observed with ASD. Association was also observed with IQ and the Vineland adaptive behaviour scales (VABS) scores. In particular, a five locus haplotype block (rs237897-rs13316193-rs237889-rs2254298-rs2268494) was significantly associated with ASD (nominal global $p = 0.000019$; adjusted global $p = 0.009$), and a single haplotype (carried by 7% of the population) within that block showed highly significant association ($p = 0.00005$).

Our study was the third association study, in a third ethnic group, revealing that SNPs and haplotypes in the *OXTR* gene confer risk for ASD. We also showed association with IQ and total VABS scores (as well as the communication, daily living skills and socialization subdomain scores), suggesting that this gene shapes both cognition and daily living skills which may have a role in other disorders, as well as non-clinical populations.

A role for the *OXTR* in autism is further strengthened by two genome-wide scans highlighting the 3p25 region, containing the *OXTR* receptor gene, as a putative linkage site for ASD (McCauley et al., 2005; Lauritsen et al., 2006). Finally, a unique case study that lends additional credence to the role of *OXTR* in autism is the

description of a 9-year-old boy referred for genetic testing and presented with pervasive developmental disorder, delayed speech and rapid onset obesity. Extensive genetic analysis revealed an apparent duplication of chromosome region 3p25.3p26.2 and a twofold–threefold increase of *OXTR* expression relative to comparison subjects (Bittel et al., 2006).

Other clinical studies

Investigations of other clinical groups extended the evidence about the influence of AVP receptors in a broader set of phenotypes, still linked albeit indirectly, to social behaviour. For example, *AVPR1a* microsatellites have been associated with anorexia nervosa and child and adolescent perfectionism (Bachner-Melman et al., 2007) as well as with general eating pathology in a non-clinical population (Bachner-Melman et al., 2004); behaviours that we hypothesize are inextricably entrenched in social settings and rituals, in culinary and consumption customs and in cultural habits and norms. Geller et al. (2005) explored an association between *AVPR1a* and child hypersexuality in 32 bipolar families, finding no significant associations between RS1 or RS3 repeats and uninhibited behaviour. In one of the rare reported studies examining the 1b receptor, van West et al. (2004) genotyped five SNPs in both Belgian and Swedish populations, and found a significant protective effect of an *AVPR1b* haplotype on major depression.

AVPR1a and social behaviour in non-clinical populations

Interpersonal relationships: siblings and others

We (Bachner-Melman et al., 2005c) examined RS1 and RS3 promoter-region repeat markers and tested for linkage to two complex social behaviours in humans: sibling relationships and self-presentation style. We evaluated the perceived quality of the relationship between siblings using the sibling relationship questionnaire (SRQ; Furman and Buhrmester, 1985) and assessed three dimensions including: (1) relative status/power, (2) warmth/closeness and (3) conflict. Self-presentation style was assessed by employing the concern for appropriateness scale (CFA), which measures a defensive and fearful social approach associated with conformity and aimed at gaining acceptance and approval, and avoiding social threats (Lennox and Wolfe, 1984). The CFA reflects social orientations with a high degree of concern for social cues and social approval and correlates negatively with self-esteem and extraversion. One might expect the prairie vole to score high on both the SRQ (e.g. warmth/closeness) and the CFA scale.

These two self-report questionnaires were administered to 552 same-sex siblings from 248 families. Suggestive linkage was observed between both microsatellites (RS1 and RS3) and the SRQ conflict scale (RS1: $\chi^2 = 13.65$, LOD = 2.96, $p = 0.0001$; RS3: $\chi^2 = 14.54$, LOD = 3.16, $p = 0.00007$) and the CFA scale self-presentational style (RS1: $\chi^2 = 8.25$, LOD = 1.79, $p = 0.002$; RS3: $\chi^2 = 8.81$, LOD = 1.91, $p = 0.002$). These results provided the first provisional evidence that the *AVPR1a* polymorphism predicts normal social behaviour in humans and linked a specific genetic element to perceived sibling interactions. It is tempting to speculate that sibling relationships and the phenotypes represented by the CFA scale are human representations of some of the behaviours observed in other mammals that are also partially mediated by the *AVPR1a* receptor.

Music

Dance

As evidenced by several prominent reviews (Koelsch and Siebel, 2005; Zatorre and McGill, 2005), there is increasing interest in the neurobiological substrates of musical ability and appreciation. Additionally, various theories of the 'why and how' of musical evolution have been suggested including its importance in mother–infant communication, sexual selection and group cohesion (see discussion in Fitch, 2005, 2006).

In a first study of its kind, we recruited 85 current performing dancers and their parents who were genotyped for the serotonin transporter (*SLC6A4*: promoter-region HTTLPR and intron

2 VNTR) and *AVPR1a*: promoter microsatellites RS1 and RS3 (Bachner-Melman et al., 2005a). We also genotyped 91 competitive athletes and a group of non-dancers/non-athletes ($N = 872$ subjects from 414 families). Consistent with the emotional side of dancing, dancers scored higher on the Tellegen absorption scale (TAS) (Tellegen and Atkinson, 1974; Tellegen, 1982), a questionnaire that correlates positively with spirituality and altered states of consciousness, as well as the reward dependence factor in Cloninger's TPQ (Cloninger, 1987), a measure of need for social contact and openness to communication. Highly significant differences in *AVPR1a* haplotype frequencies (RS1 and RS3), especially when both *SLC6A4* polymorphisms (HTTLPR and VNTR) were also considered in the genetic analysis, were observed between dancers and athletes. Similarly, dancers differed from a group of non-dancers and non-athletes. Thus, dancers differed from both control groups: athletes as well as non-dancers and non-athletes. Association was also observed between TAS scores and *AVPR1a*. Significant association was observed between TPQ reward dependence scores and *AVPR1a*. Therefore, based on the social role of AVP across vertebrates and the association between *AVPR1a* and the TAS and TPQ reward scale in humans, we hypothesized that the association we observed between *AVPR1a* (and *SLC6A4*) and dance reflects the social communication, courtship and spiritual facets of the dancing phenotype, rather than other aspects of this complex phenotype such as sensorimotor integration. Indeed, as discussed below, AVP and OXT play a role in mouse ultrasonic vocalizations (USVs) that are likely to be related to the affiliative actions of these two neuropeptides in facilitating dyadic (mother–pup) and group interactions. Therefore, the role of *AVPR1a* in dance is not surprising as it fits well with the role of this hormone as a facilitator of social and affiliative relationships in other species.

Musical memory

An appreciation for the direct effects of AVP on central nervous system (CNS) function did not emerge until 1965 by the seminal observations of de Wied (1965), who had been investigating the relationships between conditioned behaviour and neuro-endocrine mechanisms. In the often referenced study, de Wied demonstrated that removal of the posterior and intermediate lobes of the pituitary accelerated extinction of conditioned avoidance behaviour in rats without affecting its acquisition, an effect that could be normalized by peripheral administration of crude pituitary extract (pitressin) or lysine vasopressin (de Wied, 1965). This provided the first evidence for a direct effect of vasopressin on CNS function. For inclusive reviews of the role of AVP and OXT as neuromodulators especially of memory processes, see McEwen (2004a, b, c, d).

The role of AVP in memory processes just discussed, and our study of *AVPR1a* and dance (Bachner-Melman et al., 2005a) suggested to us that it would be worthwhile to examine the role of this receptor in musical memory as well. Together with Roni Granot of the Musicology Department at the Hebrew University (Granot et al., 2007), 82 university students were administered an extensive battery of musical and phonological memory tasks. Their scores were examined for an association with promoter repeats in the *AVPR1a* and serotonin transporter genes. Highly significant, gene × gene (epistatic) interactions were observed between promoter-region polymorphisms and musical as well as phonological memory using family-based and population-based tests. Given the prominent role of vasopressin in social behaviour, the preliminary association found in our study between musical memory and vasopressin could serve to support evolutionary accounts postulating a social adaptive role in music (see above) and even early protolanguage.

In infant mice, both neuropeptides, OXT and AVP, contribute to infant USVs. For example, Winslow and Insel showed that central administration of AVP decreased the number of rat pup USV and that co-administration of AVP and receptor antagonists suggested that changes in vocal behaviour were mediated by the V1 receptor subtype (Winslow and Insel, 1993). Conversely, OXT knockout pups emit fewer USVs with maternal separation (Winslow and Insel, 2002). The contrary actions of these two neuropeptides

may not be so unusual. For example, OXT and AVP affect endocrinological systems often with oppositional effects to one another (de Wied et al., 1993). This functional overlap of AVP and OXT has led some researchers to refer to these neuropeptides as 'ying-yang' neurohormones (Legros, 2001). Interestingly, in male mice adults, USVs have the characteristics of song, consisting of several different syllable types whose temporal sequencing includes the utterance of repeated phrases (Holy and Guo, 2005). Individual males produce songs with characteristic syllabic and temporal structure. More recently, it was shown that USV production was positively correlated with the social investigation responses of mice from two genetically differentiated strains. Interestingly, several USV characteristics segregated with the genetic background of young mice, including a higher average frequency and shorter duration for the USVs emitted by B6 mice. However, the possible role of OXT and AVP in adult male vocalizations remains to be investigated.

In the fish, *Porichthys notatus*, vasotocin (evolutionary precursor of vasopressin/oxytocin) produced dose-dependent inhibitions of parameters associated with call initiation (burst latency and number of vocal-motor bursts elicited) but not of vocal-motor patterning (fundamental frequency and burst duration) (Goodson and Bass, 2000). Together, these findings provide support for the suggestion that AVT modulates some of the neuronal processes underlying social/acoustic communication.

It is worthwhile noting that many individuals with autism have been reported to have unusual musical abilities compared to their other abilities. Musical savants, along with their performance skills and prodigious musical memories, possess absolute pitch (AP), and many, if not most, of these savants have autistic features (Miller, 1989). Further, a survey of savant skills in 5400 children with autism suggests that 5% of them have musical savant skills (Rimland and Fein, 1988), so the prevalence of AP among people with autism may be as high as 1 in 20. In a recent study (Heaton et al., 1998), paired single notes with animal pictures was used as an analogy for AP, and it was shown that in comparison to mental-age-matched control subjects, musically naïve autistic children were better able to identify and remember single notes. Brown et al. (2003) showed that musicians with AP show some of the personality, language and cognitive features associated with autism.

From fish to humans, AVP appears to participate in the shaping of a broad 'musical phenotype', including USVs in lower vertebrates and higher functions such as dance and musical memory in humans. Ultimately, vocalization/music appears to be an expression of social communication and affiliative behaviour. Remarkably, the same neuropeptides partially contribute to these varied yet coordinated phenotypes across vertebrates. These conjectures are supported by our provisional findings showing association between dance/musical memory and *AVPR1a* (Bachner-Melman et al., 2005a; Granot et al., 2007), the role of AVP in USVs and affiliative behaviours in fish and mice (Winslow and Insel, 1993; Goodson et al., 2004), the relationship between autistic traits and AP (Brown et al., 2003) and the association between autistic disorder itself and *AVPR1a* (Kim et al., 2002; Wassink et al., 2004; Yirmiya et al., 2006).

Neuroeconomics: AVPR1a and altruism/prosocial behaviour

The dictator game

We had previously reported that the dopamine D4 receptor (DRD4) common polymorphisms contributed to individual differences in a self-report questionnaire of altruism or prosocial behaviour (Bachner-Melman et al., 2005b). However, the limitation of self-report questionnaires prompted us to employ a "costly" measure of altruism/prosocial behaviour to substantiate that common polymorphisms indeed contribute to this uniquely human trait. We collaborated with Gary Bornstein (experimental economics) and Ariel Knafo (developmental psychology) and in a seminal paper by Knafo et al. (2008), we examined the contribution of a common genetic polymorphism, the *AVPR1a* RS1 and RS3 repeat regions, to individual

differences in allocation of funds in the so-called dictator game.

Economic games provide a method for observing human behaviour in the laboratory that has many advantages over the standard self-report questionnaires (Camerer and Fehr, 2003). Games recreate social interactions in the laboratory using real money payoffs and thus engage people in 'put your money where your mouth is' decisions. A well-defined game also provides the benefits of quantifiability, replicability and comparability across participants and therefore constitutes a more reliable tool for measuring social decision-making.

A robust body of experimental evidence based on laboratory games shows that human behaviour deviates from economic predictions of profit maximization. A game that best demonstrates this incongruity is the dictator game. The first player, or "dictator", makes a unilateral decision regarding the distribution of a fixed sum of money between herself and the second player, the "recipient". Because the recipient is completely powerless, the dictator is unconstrained by fear of reprisal or other strategic considerations, and her allotment can be seen as a measure of pure altruism (Kahneman et al., 1986; Forsythe et al., 1994).

As such, the dictator game is the most prominent paradigm used by economists to test the existence of altruism (Bolton et al., 1998; Henrich et al., 2001; Camerer and Fehr, 2004). As noted by Eckel and Grossman (1996), the behaviour of subjects in dictator games is well documented and deviates from payoff maximization. Contrary to a strategy of maximizing fitness, participants do donate part of the money, with typical games resulting in around 80% of the participants electing to donate some money and some (about 20%) even splitting the pie evenly (Forsythe et al., 1994). The common explanation given for these observed results is that most participants are motivated by "other regarding preferences" (altruism or fairness) in addition to monetary payoffs.

An attractive candidate that we hypothesized might partially explain individual variance in altruistic giving in the dictator game is the *AVPR1a* gene. We conjectured that allocation of funds in the dictator game may be modulated by trait-influenced patterns of social interactions. Therefore, the *AVPR1a* receptor appeared as a likely candidate for influencing proself vs. prosocial styles of behaviour.

In Fig. 4, we show the allocation of Shekels (₪), out of a 50 ₪ or $12 pie, given to recipients by the 'dictators' in this study. For example, 14.9% of the participants allocated nothing to the 'other', 34.6% allocated half their endowment (25 ₪) and 6.7% allocated the entire sum. Although some subjects allocated intermediary sums, there was a pattern of modal allocating.

As shown in Fig. 5, significantly fewer participants with short versions of the *AVPR1a* RS3 repeat allocated high sums to the 'recipient' than participants with long versions. Additionally, the presence of RS3 long repeats had an additive effect on allocation amounts. Subjects homozygous for short repeats gave 15.4 ₪ whereas subjects homozygous for long repeats gave 22.2 ₪, an effect size of approximately 0.5 S.D.

Participants reported their own prosocial behaviour with the value expressive behaviour scale by Bardi and Schwartz (2003). Two subscales were used, that represent two different aspects of prosocial values. The universalism behaviour subscale taps behaviours that represent a prosocial motivation for understanding, appreciation, tolerance and protection of the welfare of all people (e.g. "make sure everyone I know receives equal treatment"; "donate money for saving people who suffer from war, famine etc. in distant countries"). Significant association was observed between scores on the universalism behaviour subscale and the RS3 repeat.

The other subscale is the benevolent behaviour subscale (Bardi and Schwartz, 2003). This subscale taps behaviours that represent a prosocial motivation to help and support others with whom one is in close or daily social contact (e.g. "agree easily to lend things to neighbours"; "help my friend to perform tasks such as moving and studying"). Significant association was observed between scores on the benevolent behaviour subscale and the RS3 repeat.

We also examined the robustness of our first analysis by using UNPHASED, a procedure that implements a family-based design and avoids the

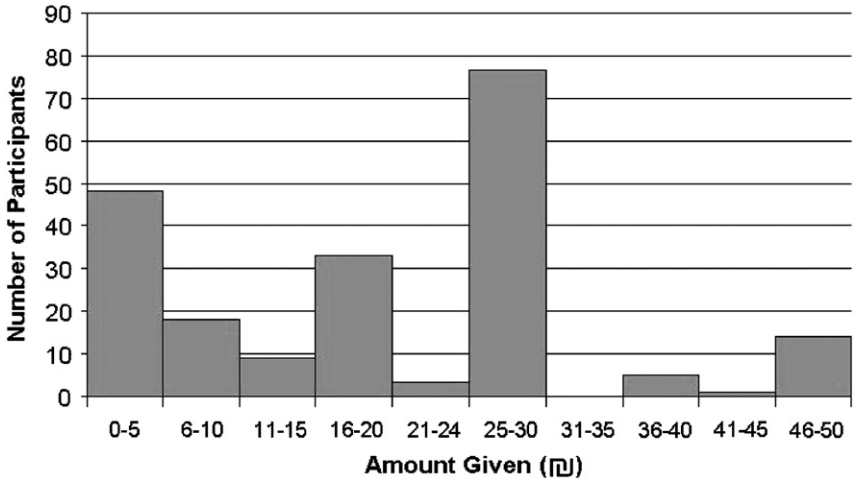

Fig. 4. Distribution of allocation sums by participants in dictator game. 25 ₪ (shekels) was the modal value in this distribution and was used as the cutoff point to divide participants into low and high allocators. Altogether, 46% of the participants were designated as high allocators. The current results can be compared to Forsythe et al. (1994) who explored the replication and statistical properties of the dictator game. The standard perfect equilibrium analysis of the dictator game begins with the assumption that each player prefers more money to less (Bolton and Ockenfels, 2000). In the dictator game, the so-called 'dictator' should keep all the money. However, in the case of the $10 game, 79% did not take the entire sum, with 20% leaving half. The mode of the distribution was $3 or 30%. Notably, Forsythe et al. (1994) showed distributions of dictator giving, which are both anomalous to standard economic theory of maximizing profit as well as robustly replicable.

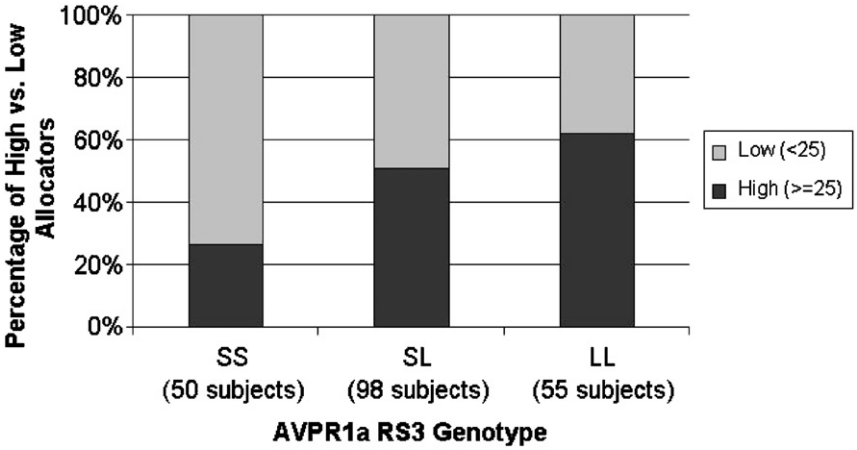

Fig. 5. Mode of giving in the dictator game. High vs. low allocation amounts in ₪ (shekels) grouped by short (308–325 bp) vs. long (327–343 bp) *AVPR1a* RS3 promoter-region repeat length (SPSS v13 Crosstabs two-tailed: likelihood ratio = 14.75, $p = 0.0006$, DF = 2). Percentages indicate ratio of high (≥ 25 ₪) vs. low (<25 ₪) allocators for each of the three genotype groupings. We chose the short and long lengths of the RS3 and promoter length so that approximately equal numbers of participants were present in each group. Any other split led to very small groups in either the long or short category for a total sample size of $N = 203$.

conundrum of population admixture or stratification in testing association between money allocations and RS1 and RS3 repeats. As expected from our first analysis, association and dictator game allocations was significant (global $p < 0.05$) only for the RS3 repeat. The third most common allele (12%), 329 bp, showed significant association with allocation ($p = 0.008$).

Importantly, as noted above (Fig. 2), levels of *AVPR1a* mRNA in post-mortem human hippocampal specimens correlates with the length of the RS3 repeat region, suggesting that promoter repeat serves a similar regulatory function in humans as in the vole. Nevertheless, the possibility that RS3 is in LD with other functional polymorphisms in the 5′ upstream region, that might explain some of our results, cannot be excluded.

AVPR1a and infidelity

Cherkas and colleagues investigated the genetics of infidelity in more than 800 twin pairs; after accounting for potential confounds such as divorce, number of sexual partners and age, they reached a heritability estimate of 41% for infidelity. This prompted them to genotype the *AVPR1a*.RS3 on a subgroup of 149 dizygotic twins; however, their results showed no significant

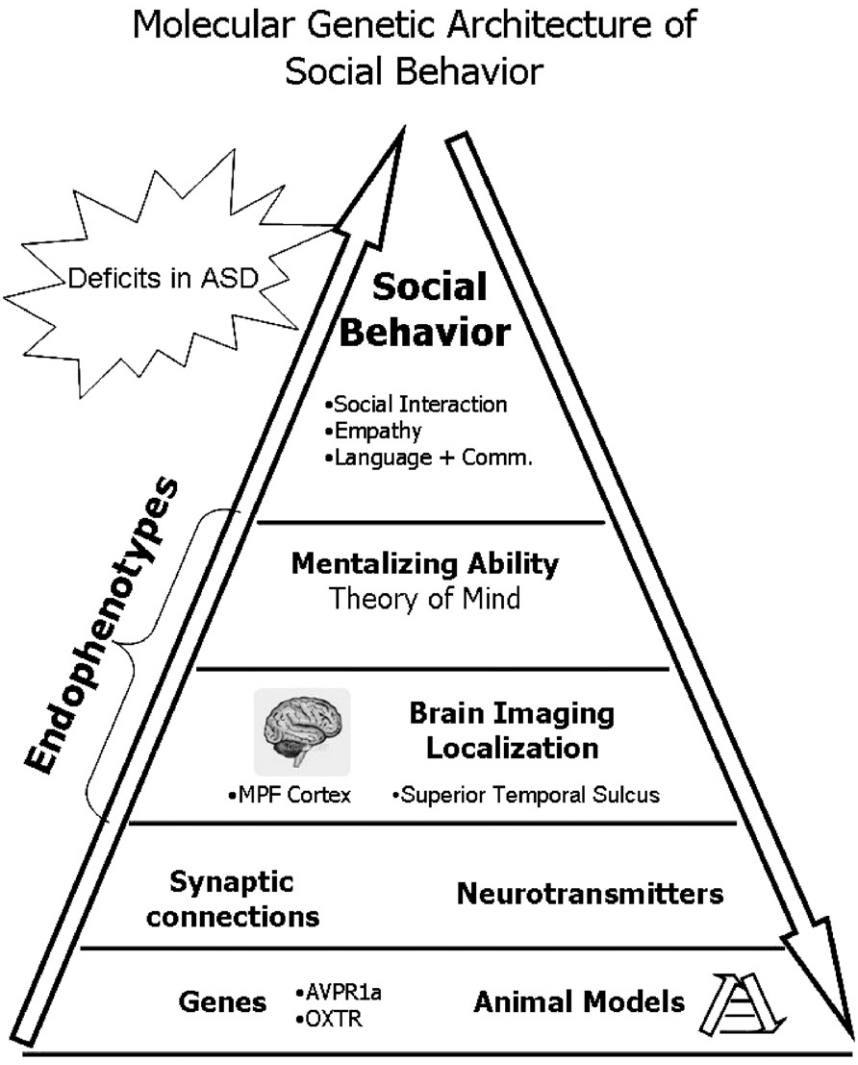

Fig. 6. Molecular genetic architecture of social behaviour.

association between RS3 microsatellite variability and infidelity or number of sexual partners (Cherkas et al., 2004). We suggest that although fidelity may seem to be an indicator of the global endophenotype of prosocial responding, the reason for this null finding may be that infidelity is affected by many additional factors such as sexual arousal.

Future directions

Our research group has for more than a decade sought to understand how common polymorphisms impact on individual differences spanning a broad spectrum of human behaviours (Ebstein, 2006). One of the most intriguing gene families we have studied is the OXT-AVP neuropeptides that across millions of years of vertebrate evolution from fish to man have become important modulators of social communication and affiliative behaviours. Our own studies of these peptides as discussed in this review attest to the diverse phenotypes that polymorphic variants of the *OXTR* and *AVPR1a* genes contribute to. Remarkably, from autism to altruism with musical notes in between, our studies suggest that common polymorphisms in genes coding for elements of AVP and OXT neurotransmission account for some of the individual differences in a super-phenotype of social communication and affiliative behaviour.

Finally, future studies should continue to leverage interdisciplinary strategies to clarify the pathway from genome to higher social behaviour in man. We have summarized our model of the molecular genetic architecture of social behaviour in Fig. 6.

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