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Hormonal and neuronal mechanisms of social attention and memory in the rhesus macaque (*Macaca mulatta)*

By

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An abstract of
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Abstract

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Disorders impairing social behavior including autism and schizophrenia collectively affect over 2% of the population, and our limited understanding of the neurobiological mechanisms underlying these impairments has hindered the development of treatment strategies targeting these disorders. The goal of the present experiments was to advance our understanding of the neuronal and hormonal mechanisms mediating attention to and memory for social information. In doing so, we aimed to identify candidate mechanisms to be used in the development of optimal treatments for social impairments. To this end, the present experiments have examined in the rhesus macaque how neurons in the hippocampus encode faces into memory, and how social scenes are viewed under the influence of saline and oxytocin. We demonstrate that neurons in the macaque hippocampus discriminate both the social content and novelty of images through selective changes in firing rate for their preferred stimulus category. Using methods informed by screening tools for autism, we found that experience shifts exploration strategy, and that visual social cues drive the allocation of attention independent of the salience of low-level image features. Treatment with oxytocin amplifies this shift in exploration strategy and selectively increases attention towards social stimuli independent of low-level salience. Taken together, these data support previous work showing that the encoding of social information occurs within networks specific for social content and that the peptide oxytocin specifically regulates attention towards social information. Accordingly, our experiments have advanced our understanding of how social information is encoded in the brain and how social attention is regulated by exogenous oxytocin. These advances fill critical gaps in our knowledge of how social behavior is mediated through neurobiological mechanisms, and informs an ongoing movement towards optimizing treatment strategies for disorders impairing social function.

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Chapter 1. Introduction

1.1 Alterations in attention to social stimuli in autism spectrum disorder

Autism spectrum disorders (ASD) are characterized by deficits in social behavior, verbal or non-verbal communication and stereotyped or restricted interests and behaviors (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000). Diagnosis requires at least two of these three criteria to be met, and the severity and expression of these symptoms varies greatly throughout the broad range of disorders classified as an ASD. While many on the spectrum exhibit significant language impairments, others, particularly those with Asperger syndrome, show no delay in language development or its use in adulthood (*DSM-IV-TR;* Baskin, Sperber, & Price, 2006; J. McPartland & Klin, 2006). In fact, this group is typically highly verbose and almost professorial in their language and does not suffer the debilitating cognitive delays common among many other ASDs (Ghaziuddin & Gerstein, 1996; Koning & Magill-Evans, 2001).

Perhaps the most defining feature of autism is its striking impairment in social behavior and the use of language and non-verbal communication in social situations (Simon Baron-Cohen, Leslie, & Frith, 1985). Even in ASDs such as Asperger syndrome where cognitive skills and verbal and non-verbal communication are at highly functioning levels, these skills are often employed in ways that are socially inappropriate or miss subtle social meanings (Ghaziuddin & Gerstein, 1996; Koning & Magill-Evans, 2001). Specifically, individuals with Asperger syndrome have difficulty understanding the meaning of facial expressions and the rules governing social interactions (Wing, 1981), as well as detecting the emotions of others (Szatmari, Archer, Fisman, Streiner, & Wilson, 1995) and adjusting their language to work with different audiences and contexts

(Tantam, 1988). The striking specificity of impairment of cognition in the social domain motivates the central question of this thesis: By what mechanisms is social information processed in the brain? The aim of this research is to understand these mechanisms and in doing so generate hypotheses about what mechanisms may be altered in autism and identify potential avenues for treating these impairments.

Seminal work by Hubel & Wiesel demonstrated the importance of sensory experience during the highly plastic phase of early development of neural systems (Wiesel & Hubel, 1963). Similarly, reduced social interaction during early development has profound effects on the development of cognitive function and systems crucial for regulating social behavior (Bos et al., 2011; Egeland, Sroufe, & Erickson, 1983; Widom, White, Czaja, & Marmorstein, 2007). This experience is particularly important for development in group-living primates (Sánchez, Hearn, Do, Rilling, & Herndon, 1998), where social deprivation can result in radically atypical social behavior and stereotyped behaviors that resemble the stereotyped behavior of autistic individuals (Harlow, Dodsworth, & Harlow, 1965; Suomi, Harlow, & Domek, 1970).

Indeed, one influential theory suggests that disruption in the normative development of social behavior leads to increasingly atypical behavior that can even extend into non-social domains (Jones & Klin, 2009). The face is perhaps the most important source of social information, and captures attention within even the first few hours of birth (Haith, Bergman, & Moore, 1977). Even when only crude depiction of a face is used, the canonical arrangement of two eyes above a mouth attracts attention in infants more so than a scrambled version of the face configuration (Goren, Sarty, & Wu, 1975; Johnson, Dziurawiec, Ellis, & Morton, 1991; Valenza, Simion, Cassia, & Umiltà,

1996). Although infants who will later be diagnosed with autism begin life attending to the eyes of faces, this declines over the first 6 months of development while typically developing infants maintain their level of attention to the eyes (Jones & Klin, 2013). Typical newborns are also more likely to attend to motion that is perceived as biological (Simion, Regolin, & Bulf, 2008), but autistic children do not have this preference, instead responding to physical contingencies that are non-social and unimportant to healthy children (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009). These early impairments in preferential attention to socially relevant stimuli may then derail the typical development of more complex social cognitive skills that require close attention to signals of success or failure in the back and forth of social interaction (Jones & Klin, 2009).

Many studies have supported these findings of reduced social attention in autistics (Corden, Chilvers, & Skuse, 2008; Falck-Ytter, 2008; Hernandez et al., 2009; Jones, Carr, & Klin, 2008a; Klin & Jones, 2008; Pelphrey et al., 2002; Trepagnier, Sebrechts, & Peterson, 2002). Perhaps one of the most influential and striking reports found that while viewing video clips of social interactions, individuals with autism spent less time viewing the eyes of people in the scenes and more time viewing the mouth, body, and objects (Klin, Jones, Schultz, Volkmar, & Cohen, 2002b). While controls spent 65% of their time looking at eyes, autistics spent half as much time viewing this region and instead preferred to view the mouth. Interestingly, more time spent viewing the mouth and less time viewing objects were strong predictors of greater social competency, as rated by standard diagnostic scales (Klin et al., 2002b).

A preference for the mouth over the eyes has also been replicated with static images, where a deficit in emotion recognition was also observed (Pelphrey et al., 2002).

The latter effect was mostly due to an inability to identify fear, which may be related to reduced attention to the eyes as this feature is highly diagnostic of fear (Ralph Adolphs, 2008; Ralph Adolphs et al., 2005). This is supported by the finding that in autistics, time spent viewing the eyes or mouth is positively and negatively correlated, respectively, with the ability to recognize emotion in facial expressions (Kirchner, Hatri, Heekeren, & Dziobek, 2011).

The difference between autistics and controls in their use of the mouth and eyes to recognize emotion is elegantly quantified by the "Bubbles" task (Spezio, Adolphs, Hurley, & Piven, 2007). This method asks participants to judge the emotion of faces that are obscured by an opaque mask, with iterative trials randomly revealing additional areas of the face through transparent Gaussian "bubbles" (Gosselin & Schyns, 2001). After averaging performance across many trials, a "diagnostic image" shows which parts of the face were visible when the participant made a correct judgment. Subtracting the image of the controls from the autistic group reveals that the autistic group relies more heavily on the mouth, while the converse subtraction shows that the controls make more use of the eye region (Spezio et al., 2007). A shift in the use of the mouth region over the eyes relative to controls is also related to recognizing face identity. When viewing only isolated parts of a face during identity judgments, autistics performed better when using the mouth than the eyes (Joseph & Tanaka, 2003).

Why is it that autistics prefer to view the mouth compared to the eyes? One hypothesis is that while healthy infants prefer to view coordinated motion that is perceived as biological (Fox & McDaniel, 1982), autistic infants ignore biological motion and prefer to view non-social physical contingencies (Klin & Jones, 2008; Klin et al.,

2009). This hypothesis was generated by the serendipitous observation of an infant with autism who did not attend to biological motion with the exception of an animation where the figure clapped their hands to produce a contingent sound (Klin & Jones, 2008). The authors suggest that the mouth is preferentially viewed because this is the location on the face with the greatest audiovisual synchrony (Klin et al., 2009).

These results illustrate the power of eye tracking measures to quantify atypical social behavior and suggest that the relative preference for viewing non-social objects compared to social stimuli could be a useful diagnostic feature (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998).

However, other studies have failed to replicate a reduction in eye viewing or reported no difference from neurotypical (healthy) individuals (Bar-Haim, Shulman, Lamy, & Reuveni, 2006; de Wit, Falck-Ytter, & von Hofsten, 2008; JC McPartland, Webb, Keehn, & Dawson, 2011; Rutherford & Towns, 2008; van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2002; van der Geest, Kemner, Verbaten, & van Engeland, 2002). When viewing isolated grayscale upright human faces, inverted human faces, monkey faces, geometric patterns and three-dimensional curvilinear objects known as Greebles (Gauthier & Tarr, 1997), autistic individuals did not differ from controls (McPartland et al., 2011). The authors attributed their results to the reduced ecological validity of grayscale, static images, noting that other studies which failed to detect a difference between controls and autistics also used similarly impoverished stimuli (Speer, Cook, McMahon, & Clark, 2007; Sterling et al., 2008; van der Geest, Kemner, Camfferman, et al., 2002).

1.2 The importance of ecological relevance

Others have also highlighted this difference in complexity of social stimuli as a potential source of discrepancy is the used across behavioral tasks (Riby & Hancock, 2008b). Indeed, a direct comparison of isolated faces and social scenes revealed that individuals with Asperger's syndrome looked less at the eyes when faces were embedded in social scenes but were no different than neurotypical individuals when faces were presented in isolation (Hanley, McPhillips, Mulhern, & Riby, 2012).

Historically, studies investigating face perception and social attention have almost exclusively used images of faces cropped from the body. These studies have found that healthy humans prefer to view faces and are especially drawn to the eye region (Althoff & Cohen, 1999; Haith et al., 1977; Henderson, Williams, & Falk, 2005; Janik, Wellens, Goldberg, & Dell'Osso, 1978; Walker-Smith, Gale, & Findlay, 1977). However, in natural settings, faces are rarely seen in isolation from bodies and other individuals and objects.

Several groups have emphasized the importance of maintaining high ecological relevance when studying attention to social stimuli (Bindemann, Scheepers, & Burton, 2009; Bindemann, Scheepers, Ferguson, & Burton, 2010; Birmingham, Bischof, & Kingstone, 2008a, 2008c; Birmingham, Ristic, & Kingstone, 2012; Birmingham & Kingstone, 2009; Kingstone, Smilek, Ristic, Kelland Friesen, & Eastwood, 2003; Neisser, 1967; Riby & Hancock, 2008b; Smilek, Birmingham, Cameron, Bischof, & Kingstone, 2006). While isolated faces direct attention to the face by design, faces embedded in complex scenes demand that the viewer select among many stimuli the ones that are most relevant.

Given the far departure of isolated faces from natural settings, why are they so widely used? When eye tracking was first beginning to be used to uncover how we explore the visual world and the characteristics that guide our attention, full scenes were used as stimuli. Buswell was the first to explore this topic when he showed participants pictures of paintings as well as photographs and very carefully scrutinized what they looked at (Buswell, 1935). He observed that fixations increased in duration over the course of viewing and speculated that image regions receiving many fixations of long duration were the "principal centers of interest" (p.72).

Continuing this work, Yarbus showed participants photographs of full scenes and objects with the goal of learning "what distinguishes the elements particularly attracting the observer's attention" (p.171), remarking, "eye movements reflect the human thought processes" (p.190) (Yarbus, 1967). Many of the stimuli he used contained faces, and he observed that the main facial features of the eyes, lips and nose received the most attention, even when the face was that of an animal.

Perhaps most revealing, he found that when participants were shown the painting "An Unexpected Vistor" by Ilya Repin (1884), a scene with multiple people, their eye movements changed depending on the type of information they were instructed to gather. When he asked them to estimate the ages of the people, they spent most of their time inspecting the people's faces and when asked to remember the position of the people and objects in the room they covered more of the scene with more fixations and saccades. When he asked them to estimate how long the "unexpected visitor" had been gone, the presumed visitor in the scene was frequently fixated with many transitions going between him and the other people in the scene (Yarbus, 1967).

These observations revealed not only the rich social content and context present in scenes compared to isolated faces, but also how the importance of scene contents changed with the goal of the observer and the power of eye tracking to uncover aspects of the oberserver's internal state. However, this also illustrates how much eye movements can vary with stimulus content and the state and goal of the observer. This poses a difficult experimental challenge: How do you uncover the mechanisms guiding attention in a high-dimensional system?

Understanding how information is processed and the specific neural mechanisms that govern it has been the central goal of the "cognitive neuroscience approach" (Gazzaniga, 2004; Schacter, 2001). Critical to this approach are the assumptions that basic mechanisms governing attention remain stable across tasks and that the stimuli used and behaviors of interest should be as well controlled as possible. This approach has lead to studying behavior in very artificial and highly simplified paradigms that are amenable to laboratory research (Kingstone et al., 2003; Smilek et al., 2006).

The interpretation of these studies has been that very simple features and mechanisms guide behavior, but it is also possible that this simplicity is the direct result of constraining experiments and analysis to an array of simple factors. Thus, by reducing the dimensionality of stimuli and behavioral factors one may miss factors that are more important, conclude that a factor is not relevant, or that a factor is relevant when it is not.

In the case of social cognition where interactions between factors are incredibly complex, using simplistic and artificial stimuli is likely to obscure real effects. For example, a direct comparison of isolated faces and social scenes revealed that individuals with Asperger's syndrome looked less at the eyes when faces were embedded in social

scenes but were no different than neurotypical individuals when faces were presented in isolation (Hanley et al., 2012).

However, because complex social scenes are more diverse in their content compared to isolated faces, they may also introduce more confounds and require great control. This can be especially dangerous when relatively few stimuli are used, allowing stimulus outliers to more dramatically affect the resulting analysis. The cost is that using a high number of images demands more time and effort to draw regions of interest around scene items for automated analysis of eye data, in addition to obtaining images that meet the specified criteria of the experiment. For these reasons, in most experiments, somewhere between 12-20 images are used and regions of interest are characterized only at relatively superficial levels (e.g. eyes, mouth, body, background) while other factors like sex, age and gaze direction are ignored.

While using video for social stimuli is preferable because of its enhanced realism and ecological relevance, videos are even more difficult to obtain, control and analyze. For example, a recent experiment presented two film clips totaling 12 minutes to autistic and healthy children while monitoring their eye position. Analysis of viewing behavior required regions of interest to be drawn around all of the eyes, mouth, body and object regions in each of 14,562 frames (Rice, Moriuchi, Klin, & Jones, 2012). The process of drawing the regions of interest took several people working every day over 5 months according to W. Jones (personal communication, May 20, 2011). Because of how arduous and time-consuming this process is, relatively few stimuli are used are typically used in experiments with video stimuli. As a result, fewer trials can be obtained per subject because the visual inspection of images and the brain's response to them changes

with continued exposure (Caron & Caron, 1968; Fischer et al., 2003). To compensate, greater numbers of subjects are often used.

Moving forward, stimuli should ideally be shared across labs to maximize the benefit from the laborious process of processing the data. Using the same stimuli would also facilitate comparisons across studies.

1.3 Alterations in neural systems related to face-processing in autism spectrum disorders

In typically developing individuals, a distributed, hierarchical network of brain areas contributes to the processing of faces (Haxby & Gobbini, 2010; Haxby, Hoffman, & Gobbini, 2000, 2002). At its core lies a network in the extrastriate visual cortex involved in identifying faces at a categorical level, individuating specific faces, and distinguishing changeable aspects of the face such as expressions and movements of the head and eyes (Halgren et al., 1999; Haxby et al., 1999, 2001; Hoffman & Haxby, 2000; Ishai, Schmidt, & Boesiger, 2005; Kanwisher, McDermott, & Chun, 1997; Prince, Dennis, & Cabeza, 2009; Puce, Allison, Bentin, Gore, & McCarthy, 1998). This system is comprised of regions which respond more strongly to faces compared to other object categories, including the occipital face area (OFA) in the inferior occipital gyrus, the fusiform face area (FFA) in the lateral fusiform gyrus, and the posterior superior temporal sulcus (pSTS). Other areas outside of the visual extrastriate cortex, such as the amygdala, also contribute to face perception (R Adolphs & Spezio, 2006; Haxby & Gobbini, 2010; Mende-Siedlecki, Verosky, Turk-Browne, & Todorov, 2013; Ueli Rutishauser et al., 2011).

In autistic individuals, activity in this face-processing system appears to be disrupted (Kleinhans et al., 2008). Specifically, a reduced response in the FFA was observed when autistic individuals viewed faces (Dalton et al., 2005; Hubl et al., 2003; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; R T Schultz et al., 2000). For example, Schultz et al. (2000) found that when discriminating between different faces, but not objects, autistic individuals exhibited greater activation in the inferior temporal gyrus (ITG) and less activation in the FFA relative to controls. Interestingly, controls showed greater activation of the ITG when discriminating objects. It has been suggested previously that while healthy individuals process faces as a holistic configuration, autistics employ a more feature-based strategy that is used to process objects in neurotypicals (Hobson, Ouston, & Lee, 1988; Langdell, 1978).

These data are in line with the conclusion of Schultz et al. that autistic individuals are processing faces as objects. Others have also suggested that autistics process faces using different brain systems, highlighting that although in every control subject the FFA was maximally activated during a face perception task, autistics not only showed weak or zero activation of the FFA but were also highly variable in the magnitude of and location of responses (Pierce et al., 2001).

However, other studies have failed to find differences in autistic individuals in activation of the FFA (Bird, Catmur, Silani, Frith, & Frith, 2006; Hadjikhani et al., 2004; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007). These differences may be due to a lack of attentional modulation of the response to faces, which was lacking in a difficult task (Bird et al., 2006) or not required in an easy one (Hadjikhani et al., 2004, 2007).

Furthermore, while reduced activation may not be present in the FFA, other areas such as the amygdala are often found to be hypoactive (Hadjikhani et al., 2004, 2007).

These inconsistencies again highlight the importance of task design and the stimuli used and also raise the point that altered activity in face-processing areas may be a result of reduced attention to faces (Klin, 2008). In support of this, activation of the FFA and the amygdala was positively correlated with time spent viewing the eyes in autistic, but not healthy individuals. The absence of a significant correlation in healthy individuals was taken as evidence that amygdala activation is not the mere product of increased attention to eyes, but instead that autistic individuals may be hypersensitive to eye contact. The authors concluded that as a result of hyperactivity in the amygdala during eye contact, autistics spend less time viewing faces and this decreased exposure produces a reduction in activity of the FFA (Dalton et al., 2005).

However, amygdala activity during face perception in autism is inconsistent. Some studies have shown that amygdala activity is higher in autistics (Dalton et al., 2005; Kleinhans et al., 2009; Monk, 2010; Tottenham et al., 2014; Weng et al., 2011), while others have reported reduced amygdala reactivity (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Bookheimer, Wang, Scott, Sigman, & Dapretto, 2008; Corbett et al., 2009; Hadjikhani et al., 2007; Kleinhans et al., 2011; Perlman, Hudac, Pegors, Minshew, & Pelphrey, 2011).

In Dalton et al. (2005), a significant correlation between amygdala activity and eye gaze may not have been detected in controls due to ceiling effects. Because the images used showed close ups of faces and the eyes were placed in the center of the image where viewers are biased to gaze (Tatler, 2007; Tseng, Carmi, Cameron, Munoz,

& Itti, 2009), participants' attention was biased towards the eyes. This reveals a more widespread issue with using "passport" style photos of faces as stimuli, which, by virtue of being the only object displayed, greatly reduce the demand for autistics to attend to the face. This setup reduces the chance of detecting impairment in orienting to social stimuli, whereas images of full scenes with non-social objects demand that the viewer choose between stimuli. This approach could also bring eye viewing off of the ceiling in controls and permit a more accurate assessment of both eye viewing in more natural conditions and the correlation between eye viewing and amygdala response.

Some studies have directly manipulated attention to the eyes by requiring the initial fixation to occur on either the eyes or the mouth (Gamer & Büchel, 2009; Gamer, Zurowski, & Büchel, 2010; Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012; Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010). These studies attempt to address a difficult problem in the interpretation of reduced eye looking in autistics. Do they spend less time viewing eyes because they are aversive and actively avoided (Dalton et al., 2005; Kylliäinen & Hietanen, 2006) or because of a failure to detect social saliency (D. Neumann, Spezio, Piven, & Adolphs, 2006; Robert T Schultz, 2005)? These are not mutually exclusive alternatives, and another important consideration is that a failure to detect social saliency may be due to a reduced motivation if social stimuli are less rewarding (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Panksepp, Nelson, & Siviy, 1994; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010).

Supporting earlier work showing that the eye region is highly salient and important for discriminating the emotion of expressions, particularly fear (Ralph Adolphs, 2008; Ralph Adolphs et al., 2005), healthy individuals show a strong bias to

shift their gaze to the eyes (Gamer & Büchel, 2009). Gamer and Buchel also observed a difference between emotional expressions based on which feature was most diagnostic for identification. Participants exhibited a stronger bias to shift to the eyes when viewing fearful faces, and a stronger bias to shift to the mouth when viewing happy faces. Interestingly, participants exhibited enhanced amygdala activity when gaze began at the mouth of fearful, but not happy faces, with a corresponding positive correlation across participants between the strength of the response and the bias to shift to the eyes (Gamer & Büchel, 2009). These results highlight the role of the amygdala in directing attention to the eyes (Adolphs & Spezio, 2006).

When autistics perform this task, they are more likely than controls to move their gaze away from the eyes and, unlike controls, did not exhibit a greater preference to shift their gaze to the eyes when viewing fearful compared to happy faces (Kliemann et al., 2010). While controls showed greater amygdala activation when fixation began on the mouth compared to the eyes, autistics exhibited the opposite response pattern and were different from controls in both conditions (Kliemann et al., 2012). In addition, autistics were particularly impaired in recognizing the emotional expression when viewing the most diagnostic feature of a facial expression (eyes for fear and mouth for happy).

When autistics are given an acute dose of the hormone oxytocin through an intranasal spray, they show oxytocin-induced increases in amygdala response that predict increases in the recognition of emotion from the eyes (Domes, Kumbier, Heinrichs, & Herpertz, 2014). This suggests that Dalton et al.'s (2005) conclusion that looking at the eyes caused increases in amygdala activity and social fear in autistics could be reinterpreted in the opposite direction, that increases in amygdala activity drive eye gaze

(Domes et al., 2014). Moreover, this interpretation fits with the strong role of the amygdala in detecting the salience of the eyes as described above. Not only does oxytocin seem to provide a potentially therapeutic benefit to autistics, it may also be a valuable tool for understanding the neuropathology of autism by establishing causal relationships between brain function and social behavior.

1.4 Oxytocin and its effects on social behavior in primates

1.4.1 Oxytocin receptors and transmission

Oxytocin is a neurohypophyseal peptide that regulates reproductive functions in placental mammals through actions in the peripheral and central nervous systems (Donaldson & Young, 2008; Gimpl & Fahrenholz, 2001; Insel, 1997; Ivell, 1997). Oxytocin is comprised of 8 amino acids and is closely related to the vasopressin family of neurohypophyseal hormones, differing only in the amino acids at positions 3 and 8 (Gimpl & Fahrenholz, 2001). Vasopressin will not be the focus of this section but it is important to note that due to the similarity between the receptors of oxytocin and vasopressin, they both bind to each other's receptors. Oxytocin is evolutionarily highly conserved. Almost all vertebrates have an oxytocin-like and a vasopressin-like peptide and related peptides with reproductive functions have been identified in Caenorhabditis elegans and medicinal leeches (Garrison et al., 2012; Gimpl & Fahrenholz, 2001; Wagenaar, Hamilton, Huang, Kristan, & French, 2010).

Oxytocin receptors are located in both the peripheral and central nervous systems. In the periphery, receptors are mainly located in the tissues of the reproductive systems in both males and females. Importantly, they are also located in the heart, which raises the possibility that some of the effects of oxytocin may be due to a slowing of heart rate. In

the central nervous system, oxytocin receptors are found primarily in magnocellular neurons in the periventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. Oxytocin's receptor is a member of the G-protein coupled receptor family with a $G_{q/11\alpha}$ protein subunit, and through increases in intracellular Ca^{2+} trigger changes based on the cell type. For example, in the periphery this can lead to contraction of smooth muscle cells in the uterine myometrium (Sanborn et al., 1998). In the central system, magnocellular neurosecretory cells can modulate firing and result in transmitter release. Release is primarily from dendrites but also from axons, axon terminals, and somata into the extracellular fluid or into the blood from terminals in the posterior pituitary gland that originate in the SON and PVN (Buijs & Heerikhuize, 1982; Landgraf & Neumann, 2004; Ludwig, 1998; Ludwig et al., 2002; Morris, Christian, Ma, & Wang, 2000; Poulain & Wakerley, 1982; Son et al., 2013). Importantly, release of oxytocin into the peripheral system via the bloodstream is not tied to central levels of oxytocin, and thus peripheral measures of oxytocin from saliva or blood plasma are not reliable correlates of centrally mediated effects of oxytocin (Ludwig & Leng, 2006; Neumann, 2007).

Whereas receptors for classical neurotransmitters are typically found directly apposing the site of storage and release of the neurotransmitter, only a small proportion of neuropeptide receptors receive direct input (Liu et al., 1994). Oxytocin exerts its effects in two ways, through fibers from parvocellular neurons originating in the PVN that extend throughout the brain, and via diffuse volume transmission (Landgraf & Neumann, 2004;Ross et al., 2009; Ross & Young, 2009). In rats, fibers from parvocellular neurons project into the hippocampus, entorhinal cortex, subiculum,

amygdala, thalamus, medial and lateral septum, olfactory bulbs, substantia nigra and the dorsal raphe nucleus (Gimpl & Fahrenholz, 2001;Ross et al., 2009; Sofroniew, 1980).

Through volume effects, low concentrations of oxytocin potently modulate activity at distant targets through broad release, causing lasting effects due to its long half-life, absence of a reuptake mechanism and positive-feedback (Landgraf & Neumann, 2004; Ludwig & Leng, 2006; Mens, Witter, & Van Wimersma Greidanus, 1983; Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011; Ross et al., 2009). For example, dendritic release of oxytocin and vasopressin can be triggered during behavioral events such as stress or lactation (Ebner, Wotjak, Landgraf, & Engelmann, 2002;Neumann, Russell, & Landgraf, 1993). Lactation events trigger bursts of action potentials in oxytocin neurons, causing the release of large boluses of oxytocin. Once initiated by behavioral events, release of oxytocin is self-sustaining. When oxytocin is released, it activates its receptors on the dendrites or soma, elevating intracellular Ca^{2+} and triggering the release of more oxytocin (Ludwig & Leng, 2006; Neumann, Douglas, Pittman, Russell, & Landgraf, 2003).

In the rhesus macaque, oxytocin receptors are located in the nucleus basalis of Meynert, pedunculopontine tegmental nucleus, the superficial gray layer of the superior colliculus, the trapezoid body, and the ventromedial hypothalamus (Freeman, Inoue, Smith, Goodman, & Young, 2014). However, oxytocin can also bind to vasopressin receptors (Manning et al., 2012), which are located in the amygdala, bed nucleus of the stria terminalis, lateral septum, hypothalamus, brainstem, presubiculum, mammillary bodies and the entorhinal, prefrontal, cingulate, and pyriform cortices (Young, Toloczko, & Insel, 1999).

1.4.2 Intranasal administration of oxytocin

There is a large body of work in rodents demonstrating that oxytocin mediates sexual, maternal, social, and stress behaviors. Here I will focus primarily on its role in human and non-human primate social behavior and relate these findings back to work in rodents when it is most relevant.

Much of what we know about the effects of oxytocin in humans has been uncovered through the administration of oxytocin intranasally. Intranasal administration of radiolabeled proteins in monkeys suggested that large molecules like oxytocin are transported into the CNS along olfactory and trigeminal nerve components in the nasal epithelium to the olfactory bulb and brainstem (Lochhead & Thorne, 2012). From the olfactory bulb and brainstem compounds diffuse linearly via pulsatile flow within the perivascular spaces of cerebral blood vessels (Thorne, Emory, Ala, & Frey, 1995). This diffusion results in high accumulation in several regions with binding sites for oxytocin, including the amygdala, hypothalamus, cingulate cortex, and prefrontal cortex. When oxytocin is inhaled through an aerosolized solution, CSF levels of OT become elevated 2-3 times over baseline levels as early as 30 minutes after administration, and remain elevated for 1.5 hours after that (Chang, Barter, Ebitz, Watson, & Platt, 2012; Modi, Connor-Stroud, Landgraf, Young, & Parr, 2014). However this may underestimate its availability within the brain. When oxytocin was administered intranasally in rodents, microdialysis in the hippocampus and amygdala detected increased oxytocin while no such increase was found in the CSF (Neumann, Maloumby, Beiderbeck, Lukas, & Landgraf, 2013). Furthermore, accumulation of oxytocin in the hypothalamus also likely triggers the release of more oxytocin through positive-feedback (Ludwig & Leng, 2006; Neumann et al., 2003).

1.4.3 Effects of oxytocin on anxiety

The anxiolytic properties of oxytocin have been well documented in many species, and have been put forward as a potentially unifying explanation for the diverse range of effects on social cognition caused by OT (Chang and Platt, 2013;Churchland and Winkielman, 2012). Through a reduction in social anxiety and social avoidance, OT promotes the approach and interaction with social stimuli (Amico, Mantella, Vollmer, & Li, 2004; Averbeck, 2010; Chang & Platt, 2013; Heinrichs, von Dawans, & Domes, 2009;Neumann, Krömer, Toschi, & Ebner, 2000; Riem et al., 2011; Ring et al., 2006; Kerstin Uvnäs-Moberg, 1998;Young, 2002). As a result of the complexity of social behavior, interpersonal differences and the context in which social behavior is tested, OT treatment can result in a wide range of effects (Bartz, Zaki, Bolger, & Ochsner, 2011; Norman et al., 2012; Saphire-Bernstein, Way, Kim, Sherman, & Taylor, 2011; Strathearn, Fonagy, Amico, & Montague, 2009; Walum et al., 2012).

A role for OT in the reduction of social anxiety is well-supported by the literature (Averbeck, 2010; Bartz & Hollander, 2006; Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008). In rodents, OT attenuates HPA activity, reducing anxiety-related behavior and promoting social behavior (Amico et al., 2004; McCarthy, McDonald, Brooks, & Goldman, 1996;Neumann et al., 2000;Neumann, 2002;Uvnäs-Moberg, 1998; Windle et al., 2004). In monkeys, administration of OT reduces ACTH and salivary cortisol (Parker, Buckmaster, Schatzberg, & Lyons, 2005; Simpson et al., 2014). The amygdala is vital for regulating anxiety and fear through connections to the autonomic nervous system, and OT inhibits the central amygdala by exciting GABAergic interneurons (Adolphs, Tranel, & Damasio, 1998; Huber, Veinante, & Stoop, 2005; LeDoux, 2000; Whalen et al., 1998). One of the first studies to use intranasal oxytocin to

study social behavior in humans found that treatment reduces cortisol levels and reports of anxiety after a social stressor, and that this effect was even greater when paired with social support (Ditzen et al., 2009; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Oxytocin also reduces social anxiety in those with generalized social anxiety disorder (GSAD), normalizing a hyperreactive amygdala response to threatening faces (Labuschagne et al., 2010). In healthy individuals, OT increases trust and decreases amygdala reactivity to threatening faces and neutral faces that become aversive through fear-conditioning (Domes et al., 2007; Kirsch et al., 2005; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Petrovic, Kalisch, Singer, & Dolan, 2008). While Domes et al. (2007) found that OT decreased amygdala activation for all emotional faces, others have reported that OT decreases amygdala activation only in response to fearful faces, and exhibits an increased activation in response to happy faces (Gamer et al., 2010).

The amygdala potently modulates the activity of many regions throughout the brain (Stein et al., 2007), and by altering amygdala activity OT can strongly regulate social behavior. Treatment with OT enhances functional connectivity between the amygdala and the orbitofrontal cortex, anterior cingulate, and the hippocampus while reducing functional connectivity to brainstem regions mediating the fear response (Kirsch et al., 2005; Riem et al., 2011). Oxytocin also enhances connectivity between the amygdala and mPFC (Sripada et al., 2013), and GSAD patients exhibit reduced functional connectivity between these areas that is correlated with greater social anxiety (Dodhia et al., 2014; Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013). Oxytocin treatment in GSAD patients normalizes amygdala-mPFC connectivity to control levels, and patients with higher social anxiety showed greater enhancement induced by OT

(Dodhia et al., 2014). These results demonstrate that OT likely reduces social anxiety by altering activity within the amygdala and through the amygdala's connections to brain areas involved in emotion regulation. Interestingly, treatment with OT in healthy individuals also increases gaze to the eyes, and this effect is related to an increase in functional connectivity between the amygdala and the superior colliculus (Gamer et al., 2010). The amygdala is critical for directing gaze to the eye region, and the superior colliculus is involved generating saccades to behaviorally relevant locations (Adolphs et al., 2005; Akiyama et al., 2007; Ignashchenkova, Dicke, Haarmeier, & Thier, 2004). In the rhesus macaque, both locations have receptors that OT binds (Freeman et al., 2014;Young et al., 1999).

1.4.3 Effects of oxytocin on attention to social stimuli

Indeed, perhaps the most consistent finding related to OT administration in humans is an increased engagement with and processing of social stimuli (Bartz et al., 2011; Striepens, Kendrick, Maier, & Hurlemann, 2011). Intranasal OT given to healthy individuals increases the time spent looking at the eye region of faces viewed on a computer monitor (Gamer et al., 2010; Guastella, Mitchell, & Dadds, 2008). Perhaps due to this enhanced processing of the eyes, OT also improves participants' ability to decipher the emotional state of a face when only the eyes are shown (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001).

These improvement are particularly relevant for those with a autism spectrum disorder, who spend less time looking at eyes and do not use this region for the recognition of emotions, instead focusing on the mouth (Klin, Jones, Schultz, Volkmar, & Cohen, 2002c; Pelphrey et al., 2002; Spezio et al., 2007). Moreover, autistic teens who

spent more time viewing faces and less viewing objects had greater social functioning (Klin et al., 2002c). When given OT, autistic adults spent more time viewing the eyes of faces and engaged more with those that reciprocate their interaction (Andari et al., 2010). Demonstrating the efficacy of this link between OT, eye gaze and emotion recognition in autistics, a recent study found that autistics given OT showed increases in amygdala response that predicted increases in the recognition of emotion from the eyes (Domes et al., 2014).

In rhesus monkeys, OT increases the time spent looking at the eyes of familiar faces and the faces of dominant monkeys (Ebitz, Watson, & Platt, 2013). Oxytocin treatment also increases gaze to the face of monkeys when the subject is deciding whether to give to juice to the other monkey or not (Chang et al., 2012).

1.4.4 Effects of oxytocin on memory for social information

In rodents, OT in the medial amygdala has been found to be critical for memory for odors of conspecifics, but not non-social odors (Ferguson et al., 2000;Ferguson, Aldag, Insel, & Young, 2001;Ferguson, Young, & Insel, 2002). Oxytocin's specific enhancement of memory for social (faces), but not non-social (houses, sculptures, landscapes) information has also been replicated in humans. This social specificity has been replicated in a task that signaled correct or incorrect responses with either happy or angry faces (social), or red or green circles (non-social). When arbitrary associations were learned with social reinforcers, OT enhanced memory, but when the non-social reinforcers were used no effect was observed. Moreover, this pattern of effects was not observed in two patients without functioning amygdalae, consistent with the Ferguson et al. studies (2000 & 2001).

However, other studies in rats provide conflicting evidence, with some showing that OT impairs memory (Dantzer, Bluthe, Koob, & Le Moal, 1987) and others that it enhances it (Arletti et al., 1995). Potentially explaining this discrepancy, social memory is impaired by high doses and enhanced by low doses (Popik, Vetulani, & van Ree, 1992).

Memory enhancing effects of OT have been replicated in other studies with humans. Using the remember/know paradigm, it was found that OT enhanced recognition memory for happy, but not neutral or angry faces (Guastella, Mitchell, & Mathews, 2008). When OT was given after the stimulus study period, OT improved recognition memory for previously seen faces (Savaskan, Ehrhardt, Schulz, Walter, & Schächinger, 2008). To date there have been no examinations of whether OT alters memory in non-human primates.

1.4.5 Summary

In summary, a wide range of findings across rodents, humans and non-human primates have supported a role of OT in the amplification of social information seeking, concurrent with a decrease in social anxiety, and in some cases an enhancement of memory for social information. These studies have generated much enthusiasm for the development of treatment strategies that specifically target social deficits. While studies with rodents offer a range of powerful tools to manipulate the genetics and molecular biology for the purpose of understanding the neurobiology of OT's effects on social behavior, it can be difficult to translate their social behavior to the more nuanced social behavior of humans (Chang & Platt, 2013). On the other end of the spectrum, experiments in humans have high external validity but rely primarily on neuroimaging to

examine how OT changes blood flow in large regions, and doesn't have the temporal or spatial resolution to understand OT's effects at the neuronal level. Uncovering how single neurons and small local networks of neurons encode information about the social environment will be critical to understanding how oxytocin alters social behavior.

1.5 Face processing by single neurons in the rhesus macaque

1.5.1 Introduction

As early at 1972 (Gross, Rocha-Miranda & Bender, 1972), electrophysiological recordings of single neurons in behaving rhesus macaque monkeys (Macaca mulatta) identified neurons in the temporal lobe that respond selectively to the sight of faces compared to other stimuli ("face cells") (Bruce, Desimone, & Gross, 1981; Desimone, Albright, Gross, & Bruce, 1984; Hasselmo, Rolls, & Baylis, 1989a). Since that time, the neural mechanisms of the face-cell system of rhesus macaques has been the focus of extensive research, revealing an elegant interconnected network of neurons that encode face identity, expression, gaze direction and even eye contact (Eifuku et al., 2004; Freiwald et al., 2009; Hasselmo et al., 1989b; Moeller et al., 2008; Perrett et al., 1984, 1985; Sugase et al., 1999; Tsao et al., 2006; Young and Yamane, 1992; Zimmerman et al.,2012).

The specificity of these responses for highly complex social features has inspired decades of research revealing one of the most incredible connections between behavior and neuronal response at the level of single neurons. The remarkable specificity of these neurons and their connection to behavior parallels that found in rodent "place cells" in the hippocampus, which encode the animal's position in physical space and support memory-guided navigation (O'Keefe, 1976; Pfeiffer & Foster, 2013). Just as the place cell

network has yielded amazing insight into the mechanisms of memory, the face cell network offers an extraordinary opportunity to understand the mechanisms of social perception at the fundamental level of the brain.

Decoding activity at this level in the motor cortex of monkeys has allowed revolutionary control of external devices (Serruya, Hatsopoulos, Paninski, Fellows, & Donoghue, 2002), and this has lead to the control of prosthetic devices in a tetraplegic human (Hochberg et al., 2006). Similarly, by understanding how the face cell network encodes social information we may one day be able to restore function to those with impairments in social processing. Finally, this system offers an unprecedented capability to evaluate how potential therapeutics such as oxytocin alters social behavior, thereby optimizing treatment strategies.

1.5.2 Face-selective neurons in the macaque temporal lobe

The first report of face-selective neurons reported: "complex colored patterns (e.g., photographs of faces, trees) were more effective than the standard stimuli, but the crucial features of these stimuli were never determined" (Gross et al., 1972, p. 103). In a serendipitous observation, they found that after failing to find a visual stimulus that elicited a neuronal response, they "waved a hand at the stimulus screen and elicited a very vigorous response from the previously unresponsive neuron". Upon this observation they tested stimuli with various physical dimensions, finding that simple physical dimensions did not correlate with response, instead finding a correlation between response and similarity to the shadow of a monkey hand.

The first complete report of a face-selective neuron described cells in the temporal cortex that responded strongly to photographs of both a monkey and human face, but did

not respond much when viewing random patterns, a hand or a scrambled version of the face. Interestingly, obscuring the eye region of the monkey or human face reduced the response, and simple drawings of a face were enough to elicit a response (Bruce et al., 1981). Because responses to such a complex stimulus had not been reported before, these results were met with strong skepticism. Indeed, it was appreciated early on that it is impossible to absolutely determine that a neuron is selective for a given feature (Bruce et al., 1981; Desimone, 1991).

Subsequent reports confirmed face-specific responses in the temporal lobe (Desimone et al., 1984;Leonard, Rolls, Wilson, & Baylis, 1985;Perrett, Rolls, & Caan, 1982), and the finding that some cells in the temporal cortex were selective for specific parts of faces, for example the eyes or hair, complicated interpretation (Perrett et al., 1982). Was it the case that face cells were simply cells that responded to a specific feature of the face or are they cells that encode a combination of facial features?

1.5.3 Encoding of faces by face-selective neurons

Similar to the construction of edges from the varying angles of receptive fields for neurons in V1 (Hubel & Wiesel, 1959), face cells may arise from the combination of input from cells encoding specific facial features (Perrett, Mistlin, & Chitty, 1987). Such facial feature cells have been found in the interotemporal (IT) cortex, where they encode distance between specific features (Yamane, 1988). Recent recordings in this area using an exhaustive set of cartoon faces with customizable features found that cells in IT cortex responded to specific features as well as feature combinations. The most frequently represented relationship between features was the distance between the eyes, face direction and the layout of the face geometry (Freiwald et al., 2009).

It has been suggested that faces may be encoded in relationship to one another, varying along their different component features (Leopold, O'Toole, Vetter, & Blanz, 2001). For example, caricatured faces may be seen as distinctive because the most diagnostic features are made even more extreme, whereas faces that are more "average" are harder to discriminate (Rhodes, Brennan, & Carey, 1987; Stevenage, 1995). In line with this thinking, the responses of feature coding cells found by Freiwald et al. (2009) exhibited ramp-like tuning curves, with strong responses strongly skewed towards the maximal extreme of a feature (e.g. large eyes), and low responses to the minimal extreme (small eyes). This is in contrast to a previous finding that face cells respond either maximally or minimally to the average face, but these cells were not necessarily selective for faces and were recorded anterior to the location of Freiwald et al. (2009) (D. A. Leopold, Bondar, & Giese, 2006).

In the more posterior area of IT, face cells occur in large clusters (Perrett, Hietanen, Oram, & Benson, 1992; Zangenehpour & Chaudhuri, 2005), and cortical columns representing particular features combine to represent complex objects, including faces (Tsunoda, Yamane, Nishizaki, & Tanifuji, 2001). This suggests that faces are represented in the in temporal cortex not just by the activity of a relatively sparse population of neurons representing specific faces, but instead through a distributed, flexible coding scheme based on facial features. This arrangement is particularly robust, as a relatively small population of a few dozen neurons encoding facial features is capable of discriminating between different faces (M. P. Young & Yamane, 1992).

Because of the prevalence of cells encoding feature-relationships (Freiwald et al., 2009), this region may be optimally suited to discriminate between different face

identities. Supporting this hypothesis, face cells here are found to reliably discriminate faces from other object categories as well as individuate specific faces facial identity (Hasselmo et al., 1989a; Hung, Kreiman, Poggio, & DiCarlo, 2005;Perrett et al., 1984, 1985, 1989, 1992;Perrett et al., 1987;Rolls, 1992; Tsao et al., 2006;Young & Yamane, 1992). Confirming a causal link between face cells and face perception, electrical stimulation of small clusters of face-selective neurons in IT cortex biases a monkey to categorize a partially occluded object as a face (Afraz, Kiani, & Esteky, 2006).

While neurons with strongly selective responses for specific features likely contribute the most to this distributed code, neurons with responses to other categories may also contribute valuable information. In humans, the fusiform face area lies close to the macaque inferotemporal cortex, and exhibits face-selective BOLD activation (Kanwisher et al., 1997). In their landmark paper, Haxby et al., (2001) used multivariate pattern analysis to demonstrate that the fusiform face area actually showed significant responses to non-preferred object categories, and that the accuracy with which object category could be discriminated was not greatly affected when regions responding maximally to one category were excluded (Haxby et al., 2001). While a coding system utilizing sparse representations of objects in focal modules is limited in its representational capacity by the number of neurons available, distributed and overlapping representations can utilize nonmaximal responses within a combinatorial coding system whose storage capacity is far greater (Hanson, Matsuka, & Haxby, 2004; Haxby et al., 2001;Rolls, Treves, & Tovee, 1997). A recent study by Rigotti et al., (2013) found that in the macaque prefrontal cortex, neurons often have complex, inscrutable responses to

multiple aspects of a cognitive task, and that these mixed-selectivity neurons drastically increase the brain's computational power (Rigotti et al., 2013).

Face cells in IT cortex receive unimodal visual input and appear to encode social information that is static (identity), while neurons in the superior temporal sulcus receive multisensory input and are more involved in representing the changeable aspects of the face like expressions and gaze direction (De Souza, Eifuku, Tamura, Nishijo, & Ono, 2005; Hasselmo et al., 1989b;Perrett et al., 1985, 1990;Perrett, Xiao, Barraclough, Keysers, & Oram, 2009; Sugase et al., 1999). For example, STS neurons can distinguish between openings of the mouth made during chewing, yawning and emotional expressions (Perrett et al., 1990;Perrett et al., 2009). STS neurons can also discriminate between different facial expressions like affiliative lip smacking and open-mouth threats (Hasselmo et al., 1989a; Sugase et al., 1999).

1.5.4 Face-selectivity throughout the brain

Face-selective neurons in other areas also carry this information, for example in the amygdala, neurons representing face identity, expression and conjunctions between the two factors are found (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007a). The amygdala's role in detecting salient social information conveyed by the eyes has been supported deficits caused by selective lesions and by correlation between amygdala activation and gaze to eyes (Adolphs, Tranel, Damasio, & Damasio, 1994; Gamer et al., 2010), but only recently has a correlate at the level of single neurons been discovered (Zimmerman, Mosher & Gothard, 2012). These "eye cells" responded only when the subject is looking at the eyes of another monkey shown in a video, and a subset of these neurons are further modulated when eye contact is made between the subject and the

monkey in the video. Importantly, eye cells responded after gaze to the eyes, and thus are not likely to be involved in the generation of gaze to the eyes but instead in monitoring the social environment (Zimmerman, Mosher & Gothard, 2012).

Face selectivity has also been found in the prefrontal cortex (O Scalaidhe, Wilson, & Goldman-Rakic, 1997; Scalaidhe, Wilson, & Goldman-Rakic, 1999; Tsao, Schweers, Moeller, & Freiwald, 2008) as well as the orbitofrontal cortex (Rolls, Critchley, Browning, & Inoue, 2006; Thorpe, Rolls, & Maddison, 1983). The prefrontal face cells exhibited face-selective delay activity in a working memory task (Scalaidhe et al., 1999), and face-selective patches located in nearby ventral prefrontal areas exhibited stronger responses for emotional faces (Tsao et al., 2008), suggesting a role in regulating attention to and working memory for faces. In orbitofrontal cortex, face cells are harder to characterize and better stimulated by real faces than faces on a monitor, but have been found to differentiate between different facial identities via different response magnitudes (Rolls et al., 2006; Thorpe et al., 1983).

Finally, while the hippocampus is typically characterized as providing a domain-general memory signal, among human hippocampal neurons that discriminate familiar from novel stimuli, most are category specific, i.e., respond preferentially to faces or objects (Fried, MacDonald, & Wilson, 1997). Later reports confirmed the category-selectivity of human hippocampal neurons, finding highly selective responses for specific famous individuals and landmarks presented via different images as well as through written and spoken text (Quiroga, Reddy, Kreiman, Koch, & Fried, 2005;Quiroga, Kraskov, Koch, & Fried, 2009) In the macaque hippocampus, neurons selective for the color, shape or general category of clip-art images have been reported (Hampson, Pons,

Stanford, & Deadwyler, 2004), but neurons with selective responses to faces in particular have not been identified.

It has been proposed that face processing occurs as a sequence of stages where specific information is calculated (Bruce & Young, 1986), but until recently it has been unknown how local networks of face cells might interact with one another. Using simultaneous fMRI and electrical stimulation, six distinct, bilateral, "patches" of face-selective cortex were found across the ventral temporal cortex (Moeller et al., 2008). Stimulation within the face-selective patches, but not areas just outside of them, elicited an increase in BOLD activation in all of the patches, and the strength of this co-activation was similar to that seen during face viewing. Stimulation also produced activation of the pulvinar, claustrum and amygdala, and it was suggested that these areas may be important gating mechanisms for communication between the face patches and other areas (Moeller et al., 2008). Because stimulation in all the patches produced activation across the others, the network is not likely to be organized according to a strict hierarchy.

1.5.5 Summary

This extensive literature provides strong evidence for how social information from the face is processed by single neurons in the rhesus macaque brain. Understanding how the brain categorizes objects as a face and represents information about the important social signals emitted by faces is critical to understanding the neurobiology of social behavior. Because the degree of face-selectivity in autistic individuals predicts face discrimination performance, understanding the contribution of face-selective responses will also be important for evaluating the effects of therapeutic interventions aimed at improving social behaviors (Jiang et al., 2013).

Chapter 2. Face-selective neurons in the macaque hippocampus

2.1 Abstract

Across the primate occipitotemporal cortex, face-selective neurons discriminate face identity, gaze direction and expression, but robust memory signals have not been found. Recent reports of face-selective BOLD signal in the macaque hippocampus led us to hypothesize that we would find face-selective neurons in this region and that their responses might be related to memory specifically for faces. We recorded the activity of 108 hippocampal neurons in two monkeys while they performed a recognition memory task with complex image. We found that a significant proportion was face-selective and that a substantial proportion of these neurons exhibited significant firing-rate modulation that reflected whether stimuli were novel or familiar. Importantly, face-selective neurons exhibited stronger novelty signals for faces compared to non-faces. Working in concert with neocortical face processing networks, face-selective neurons in the hippocampus could provide a critical link through which episodic content could be stored and subsequently retrieved in content-specific networks.

2.2 Introduction

The ability to recognize previously encountered individuals as familiar is essential for survival in large, complex social groups. Success in these groups is dependent upon learning the social reputation of group members by closely monitoring their actions and signals of emotional state and behavioral intent. Faces are important sources of these dynamic signals and serve as handles for a vast repository of social information gathered from iterative interactions. How this information is processed by the brain and transformed into memory is still unclear.

Electrophysiological recordings of single neurons in the awake, behaving monkey have identified neurons in the temporal lobe that respond selectively to faces compared to other stimuli (Desimone et al., 1984; Hasselmo et al., 1989b). A major goal of these experiments has been to identify what these selective responses encode about faces. In inferotemporal (IT) cortex, face-selective neurons have been shown to reliably discriminate faces from other object categories as well as individuate specific faces (Hung et al., 2005). Critically, electrical stimulation of small clusters of face-selective neurons in IT cortex has been shown to bias a monkey to categorize a partially occluded object as a face, demonstrating a causal relationship between the activity of face-selective neurons and face perception (Afraz et al., 2006). While face cells in IT seem to be important for processing the featural aspects of faces, face-selective neurons in the superior temporal sulcus and amygdala of rhesus macaques respond selectively to specific facial expressions or gaze directions, encoding two key social signals (De Souza et al., 2005;Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007b; Hasselmo et al., 1989b;Perrett et al., 1985). Although these findings lend strong support to the role of face-selective neurons in face perception, their role in memory for faces is less clear.

Face-selective neurons in IT cortex are thought to underlie working memory for faces, because these neurons demonstrate face-selective activity during retention across short delays (Miyashita & Chang, 1988). Interestingly, IT neurons acquire selectivity for specific images across repeated presentations (Rolls, Baylis, Hasselmo, & Nalwa, 1989), and the responses of these neurons are more useful for discriminating between specific faces than between novel and familiar faces. By contrast, single neurons in the human (Rutishauser, Schuman, & Mamelak, 2008) and macaque hippocampus (Jutras & Buffalo,

2010) can distinguish novel from familiar stimuli after only one presentation of a stimulus through modulations in firing rate. Importantly, the magnitude of this firing rate modulation correlates with recognition memory strength (Jutras & Buffalo, 2010). During the delay period of a face recognition task, functional connectivity between the hippocampus and IT cortex is enhanced (Gazzaley, Rissman, & D'Esposito, 2004), suggesting that the hippocampus may be critical for providing a memory signal to neocortical face processing areas where faces can be individuated.

While the hippocampus is typically characterized as providing a domain-general memory signal, among human hippocampal neurons that discriminate familiar from novel stimuli, most are category specific, i.e., respond preferentially to faces or objects (Fried et al., 1997). It is possible that face-selectivity in the hippocampus provides an efficient method with which to connect with face-selective networks in neocortical areas. In the macaque hippocampus, neurons selective for the color, shape or general category of clip-art images have been reported (Hampson et al., 2004), but neurons with selective responses to faces in particular have not been identified.

Here we identify a significant proportion of single neurons in the monkey hippocampus that are selective for a broad range of human, animal and cartoon faces, compared with objects and landscapes or scenes. Further, these face-selective neurons display category-specific memory signals.

2.3 Methods

2.3.1 Experimental Procedures

Electrophysiological Recording, Data Collection, and Preprocessing. Procedures were carried out in accordance with National Institutes of Health guidelines and were approved

by the Emory University Institutional Animal Care and Use Committee. Neuronal recordings were carried out in two adult male rhesus monkeys (*Macaca mulatta*), which were obtained from the breeding colony at the Yerkes National Primate Research Center Field Station where they were mother-reared in large social groups for the first three years of life. Their mean weight at the start of the experiment was 6.8 ± 1.1 kg, and their mean age was 4 years and 5 months. Before implantation of recording hardware, monkeys were scanned with MRI to localize the hippocampus and to guide placement of the recording chamber. Using this information, a cilux plastic chamber (Crist Instrument Co.) for recording neural activity and a titanium post for holding the head were surgically implanted. We performed postsurgical MRI to fine-tune electrode placement and to determine recording locations.

During testing, each monkey sat in a dimly illuminated room, 60 cm from a 19-inch CRT monitor, running at 120 Hz, noninterlaced refresh rate. Eye movements were recorded using a noninvasive infrared eye-tracking system (ISCAN). Stimuli were presented using experimental control software (CORTEX, www.cortex.salk.edu). At the beginning of each recording session, the monkey performed a calibration task, which involved holding a touch sensitive bar while fixating a small (0.3°) gray fixation point, presented on a dark background at various locations on the monitor. The monkey had to maintain fixation within a 3° window until the fixation point changed to an equiluminant yellow at a randomly chosen time between 500 ms and 1,100 ms after fixation onset. The monkey was required to release the touch-sensitive bar within 500 ms of the color change for delivery of a drop of applesauce. During this task, the gain and offset of the oculomotor signals were adjusted so that the computed eye position matched targets that

were a known distance from the central fixation point.

Following the calibration task, the monkey was tested on the Visual Preferential Looking Task (Figure 2.1A). The monkey initiated each trial by fixating a white cross (the fixation target, 1°) at the center of the computer screen. After maintaining fixation on this target for 1 s, the target disappeared and a square picture stimulus subtending 11° was presented. A total of 8,800 stimuli were used in this study and were all obtained from the photo sharing website Flickr. The stimulus disappeared when the monkey's direction of gaze moved off the stimulus, or after a maximum looking time of 5 s. The VPLT was given in 51 daily blocks of 6, 8, or 10 trials each, chosen pseudorandomly, for a total of 400 trials each day. The median delay between successive presentations was 8.1 s. Reward was not delivered during blocks of the VPLT; however, five trials of the calibration task were presented between each block to give the monkey a chance to earn some reward and to verify calibration. The number of trials in each VPLT block was varied to prevent the monkey from knowing when to expect the rewarded calibration trials.

The recording apparatus consisted of a multichannel microdrive (FHC Inc.) holding a manifold consisting of a 23-gauge guide tube containing four independently moveable tungsten microelectrodes (FHC Inc.), with each electrode inside an individual polyamide tube. Electrode impedance was in the range of 1 to 2 MΩ, and electrode tips were separated horizontally by 190 μm. For each recording, the guide tube was slowly lowered through the intact dura mater and advanced to ~3.5 mm dorsal to the hippocampus with the use of coordinates derived from the MRI scans. The electrodes were then slowly advanced out of the guide tube to the hippocampus. No attempt was

made to select neurons based on firing pattern. Instead, we collected data from the first neurons we encountered in the hippocampus. At the end of each recording session, the microelectrodes and guide tube were retracted. All recordings took place in the anterior part of the left hippocampus. Recording sites were located in the CA3 field, dentate gyrus, and subiculum. Data amplification, filtering, and acquisition were performed with a Multichannel Acquisition Processor system from Plexon Inc. The neural signal was split to separately extract the spike and the LFP components. For spike recordings, the signals were filtered from 250 Hz to 8 kHz, further amplified, and digitized at 40 kHz. A threshold was set interactively, to separate spikes from noise, and spike waveforms were stored in a time window from 150 μs before to 700 μs after threshold crossing. Each recording typically yielded two-to-six units; single units were sorted offline using Offline Sorter (Plexon, Inc.).

2.3.2 Data Analysis

All analyses were performed using custom programming in MATLAB (The Mathworks, Inc.) and using FieldTrip (http://www.ru.nl/fcdonders/fieldtrip), an open-source toolbox for the analysis of neurophysiological data.

2.3.2.1 Recognition Memory Performance

To evaluate recognition memory performance we compared the amount of time the monkey spent looking at each stimulus during its first (Novel) and second (Repeat) presentation. Adult monkeys show a strong preference for novelty; therefore, a significant reduction in looking time from the first to the second presentation of a stimulus indicated that the monkey had formed a memory of the stimulus (Wilson & Goldman-Rakic, 1994). To control for varying interest in individual stimuli, recognition

memory performance was calculated as the absolute change in looking time between presentations as a percentage of the amount of time the monkey spent looking at the first presentation of each stimulus. Because faces were viewed longer than non-faces on average during the Novel (encoding) presentation (Figure 2.1C inset), we compared recognition memory performance between the two categories by binning stimuli according to the amount of time spent viewing the stimulus during encoding (Figure 2.1C).

2.3.2.2 Visual Responsiveness

We analyzed 108 stable, well-isolated neurons recorded from the anterior hippocampus in two monkeys (55 in Monkey A and 53 in Monkey B, respectively) while they performed the VPLT. For each neuron, we separately tested for visual responsiveness to images of faces, non-faces, as well as all images regardless of category, during each of two conditions: Novel and Repeat presentation. Only images that were viewed for at least 500 ms during the Novel presentation were included for this and all other analyses of firing rate. Additionally, when estimating average firing rate across multiple trials with variable lengths of image viewing, we only included time points with at least 10 trials where the monkey was viewing the stimulus. To test for visual responsiveness to each category and presentation period, we used paired samples *t*-tests to compare the average firing rate during successive, overlapping 200 ms bins stepped in 2 ms increments to the average firing rate during the baseline pre-stimulus period (-800 to 0 ms from stimulus onset). Neurons with at least one bin passing the criteria of significance to $p < 0.05$ for the trials in each condition were designated as visually responsive for that category and condition.

Considering all stimuli together, ninety-eight of these neurons (91%) were visually responsive, in that they demonstrated a significant ($p < 0.05$) change in firing rate during at least one 200 ms bin compared to baseline in either the Novel or Repeat stimulus presentation. The majority (57%) of these neurons exhibited a decrease in firing rate upon stimulus presentation, while 31% exhibited an increase in firing and 11% gave a different response across novel and repeat presentations, e.g. a decrease in one presentation period and an increase in the other.

2.3.2.2 Response Latency

The response latency for each neuron was determined by first calculating the spike density function of the neuron's firing activity separately for each trial in the Face and & Non-Face categories using a Gaussian kernel with a standard deviation of 100 ms, and then, across trials, comparing the smoothed activity taken in each successive 10-ms bins (stepped in 2-ms increments starting from stimulus onset) to the baseline, pre-stimulus firing rate using a paired-samples *t*-test. Upon identifying the first instance in which five consecutive bins showed a significant difference ($p < 0.05$) from the baseline firing rate, the onset time of the first bin plus the midpoint of the bin window (5 ms) was designated as the response latency for the neuron. The response latency to faces and non-faces did not differ between face-selective (Faces: M=185 ± 21 ms, Non-Faces: M=151 ± 21 ms, p>.05) and non-selective face-responsive neurons (Faces: M=177 ± 19 ms, Non-Faces: M=138 ± 15 ms, p>.05).

2.3.2.3 Category Selectivity

To determine selectivity in each presentation period, we first computed the spike-density function for each trial in the face and non-face categories separately by

convolving the spike trains with a Gaussian kernel with a standard deviation of 200 ms. Then for each category we subtracted the category's average baseline response from the average spike density and identified the timepoints of the maximum increase and decrease from baseline across both stimulus categories. Finally, we compared between face and non-face trials the mean change in firing rate during a 100 ms bin centered on both the maximum increase and decrease for that presentation period. Both the maximum and minimum periods were analyzed because some neurons exhibited a biphasic response profile (e.g. the neuron in Figure 2A). Neurons were identified as face-selective if there was a significant difference in firing rate between face and non-face trials at the maximum increase or decrease period during either the Novel or Repeat presentation ($p < 0.05$).

2.3.2.4 Receiver Operating Characteristic

We computed the area under the curve (AUC) during the Novel and Repeat presentation periods for both the maximum increase and decrease in response from baseline and took the greater AUC of the two, yielding one AUC for each presentation period. To compare AUC values between face-selective and face-responsive neurons (Figure 2D) for each neuron we included the AUC for both the Novel & Repeat presentations.

2.3.2.5 Firing Rate Modulation

The time periods of significant differences between Novel and Repeat viewings were computed using a cluster-based non-parametric permutation test ($p < 0.05$, 1,000 randomizations per unit, $p < 0.1$ cluster threshold using a dependent samples t-test for each randomization), and these time periods were used to assess the magnitude of change

across presentations of faces and non-faces for each neuron. To compare the magnitude of response modulation for each stimulus category across all differentially-responsive neurons, we computed an index of the difference in response to Novel and Repeat presentations of face and non-face stimuli (Novel-Repeat/Novel+Repeat). To illustrate the degree to which neurons exhibited preferential modulation for faces or non-faces (Figure 3), we calculated a face-specific modulation index, i.e. the percentage of the combined modulation for faces and non-faces that was accounted for by face trials (Face modulation/[Face modulation + Non-Face modulation]).

To equate for encoding response across stimulus categories we first ranked the responses to each stimulus at encoding during the time period of significant modulation. Then we compared the mean response to the 10 best stimuli for each category, and if the means differed by less than 5%, we considered the responses equated and analyzed response modulation for these 20 stimuli as previously described. If the mean response to the ten best stimuli differed between categories, we excluded the best stimulus response of the category with the higher mean and replaced this stimulus response with 11^{th} best and so forth until the encoding responses differed by less than 5%. We chose to include 10 stimuli and limit the difference to 5% because these values maximized the responses in each category while still limiting the difference between categories.

2.4 Results

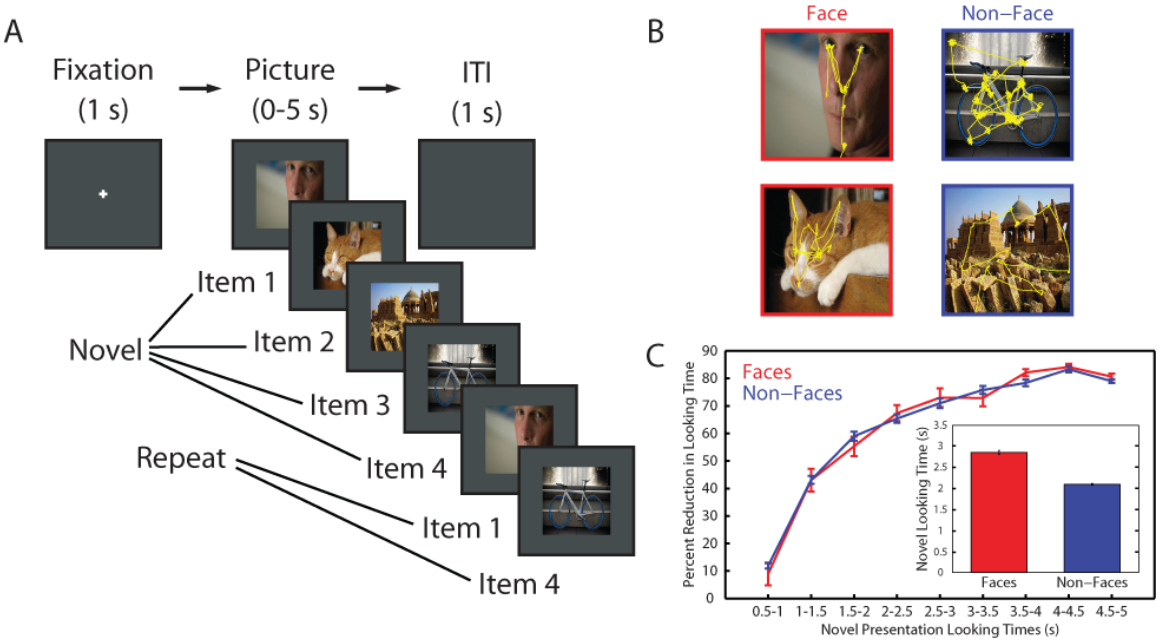
2.4.1 Behavioral Results

We recorded extracellular spikes from hippocampal neurons in two male rhesus macaques (*Macaca mulatta*) while they performed the Visual Preferential Looking Task (VPLT, Fig. 2.1A) (Jutras & Buffalo, 2010; Jutras, Fries, & Buffalo, 2009, 2013; Killian,

Jutras, & Buffalo, 2012; Wilson & Goldman-Rakic, 1994). During each recording session, monkeys were presented with two hundred novel, large (11°), complex visual stimuli, one at a time, on a computer screen. Each stimulus was presented twice during a given session, with up to eight intervening stimuli between successive presentations. Each stimulus remained on the screen until the monkey's gaze moved off the stimulus or for a maximum of 5 s. In this way, the monkey controlled the duration of stimulus presentation, and this duration provided a measure of the monkey's stimulus preference. We compared the amount of time the monkey spent looking at each stimulus during its first (Novel) and second (Repeat) presentation. Adult monkeys show a strong preference for novelty; therefore, a significant reduction in looking time from the first to the second presentation of a stimulus indicated that the monkey had formed a memory of the stimulus.

Images of faces accounted for an average of 30.7 ± 1.3 of the 200 images shown per recording session, and an image was considered to be a member of this category if a face was present in the image and if the monkey fixated on the face during the Novel presentation. All other images were considered non-faces. Face images included human, animal, and cartoon faces while non-face images contained various objects, landscapes, and buildings. Across the broad range of face images, monkeys exhibited a remarkably consistent pattern of fixating the features of the face, with a greater preference for the eye region (Fig. 1B). While faces were viewed significantly longer than non-faces during the Novel presentation (Faces: M=2.8 ± 0.05s; Non-Faces: M=2.1 ± 0.02s ; $p < 0.0001$, Fig. 1C inset), memory for faces and non-faces did not differ after equating for encoding time ($F(1, 6125) = 0.7$, $p > 0.05$, Fig. 1C).

Figure 2.1 The Visual Preferential Looking Task

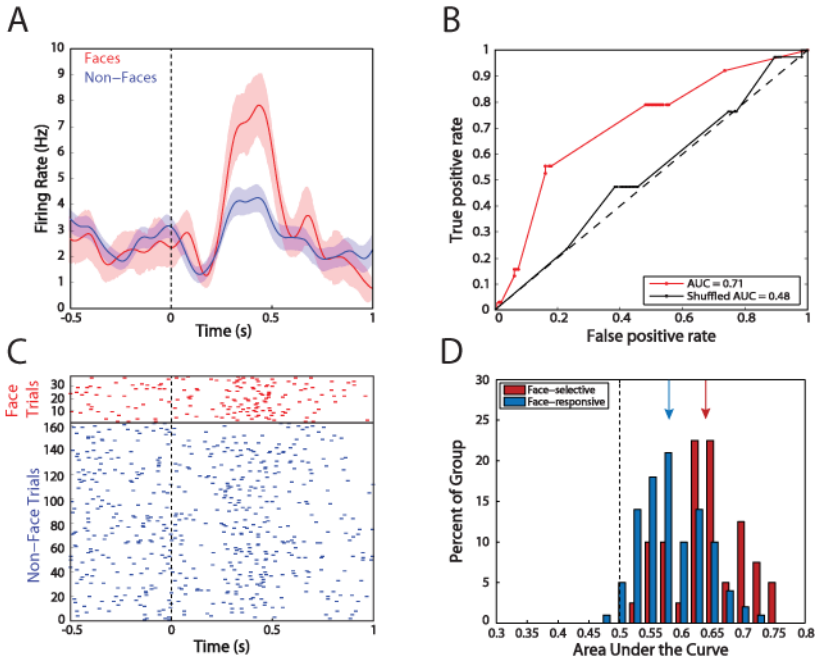


(A) 200 unique images were presented twice in each session with up to 8 trials intervening between Novel and Repeat presentation. (B) Example face and non-face images with scanpath during Novel presentation overlaid. (C) Recognition memory performance for face and non-face images binned by time spent viewing stimulus during Novel presentation. Inset shows time spent viewing faces and non-faces during Novel presentation.

2.4.2 Hippocampal Neurons Display Face-Selective Responses

We analyzed the responses of 108 stable, well-isolated hippocampal neurons recorded from two monkeys performing the VPLT. Seventy neurons (65%) were visually responsive to faces (face-responsive neurons). A comparison of the responses to faces and non-faces revealed that 34 (49%) of the face-responsive neurons exhibited a significant difference in their firing rate for these two categories. Neurons were identified as face-selective if there was a significant difference in firing rate between face and non-face trials during either the Novel or Repeat presentation ($p < 0.05$) (Figure 2.2A). Across all face-selective neurons, the average absolute difference in relative change from baseline between faces ($M = 120 \pm 27\%$) and non-faces ($M = 53 \pm 14\%$) was 101 ± 13%.

Figure 2.2 Face-Selective Hippocampal Neurons

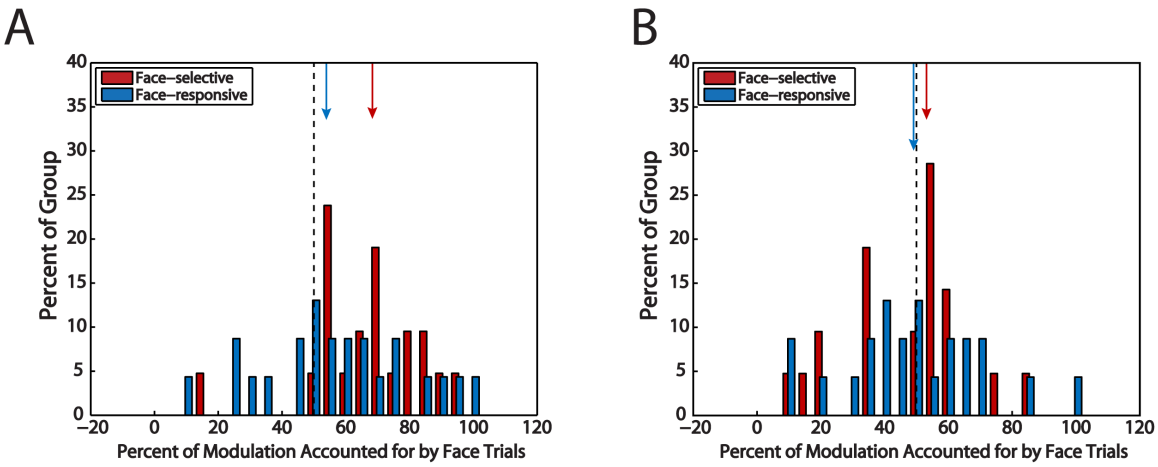


(A) Example face-selective neuron's response averaged across Novel face (red) and non-face (blue) stimuli. Red and blue shaded areas represent SEM. Stimulus-evoked firing rates were significantly higher for face trials versus non-face trials (p = 0.01). (B) Receiver operating characteristic curve for the neuron in (A) used to calculate the area under the curve (AUC) value for this neuron during the Novel presentation (red line, AUC = 0.71). (C) Raster plot for the neuron in (A) showing each action potential for every face (red) and non-face (blue) trial analyzed during the Novel presentation period. (D) Histogram of the AUC values for face-selective (red bars and arrow, median AUC = 0.64 ± 0.05) and non-selective face-responsive neurons (blue bars and arrow, median AUC = 0.58 ± 0.05). The AUC values were significantly higher for face-selective compared to face-responsive neurons (rank-sum test, $p < 0.001$). Dashed-line indicates chance classification performance.

2.4.3 Hippocampal Neurons Discriminate Image Category

To further examine the selectivity of these neurons, we conducted a receiver operating characteristic (ROC) analysis for each face-responsive neuron. This analysis used the change in firing rate relative to baseline to predict whether the monkey was viewing an image of a face or non-face on a trial-by-trial basis. With this analysis, we compared the true and false positives ratio at different thresholds of neuronal response and computed the area under the curve (AUC) formed by these data points as a measure of the probability of correctly predicting the stimulus category. Face-selective neurons had significantly greater AUC values than non-selective, face-responsive neurons (Figure 2D, rank-sum test, $p < 0.001$). The average AUC was 0.62 ± 0.06 for face-selective neurons and 0.59 ± 0.05 for non-selective face-responsive neurons. The example face-selective neuron shown in Figure 2.2A & 2.2C had an AUC value of 0.71 ± 0.05, indicating that the activity of a single hippocampal neuron can predict category membership with high accuracy (Figure 2.2B).

Figure 2.3 Modulation of Firing Rate by Stimulus Novelty in Face-Selective Neurons



(A) Distribution of the proportion of total firing rate modulation observed for both face and non-face trials accounted for by face trials alone (face modulation/face + non-face modulation). When including all stimuli, face-selective neurons exhibited greater modulation of firing rate for face trials than non-face trials (rank-sum test, $p < 0.01$), whereas firing rate modulation in non-selective face-responsive neurons did not differ by image category (rank-sum test, $p > 0.05$). (B) When the Novel response was equated for face and non-face stimuli, the magnitude of firing rate modulation did not differ by image category for face-selective or non-selective face-responsive neurons (both rank-sum tests $p > 0.05$).

2.4.4 Face-Selective Hippocampal Neurons Show Modulations in Firing Rate Related to Stimulus Novelty and Category

The degree to which stimulus novelty influenced the activity of hippocampal neurons was measured by analyzing the relative percent change in firing rate across the Novel and Repeat presentation conditions for face and non-face stimuli separately. The firing rates of 23 face-responsive neurons (23/36, 64%) and 21 face-selective neurons (21/34, 62%) were significantly modulated by stimulus novelty. Among differentially-responsive face-responsive neurons, there was no significant difference in the degree of novelty modulation shown for faces ($M = 21.4 \pm 4.3\%$) and non-faces ($M = 12.4 \pm 1.8\%$, rank-sum test, $p > 0.05$). However, face-selective neurons exhibited significantly greater modulation for faces ($M = 30.1 \pm 3.8\%$) compared to non-faces ($M = 15.3 \pm 2.8\%$, rank-sum test, $p < 0.01$). Figure 2.3A illustrates this difference as the proportion of the combined novelty modulation for both categories that was accounted for by face trials in face-selective neurons ($M = 66.5 \pm 3.8\%$) compared to non-selective, face-responsive neurons ($M = 56.3 \pm 4.9\%$).

We next asked whether this category-specific novelty signal was simply due to the fact that these neurons gave a greater response to faces. To address this question we selected a subset of trials in each stimulus category in order to equate the response during the Novel presentation, and we then analyzed the response modulation. After equating for the magnitude of response during the Novel presentation, face-selective neurons did not exhibit greater modulation across repeated presentation of faces ($M = 35.1 \pm 4.7\%$) compared to non-faces ($M = 38.7 \pm 4.7\%$) and this similarity is illustrated in Figure 2.3B. These data suggest that while face-selective neurons do exhibit greater response modulation for their preferred category, the difference is dependent upon the neuron's

intial response to the stimuli. This finding is consistent with a previous report which demonstrated that for stimuli which elicited a greater initial response in IT neurons, a greater change in response across multiple stimulus presentations was also observed (Li, Miller, & Desimone, 1993). A significant difference from the present results is that the change in response in IT neurons was stimulus-specific and occurred over dozens of trials, whereas the hippocampal neurons reported here exhibited a change that was category-specific and occurred after only a single exposure.

2.5 Discussion

Here, we report that during passive viewing of a large, diverse set of complex images, a substantial population of hippocampal neurons displayed a category-specific response to faces. As a group, these neurons were capable of discriminating faces from non-faces, thereby demonstrating that information about stimulus category can be preserved in the firing rate of single hippocampal neurons. Moreover, face-selective neurons in this region that displayed differential responses related to stimulus novelty did so preferentially for faces. Our results extend recent findings of face-selective BOLD signal in the monkey hippocampus (Ku, Tolias, Logothetis, & Goense, 2011) to the level of single neurons and demonstrate face-specific novelty responses among these neurons. These findings are in agreement with single-neuron recordings in human epileptic patients, which have demonstrated that hippocampal neurons display category-selectivity (R Quiroga et al., 2005) and category-selective memory responses (Fried et al., 1997).

The hippocampus has most often been characterized as carrying domain-general signals of the novelty or familiarity of relations between item and context (Davachi, 2006; Manns & Eichenbaum, 2006; Strange, Fletcher, Henson, Friston, & Dolan, 1999).

Previous experiments have reported that neurons in the monkey hippocampus do not respond selectively to individual stimuli (Naya & Suzuki, 2011) or exhibit stimulus-selective recognition signals (Suzuki & Eichenbaum, 2000). We also did not find neurons that selectively responded to individual stimuli, instead we found that responses that were selective for a specific category of stimuli. Our data provide evidence that given a strong initial response, single neurons in the hippocampus exhibit robust memory signals. However, in addition to this domain-general memory signal, we found that neurons which respond more strongly to faces also exhibit a greater modulation of firing rate for their preferred category by virtue of their greater initial response to this category.

Recent neuroimaging experiments have demonstrated that there is a representational gradient for faces and scenes along the anterior-posterior axis of the human medial temporal lobe (Ku et al., 2011; Kuhl, Rissman, & Wagner, 2012; Lee et al., 2005; Liang, Wagner, & Preston, 2013; Litman, Awipi, & Davachi, 2009; Preston et al., 2010). These studies revealed that the anterior portion of the hippocampus displays greater activation for faces compared to the posterior extent, where activation in response to scenes predominates. These responses parallel those in the parahippocampal gyrus, with the more anterior perirhinal cortex carrying strong item representation and the more posterior parahippocampal cortex displaying selectivity for spatial contexts (Buffalo, Bellgowan, & Martin, 2006; Epstein & Kanwisher, 1998; Liang et al., 2013; Spiridon, Fischl, & Kanwisher, 2006). By contrast, one recent study reported equivalent BOLD response to objects and scenes across the entire anterior hippocampus (Liang et al., 2013). However, this does not preclude the existence of category-selectivity within single neurons if category selectivity is sparsely distributed within a region. Notably, our

hippocampal recordings were all performed within the anterior hippocampus, providing further support for the idea that information about stimulus category is represented in this region.

The representational gradient along the medial temporal lobe is also accompanied by a gradient in novelty-related signals, with stronger memory signals in the anterior hippocampus than the posterior (Liang et al., 2013; Litman et al., 2009; Sperling et al., 2003). In support of these findings, a significant proportion of the face-selective neurons recorded in the current study exhibited strong novelty-related signals after only one presentation of a stimulus. Encoding of successfully retrieved face memories has been associated with significantly greater functional connectivity between the anterior hippocampus and the fusiform gyrus (Sperling et al., 2003). This coordination of memory-related processing may occur within content-specific networks, because trial-wise face-specific encoding strength in occipitotemporal cortex predicts hippocampal activity during the encoding of face memories (Gordon, Rissman, Kiani, & Wagner, 2013). Supporting this notion, a number of fMRI experiments have demonstrated that activity in voxels selective for faces or places is correlated with memory specifically for faces or places, respectively (Mundy, Downing, Dwyer, Honey, & Graham, 2013; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Polyn, Natu, Cohen, & Norman, 2005; Prince et al., 2009; Ranganath, Cohen, Dam, & D'Esposito, 2004). Our results are consistent with these data, demonstrating that face-selective neurons in the anterior hippocampus display stronger novelty-related modulations in firing rate for their preferred stimulus category. Working in concert with neocortical face processing networks, face-selective neurons in the hippocampus could provide a critical link through which episodic content

can be stored and subsequently retrieved in content-specific networks.

However, face-selective hippocampal neurons may also be involved in memory for other stimulus categories. Importantly, all of the face-selective neurons we recorded in the hippocampus also gave significant responses to non-faces, and response modulation by novelty was similar for faces and non-faces after equating for the response during encoding. In their landmark paper, Haxby et al., (2001) used multivariate pattern analysis to demonstrate that the fusiform face area actually showed significant responses to non-preferred object categories, and that the accuracy with which object category could be discriminated was not greatly affected when regions responding maximally to one category were excluded (Haxby et al., 2001). While a coding system utilizing sparse representations of objects in focal modules is limited in its representational capacity by the number of neurons available, distributed and overlapping representations can utilize nonmaximal responses within a combinatorial coding system whose storage capacity is far greater (Hanson et al., 2004; Haxby et al., 2001;Rolls et al., 1997). A recent study by Rigotti et al., (2013) found that in the macaque prefrontal cortex, neurons often have complex, inscrutable responses to multiple aspects of a cognitive task, and that these mixed-selectivity neurons drastically increase the brain's computational power (Rigotti et al., 2013). Thus, while face-selective hippocampal neurons are likely an important part of a network utilized for face recognition memory, it is also possible that they participate in memory for other object categories through submaximal responses.

Another possibility is that the broad tuning we observed in face-selective hippocampal neurons may be an important property that allows hippocampal neurons to associate related content for long-term memory formation (Miyashita & Hayashi, 2000).

Indeed, around 40% of responsive single hippocampal and entorhinal neurons recorded in human epileptic patients exhibit selective multimodal responses to the spoken and written names of the same person or object presented visually (Quiroga, Kraskov, Koch, & Fried, 2009). Given the anatomical convergence of input from multiple sensory modalities in the medial temporal lobe, MTL neurons are optimally situated to participate in the formation of new abstract associations that are the hallmark of long-term memory (Wirth et al., 2003).

One limitation of the current study is that among our pool of stimuli, only face stimuli were well-represented enough to provide a sufficient number of trials with which we could reliably estimate a category response. Thus, we are unable to rule out responses to other untested categories (Desimone, 1991). It could be argued that the responses we observed were due to the higher salience of faces, and because we do not have a comparable category of similar salience we cannot rule out this possibility. However, it is of note that face-selective neurons do not often respond as strongly to other categories salient to monkeys, such as fruit (Tsao et al., 2006).

In conclusion, we have demonstrated that a significant proportion of hippocampal neurons selectively respond to a broad range of faces and that many of these face-selective neurons exhibit a stronger modulation in firing rate for their preferred category after only a single exposure. Our findings are consistent with reports of human hippocampal neurons that display category-selectivity (Quiroga et al., 2005) and category-selective memory responses (Fried et al., 1997).

Chapter 3. Social relevance drives viewing behavior independent of low-level salience in rhesus macaques

3.1 Abstract

Quantifying attention to social stimuli during the viewing of complex social scenes with eye tracking has proven to be a sensitive method in the diagnosis of autism spectrum disorders years before average clinical diagnosis. Rhesus macaques provide an ideal model for understanding the mechanisms underlying social viewing behavior, but to date no comparable behavioral task has been developed for use in monkeys. Using a novel scene-viewing task, we monitored the gaze of three rhesus macaques while they freely viewed well-controlled composed social scenes and analyzed the time spent viewing objects and monkeys in the scene. In each of six behavioral sessions, the monkey viewed a set of 90 images (540 unique scenes) with each image presented twice. The image remained on the screen until the monkey accumulated 10s of viewing time for novel images and 6s of viewing time for repeated images. In two-thirds of the repeated scenes, either a monkey or an object was replaced with a novel item (manipulated scenes). Eye movements were recorded using a noninvasive infrared eye-tracking system (ISCAN) and were sampled at 200 Hz. The monkey was not rewarded during the scene presentation, but received rewarded trials on an unrelated task between scene viewing trials. When viewing a repeated scene, monkeys made longer fixations and shorter saccades, shifting from a rapid orienting to global scene contents to a more local analysis of fewer items. This is consistent with previous findings of scene viewing in humans (Smith et al., 2006). In addition to this repetition effect, in manipulated scenes, monkeys demonstrated robust memory by spending more time viewing the replaced items. By

analyzing attention to specific scene content, we found that monkeys strongly preferred to view objects of social relevance and that this was not related to their salience in terms of low-level image features. A model-free analysis of viewing statistics found that monkeys who were viewed earlier and longer had direct gaze and red sex skin around their face and rump, two important visual social cues. These data provide a quantification of viewing strategy, memory and social preferences in rhesus macaques viewing complex social scenes, and provide an important baseline with which to compare to the effects of therapeutics aimed at enhancing social cognition. In addition, the method by which the scenes were composed offers significant control and flexibility that can be used to address a variety of questions about social cognition.

3.2 Introduction

For decades, eye tracking has been used to uncover how we explore the visual world and the characteristics that guide our attention. Buswell was the first to explore this topic when he observed that fixations increased in duration over the course of viewing and speculated that image regions receiving many fixations of long duration were the "principal centers of interest" (Buswell, 1935, p.72). Mackworth and Morandi extended this line of research by directly quantifying the "informativeness" of each part of an image on a 9-point scale, finding that regions rated as highly recognizable received more fixations (Mackworth & Morandi, 1967). While Mackworth and Morandi separated the image regions using a standard 8x8 grid, Antes was the first to implement the modern region-of-interest approach by dividing the images according to object contours and informativeness (Antes, 1974). Using this approach, he described a subject's scan pattern across a scene as a dynamic process, beginning with long saccades and quick fixations

landing on highly informative regions as participants quickly oriented to the global gist of the scene, with fixations then increasing in duration and saccades decreasing in amplitude as participants focused on local details.

This seminal work demonstrated that exploration of the visual world is a dynamic process that changes with experience and is driven by distinguishable features. The trace of this experience is retained not just within a given encounter but also across repeated episodes. When viewing repeated scenes, participants make fewer fixations and sample fewer regions compared to when the image was novel, suggesting that they retain some knowledge of its contents (Smith, Hopkins, & Squire, 2006). When presented with scenes that have been manipulated after the initial exposure, participants spend a greater amount of time investigating altered scene items than those repeated without manipulation, and this behavior correlates with the participant's explicit memory of the scene (Smith et al., 2006; Ryan et al., 2000). Studies have also demonstrated that this viewing behavior depends on the integrity of medial temporal lobe structures. Amnesic patients with medial temporal lobe damage that includes damage to the hippocampus demonstrate impaired viewing behavior for manipulated scenes (Ryan et al., 2000;Smith et al., 2006;Smith & Squire, 2008). Eye tracking has also been used in schizophrenic patients to assess attentional allocation (Sprenger et al., 2013), face recognition (Frith et al., 1983; Gordon et al., 1992; Phillips and David, 1997; Streit et al., 1997; Williams et al., 1999) and the exploration of complex scenes (Gaebel et al., 1987; Phillips et al., 2000), as well as reduced attention towards socially relevant stimuli in individuals with autism spectrum disorders (Jones, Carr, & Klin, 2008b; Jones & Klin, 2013; Klin et al., 2002c). Rhesus macaque monkeys provide an excellent model for understanding the neural mechanisms

that underlie these disorders, because exactly the same image viewing tasks can be used in humans and monkeys. Such tasks rely on natural gaze behavior, thereby reducing potentially confounding effects of extensive training upon task strategy, enhancing the face validity of the behavioral correlates investigated and making direct comparisons to humans more valid. However, despite the high prevalence of disorders like schizophrenia and autism that impair attention to and memory for social stimuli, appropriate tasks for assessing these behaviors in rhesus macaques have not been as well explored.

Sackett (1965) was one of the first to record how monkeys respond to social images when he presented monkeys with slides of monkeys engaged in a variety of social behaviors and reported that monkeys reared in the wild spent more time looking at slides depicting sexual or aggressive content. Since then, studies have almost exclusively used images of rhesus faces cropped from the body to examine preference for viewing faces compared to other stimuli (Guo, Mahmoodi, Robertson, & Young, 2006; Wilson & Goldman-Rakic, 1994), which parts of faces are viewed (Gothard, Brooks, & Peterson, 2009; Keating & Keating, 1982) and the moderating effects of face familiarity (Guo, Robertson, Mahmoodi, Tadmor, & Young, 2003;Leonard, Blumenthal, Gothard, & Hoffman, 2012) expression (Gothard, Erickson, & Amaral, 2004; Nahm, Perret, Amaral, & Albright, 2008) gaze direction (Leonard et al., 2012; Mendelson, Haith, & Goldman-Rakic, 1982), social status (Deaner, Khera, & Platt, 2005), vocalization (Ghazanfar, Nielsen, & Logothetis, 2006) and sex (Leonard et al., 2012). The results of these studies indicate that rhesus macaques prefer to view faces, particularly the eye region.

Using isolated faces to investigate face perception in humans (Althoff & Cohen, 1999; Haith et al., 1977; Henderson et al., 2005; Janik et al., 1978; Walker-Smith et al.,

1977), studies have found that, like monkeys, humans prefer to view faces and are especially drawn to the eye region. However, in natural settings, faces are rarely seen in isolation from bodies and other individuals and objects. Several groups have emphasized the importance of maintaining high ecological relevance when studying attention to social stimuli (Bindemann et al., 2009, 2010; Birmingham et al., 2008a, 2008c, 2012; Birmingham & Kingstone, 2009; Kingstone et al., 2003; Neisser, 1967; Riby & Hancock, 2008b; Smilek et al., 2006). While isolated faces direct attention to the face by design, faces embedded in complex scenes demand that the viewer select among many stimuli the ones that are most relevant.

It has been suggested that this difference in stimulus complexity (Riby & Hancock, 2008b) might explain why some studies have found that attention to faces is reduced in autism spectrum disorders (ASD) (Jones et al., 2008b; Klin et al., 2002b; Nacewicz et al., 2006; Pelphrey et al., 2002; Riby & Hancock, 2008a; Spezio et al., 2007; Sterling et al., 2008; Trepagnier et al., 2002) while other studies reported no difference from neurotypical individuals (Bar-Haim et al., 2006; de Wit et al., 2008; Rutherford & Towns, 2008; van der Geest, Kemner, Camfferman, et al., 2002; van der Geest, Kemner, Verbaten, et al., 2002). A direct comparison of isolated faces and social scenes revealed that individuals with Asperger syndrome looked less at the eyes when faces were embedded in social scenes but were no different than neurotypical individuals when faces were presented in isolation (Hanley et al., 2012).

Studies using social scenes as stimuli have found that even when presented with other objects competing for attention, neurotypicals preferentially view faces and eyes, oftentimes on the first fixation (Birmingham et al., 2008a; Birmingham, Bischof, &

Kingstone, 2008d; Smilek et al., 2006). By using staged photographs to control the number of people in each scene (1 or 3) as well as the activity of those persons (Active or Inactive), Birmingham and colleagues found that participants looked more at the eyes in scenes with more people, but only when those people were engaged in an activity (Birmingham et al., 2008d), suggesting that scene content and context can significantly affect viewing behavior.

To the best of our knowledge, only two studies have presented still images of social scenes to a monkey species and examined their eye movements (Berger et al., 2012; McFarland et al., 2013). McFarland and colleagues showed humans and male rhesus monkeys photos of either affiliative (grooming) or aggressive (chasing) interactions between two individuals from various primate species. They found that while both subject groups spent more time viewing faces compared to bodies, humans spent almost twice as much time viewing the individuals in the scene as did the rhesus. One important caveat is that the rhesus subjects used were not raised in a species-typical environment and spent only 3.1 seconds out of the available 10 exploring the images, of which only 8 images out of the 40 depicted conspecifics.

Interestingly, Berger and colleagues (2012) found that fixation location was correlated with low-level features of image salience, except for images that contained primate faces (2 of humans and 1 of a chimpanzee). However, these data should be interpreted cautiously as there were only 3 and none were of consepecifics. In humans, salience does not account for fixations on objects of social relevance (faces and eyes) made by humans viewing social scenes (Birmingham, Bischof, & Kingstone, 2009). While there is evidence that during free viewing of natural scenes, attention is allocated

to the most salient low-level features such as orientation contrast, intensity and color information (Itti & Koch, 2000; Parkhurst, Law, & Niebur, 2002), this may not be true for scenes that contain social stimuli. In line with this idea, the predictive power of low-level features has been challenged, citing the "cognitive relevance" of items related to the needs and preferences of the viewer in determining which features are selected for attentive processing (Henderson, Malcolm, & Schandl, 2009).

Here we aimed to assess the relative contributions of cognitive relevance and salience in the allocation of attention, as well as the effect of experience on attention and memory.

3.3 Methods

3.3.1 Data Collection

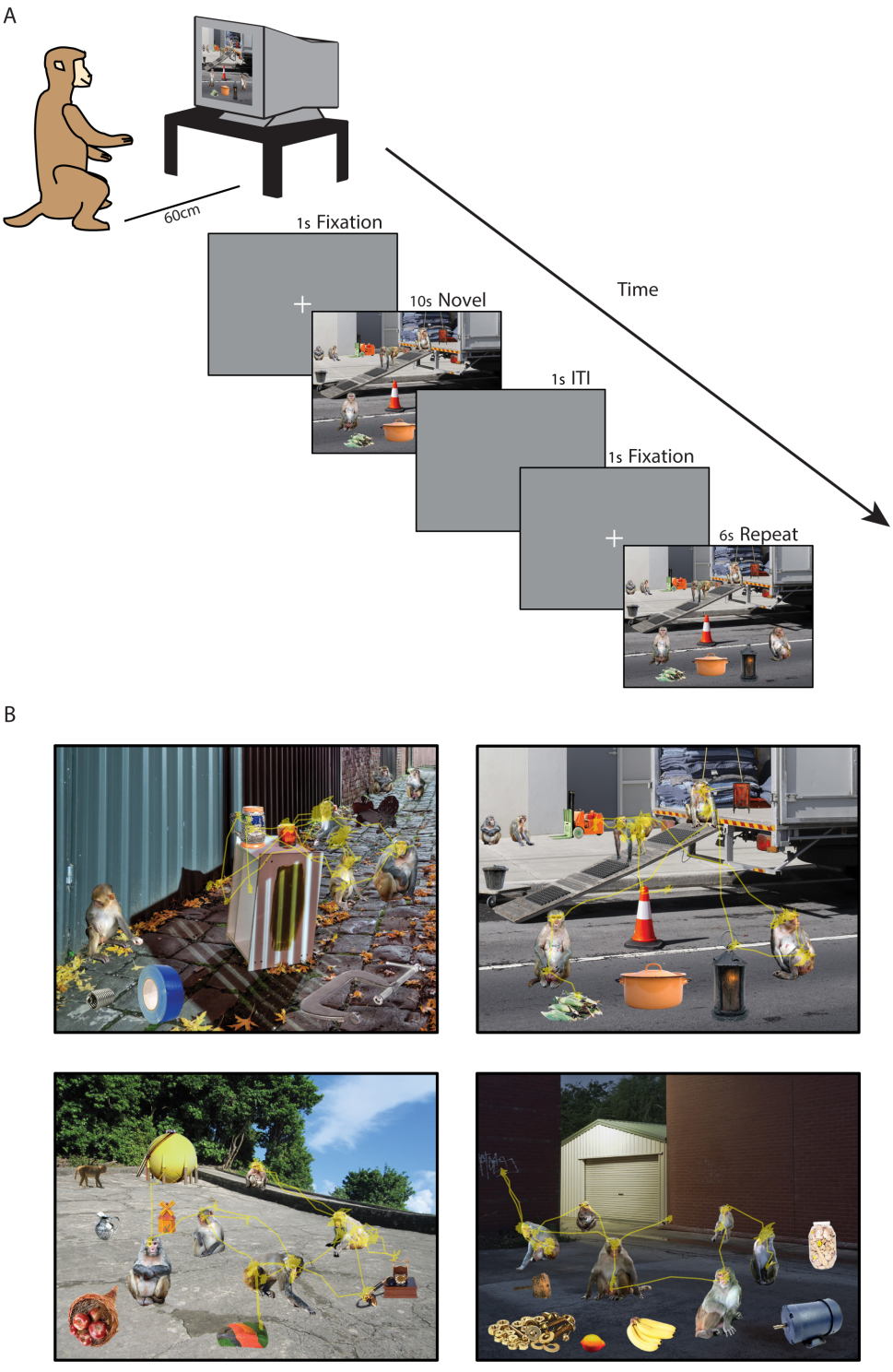
Procedures were carried out in accordance with National Institutes of Health guidelines and were approved by the Emory University Institutional Animal Care and Use Committee. Three adult male rhesus monkeys (*Macaca mulatta*) were obtained from the breeding colony at the Yerkes National Primate Research Center Field Station where they were mother-reared in large, multi-family social groups for the first three years of life. Their mean weight and age at the start of the experiment was: M1: 19 kg, 9 yrs; M2: 19 kg, 10 yrs; M3: 13 kg, 11 yrs.

During testing, each monkey sat in a dimly illuminated room, 60 cm from a 19-inch CRT monitor, running at 120 Hz, non-interlaced refresh rate, with a resolution of 800 x 600 pixels. Eye movements were recorded using a noninvasive infrared eye-tracking system (ISCAN) that measured the position of the pupil and corneal reflection of the right eye. Eye movements were sampled at 200 Hz and saccades were detected offline

using a velocity threshold of 30°/s and measured in degrees of visual angle (dva). Stimuli were presented using experimental control software (CORTEX, www.cortex.salk.edu). At the beginning of each behavioral session, the monkey was administered 2 mL of aerosolized saline solution through a Pari Baby™ pediatric mask placed over the nose (Pari Respiratory Equipment Inc., Midlothian, VA) using a Drive Pacifica Elite nebulizer (Drive Medical Design & Manufacturing, Port Washington, NY). Over the course of ~15 training sessions, subjects were gradually acclimated to the mask and the nebulization procedure using positive reinforcement until no signs of distress were shown. Following saline administration, the monkey performed an eye position calibration task, which involved holding a touch sensitive bar while fixating a small (0.3°) gray fixation point, presented on a dark background at one of 9 locations on the monitor. The monkey was trained to maintain fixation within a 3° window until the fixation point changed to an equiluminant yellow at a randomly-chosen time between 500 ms and 1,100 ms after fixation onset. The monkey was required to release the touch-sensitive bar within 500 ms of the color change for delivery of food reward. During this task, the gain and offset of the oculomotor signals were adjusted so that the computer eye position matched targets that were a known distance from the central fixation point. Following the calibration task, the monkey performed either a delayed match-to-sample task or another calibration task identical to the 9-point task but with 63 locations covering the entire monitor in a grid with 4° spacing between each location. Data collected during the 63-point calibration task were used to compute a linear or polynomial transformation of the eye data to improve the calibration post hoc.

Forty minutes after the saline was administered, the monkey was tested on the Social Scene Viewing Task (Figure 3.1A), a variant of a scene memory task used to test memory in healthy and amnesic humans (Chau, Murphy, Rosenbaum, Ryan, & Hoffman, 2011; Cohen et al., 1999; Hannula et al., 2010; Ryan et al., 2000; Ryan & Cohen, 2004;Smith et al., 2006;Smith & Squire, 2008). The monkey initiated each trial by fixating a white cross (the fixation target, 1°) at the center of the computer screen. After maintaining fixation on this target for 1 s, the target disappeared and a Novel picture of a social scene measuring 25° by 33° was presented (see *Scene Creation* for details about scenes). The image remained on the screen until the monkey accumulated 10 s of viewing time, and any fixations made outside of the image bounds were not counted towards this viewing requirement and were not analyzed. After a 1 s inter-trial interval, the monkey initiated a second presentation of the scene by fixating a white cross (1°) at the center of the screen for 1 s. The second presentation of the scene remained onscreen until the monkey accumulated 6 s of viewing time on the scene. The monkey was not rewarded during the scene presentation. Between each block of two scene presentations, the monkey was able to obtain reward by completing 3 trials of the 9-point calibration task. This procedure enabled us to maintain motivation and verify calibration throughout the session. In each session lasting approximately 50 minutes, 90 novel scenes were each presented twice for a total of 180 scene viewing trials.

Figure 3.1 Social Scene Viewing Task



(A)Three adult male rhesus macaques freely viewed images of social scenes composed of objects and unfamiliar rhesus monkeys while their point of gaze was monitored. In each session, 90 novel scenes were each presented twice for 10 sec (Novel presentation) and 6 sec (Repeat presentation) of cumulative viewing time. (B) Example scenes with the scanpath overlaid showing the point of gaze during one trial.

3.3.2 Scene Creation

A total of 540 unique social scenes (6 sets of 90 scenes) were composed in Adobe Photoshop® by manually arranging cropped images of rhesus monkeys and objects (referred to collectively as items) onto a unique background scene (Figure 3.1B). The background scenes included mainly outdoor scenes and city streets, and were relatively free of other objects and all of a similar spatial perspective. The objects were automatically cropped in Photoshop from stock photos and included trucks, industrial equipment, furniture and fruit. To obtain source material for rhesus images, we used photos taken at the Yerkes National Primate Research Field Station in Lawrenceville, GA (courtesy of Dr. Lisa Parr) and the Caribbean Primate Research Center in Cayo Santiago, Puerto Rico (taken by James Solyst). From these images, we cropped 635 images of 307 rhesus macaques and 635 photos of objects in Photoshop. All of the monkeys had neutral facial expressions. All of these items were then automatically scaled to occupy one of three set areas (2, 1 or 0.4% of the scene) using custom JavaScripts that interfaced with Photoshop, ensuring that item size was precisely controlled. For each scene in a set of 90 scenes we used custom scripts in MATLAB® (The Mathworks, Inc.) to randomly select a novel background scene and a unique combination of items from the pool of rhesus macaques and objects. Each scene contained 6 objects and 6 monkeys of different identities, with 4 items scaled to each of the 3 potential sizes. In each scene, one of the two monkeys occupying 2% of the scene area gazed directly at the subject while all others had averted gaze. Within a set of 90 scenes, no item was repeated. Across the 6 sets of scenes, the same combination of items within a scene was never repeated, and no background scene was ever repeated. In order to minimize adaptation to specific individuals, images a given monkey did not appear in the 5 subsequent scenes. To create

a scene, items were added to the background scene as individual layers in Photoshop and manually arranged on the background to create a realistic perspective. No items were placed in the center of scene to prevent incidental fixations after the center fixation cross was extinguished.

Each scene was randomly assigned to be either repeated without manipulation (Repeat, N=30 scenes per session), or feature a replacement of a monkey (Replaced, Monkey, N=30) or object (Replaced, Object, N=30) in the second presentation. For Replaced Object scenes, an additional object was drawn with one randomly designated as the Replaced object and the other the Replacement object. For Replaced Monkey scenes, two juvenile or adult monkeys with two eyes visible were selected to be the Replaced and the Replacement. Infants were not used as Replaced or Replacement monkeys because of the difference between other monkeys in expected size. Repeat scenes selected one monkey with two eyes visible and one object to be compared to the replaced monkey or object in Replaced scenes. All items used in these comparisons were of the same size (1% of image area).

3.3.3 Data Analysis

Eye movements with a velocity above 30 degrees of visual angle (dva) per second were classified as saccades, while all other eye movements were classified as fixations. Only fixations lasting longer than 60 ms were analyzed. To analyze the location of fixations, regions of interest (ROIs) were created in Photoshop around the whole item for monkeys and objects, the background (whole image minus all items) and around the face and rump of monkeys. The face ROIs included the entire head and the rump ROIs included the monkey's posterior. Face and rump ROIs were manually drawn in

Photoshop for each of 635 monkey images and then automatically scaled with the whole item to match each of the 3 potential scene item sizes. Whole item ROIs were created for each item using JavaScript to select an item's layer in the Photoshop scene and then expand the item's contours by 5 pixels to account for error in the accuracy of the eye position. Face and rump ROIs were also expanded by 5 pixels to account for error in eye position determination. Fixations on regions of overlap between ROIs due to this expansion were not included in analysis. Black and white images of the ROI for each item in the scene were then imported into MATLAB where the pixel coordinates of the ROI were extracted and used to filter the eye data and calculate the area occupied by the ROI and statistics about its saliency and redness within the scene image.

Salience of the image was computed in MATLAB by summing feature maps for color, edge orientation, and intensity contrast over multiple spatial scales (Itti, Koch, & Niebur, 1998). The resulting salience map was normalized from 0 to 1, ranging from the least salient pixel to the most salient. This produced an 800 x 600 pixel saliency map, which was used to calculate the mean of saliency values for pixels within ROIs.

Redness of the image was computed in MATLAB by first converting the RGB color map to a hue-saturation-value map. Then within each ROI we calculated the total number pixels with a red hue (hue value > .9). To determine if this was an accurate quantification of the redness of the sex skin on faces and rumps in our set of 635 monkey images, we selected 48 (8%) faces and 77 (12%) rumps that had strong red coloration in the sex skin in those regions and calculated the mean number of red pixels in the ROI across every appearance of the monkey within a scene. The mean number of red pixels was significantly higher in both red faces, $t(633) = 3.66$, $p < .0001$, (Non-Red: $M = 89.28$

± 3.43, Red: 147.92 ± 17.65) and rumps, $t(633) = 3.66$, $p < .0001$, (Non-Red: $M = 88.42$ ± 3.67, Red: 221.49 ± 21.59) compared to the rest of the image pool. We took these results as a proof of concept that our method accurately quantified redness of the monkey images.

To quantify the eye movements we measured fixation duration (average duration of a fixation), saccade amplitude (distance between fixations), the number of fixations, time spent viewing, latency to first fixation (time elapsed from beginning of trial to the initiation of the first fixation on an ROI) and the latency to revisit an item (time elapsed since the end of the previous fixation on the ROI and the beginning of the next transition into the ROI). The eye data measures were then averaged across all applicable ROIs within a scene presentation (e.g. all fixations that landed on monkeys). All estimates of error are expressed as standard error of the mean across trials for all 3 subjects combined. For analysis of mean fixation duration and saccade amplitude, all eye movements within image bounds were included. With the exception of analysis of memory for replaced items, fixation duration, saccade amplitude and cumulative items fixated, fixations on the replacements were excluded from analysis to avoid any influence of memory. All post-hoc tests conducted following ANOVAs were Tukey's HSD tests.

Six sessions of 90 scenes (540 unique scenes), each presented twice, were run for each monkey. Likely due to a strong preference for novel stimuli, subjects sometimes looked away from repeated images. To limit our analysis to trials where the subject was sufficiently engaged, we excluded a trial if greater than 1085 ms was spent looking outside of the image (95^{th} percentile of all trials). Subjects varied significantly in the time they spent outside per trial, $F(2,3233) = 121.45$, $p < .0001$ (M1: $M = 38.09 \pm 16.79$ ms,

M2: M = 150.17 ± 16.79 ms, M3: M = 416.73 ± 20.99 ms). Subjects spent more time looking outside during the second presentation (P2) than the first (P1), $F(1,3233) = 8.87$, $p = .0029$ (P1: M = 171.13 ± 11.79 ms, P2: M = 232.18 ± 17.56 ms) and this novelty preference effect was stronger for M3, who spent the most time outside. Out of the 3240 trials collected, 175 in total were excluded based on time outside and the following proportion of all trials were excluded for each subject: M1: .2%, M2: 1%, M3: 4%. An additional 19 trials were excluded from analysis due to errors in the display of the stimuli during the experiments, yielding a total of 3046 trials.

3.2 Results

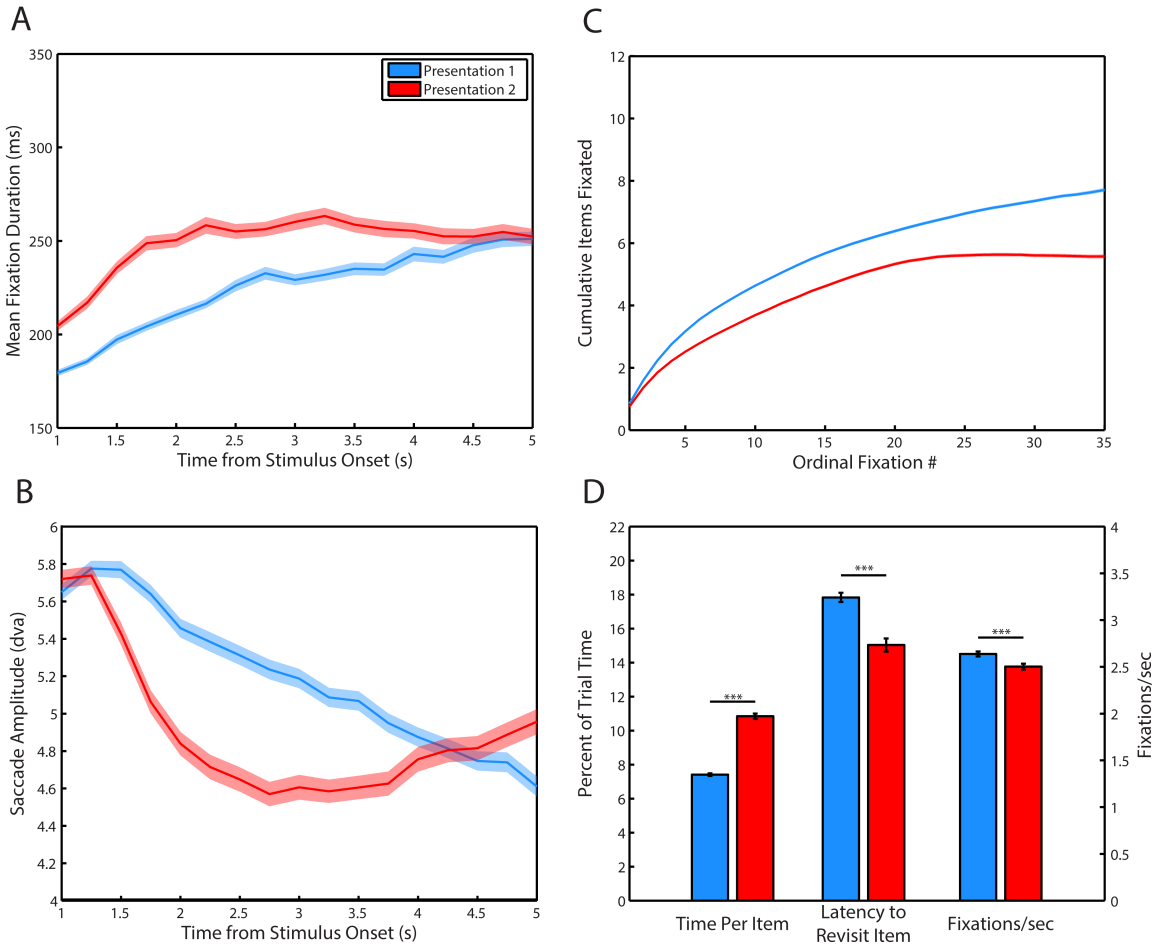
3.2.1 Viewing strategy changes with experience

We first examined how viewing behavior changed from the first presentation of a scene (P1) to the second (P2). When viewing a scene for the second time (Figure 3.2A), subjects made fixations that lasted significantly longer, $t(3044) = 11.80$, $p < .0001$ (P1: M = 203.03 ± 1.00 ms, P2: M = 224.24 ± 1.49 ms). Between these fixations there was a trend towards shorter saccades (Figure 3.2B), $t(3044) = 1.84$, $p = .06$ (P1: M = 5.09 ± .03 dva, P2: M = 4.72 ± .03 dva), with significantly shorter saccades for 2/3 subjects (M1: $t(1062) = 6.26$, $p < .0001$, P1: M = 4.79 ± .03 dva, P2: M = 4.49 ± .04 dva, M2: $t(1034)$ = 8.21, $p < .0001$, P1: M = 5.34 ± .04 dva, P2: M = 4.82 ± .05 dva) and longer saccades for the other subject who spent more time looking away from the scenes (M3: $t(944) = 8.84$, $p < .0001$, P1: M = 5.57 ± .05 dva, P2: M = 6.26 ± .06 dva).

During the second presentation, subjects viewed fewer items (Figure 3.2C), $t(3044)$ = 27.61, $p < .0001$ (P1: M = 7.64 ± .05 items, P2: M = 5.62 ± .05 items), and spent more time viewing each item, $t(3044) = 19.65$, $p < .0001$ (P1: M = 7.39 ± .08 % of trial time,

P2: M = 10.83 ± .16 %) with fewer fixations, $t(3044) = 3.09$, $p = .001$ (P1: M = 2.63 ± .03 per second, P2: M = 2.50 ± .03 per second). Subjects were also quicker to revisit previously viewed items, $t(2911) = 6.03$, $p < .0001$ (P1: M = 17.69 ± .27 % of trial time, P2: M = 14.89 ± .39 %) (Figure 3.2D).

Figure 3.2 Experience Shifts Viewing Strategy from Global to Local



(A) Mean duration of fixations across the first and second presentation of scenes. Data is plotted in 1 s bins stepped in 250 ms increments, with fixations included in a bin if the fixation was initiated during the time bin. Colored shading represents SEM for panels A-C. The second presentation lasted 6 seconds but only the first 5 seconds are plotted due to edge effects on fixation duration. (B) Amplitude of saccades across the first and second presentation of scenes. Same binning procedure as in A. (C) Cumulative items fixated (monkeys and objects combined) plotted across the first and second presentation by ordinal fixation number. (D) Time spent viewing each item as a percent of trial time, latency to make a new transition into the item after an exit expressed in percent of trial time, and the number of fixations on items per second. All measures are averaged across all fixated items within a scene. Stars represent significant differences (all $p < .001$).

3.3.2 Scene contents are remembered across experience

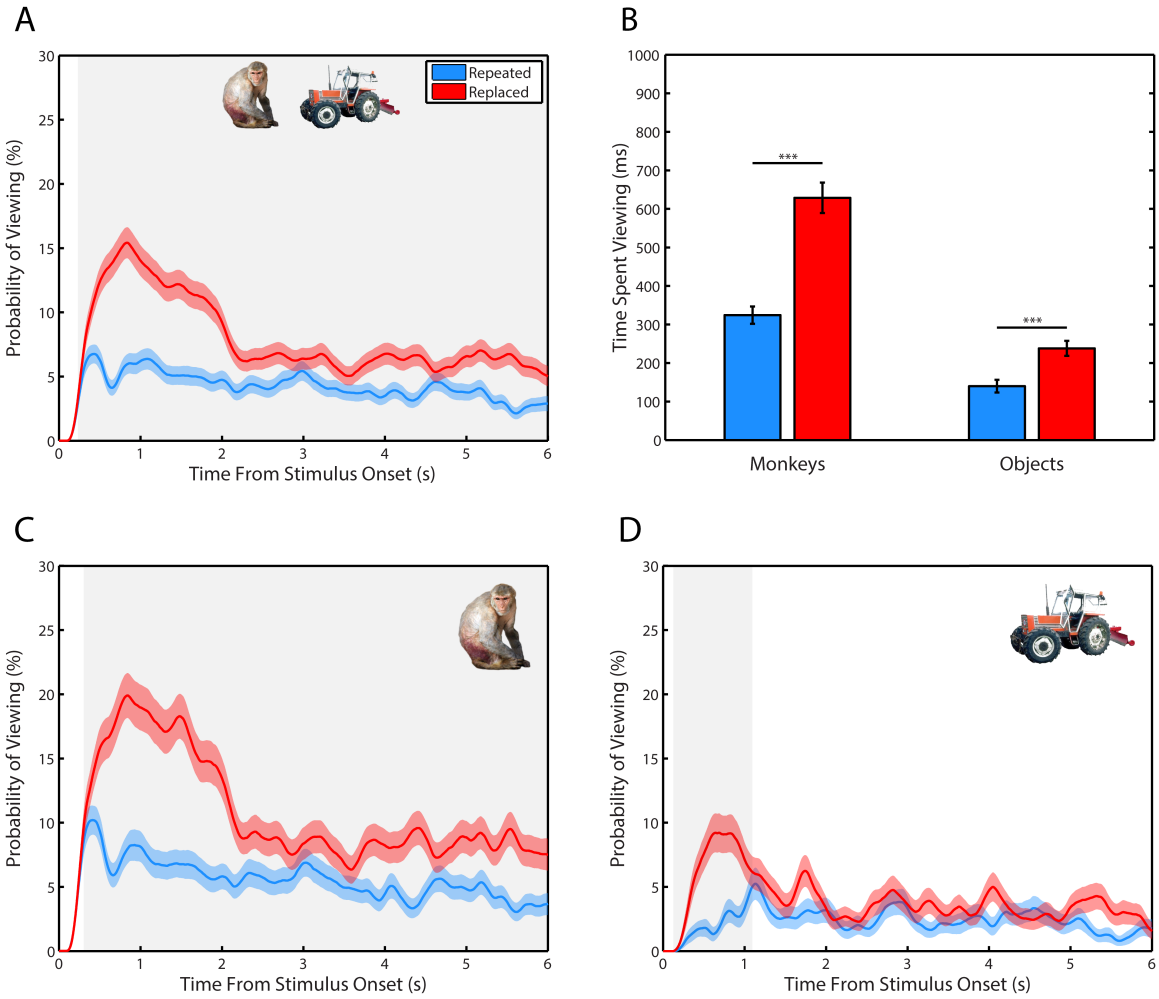
Next we examined whether subjects demonstrated memory for scene items that were altered after the first presentation (Figure 3.3). A 3-way ANOVA, including trial type (scene repeated without manipulation or featuring a replaced item), item category (monkey or object) and subject as factors revealed a significant main effect of trial type, $F(1,1421) = 45.5$, $p < .0001$, with subjects spending more time viewing an item that was replaced ($M = 465.94 \pm 25.48$ ms) than repeated without manipulation ($M = 249.63 \pm 15.31$ ms). We also found that there was a significant effect of item category, $F(1,1421) = 80.55$, $p < .0001$ and subject, $F(1,1421) = 63.71$, $p < .0001$, as well as an interaction between item category and subject, with M1 viewing monkeys more than M2 and M3, $F(1,1421) = 66.07$, $p < .0001$. Possibly related to this difference, there was an interaction between item category and trial type, $F(1,1421) = 8.16$, $p = .004$, that was specific to M1, (Category*Trial Type*Subject interaction, $F(1,1421) = 10.93$, $p < .0001$), such that M1 displayed a greater difference in viewing time between repeated and replaced monkeys compared to objects.

3.3.3 Saliency does not account for social viewing preference

To determine what subjects viewed when exploring a social scene we calculated how much time they spent looking at monkeys, objects and the scene context while taking into account the low-level salience of these regions (Figure 3.4). A 2-way ANOVA with region category (monkeys, objects and scene background) and presentation number as factors revealed a strong effect of category, $F(2,9201) = 1182.49$, $p < .0001$ (Figure 3.4A). Post-hoc tests showed that during both the first and second presentation, monkeys (P1: $M = 42.83 \pm .62$ % of fixation time, P2: $M = 36.96 \pm .62$ %) were viewed longer than objects (P1: $M = 15.61 \pm .62$ %, P2: $M = 15.77 \pm .62$ %). There was no

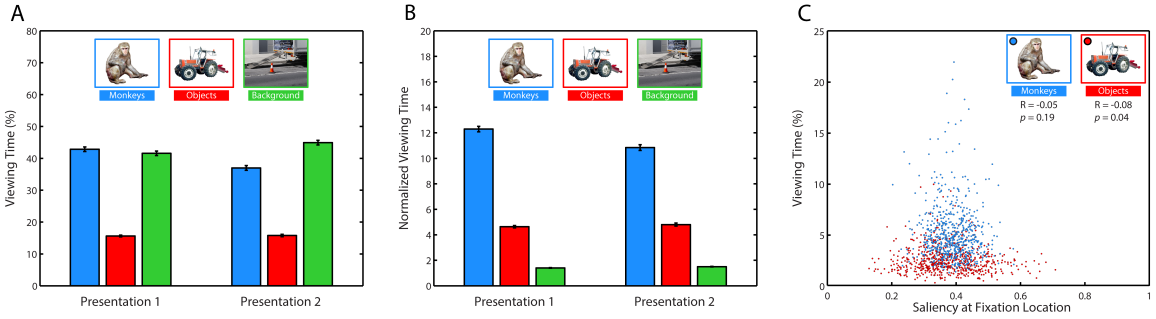
significant effect of presentation on time spent viewing, $F(1,9201) = 2.43$, $p = .12$, but there was an interaction between presentation and category, $F(2,9201) = 28.62$, $p < .0001$. Post-hoc tests demonstrated that the background was viewed significantly longer during the second presentation (P1: $M = 41.56 \pm .62$ %, P2: $M = 44.91 \pm .62$ %), and more than monkeys during this period.

Figure 3.3 Scene Contents are Remembered Across Experience



(A) Probability of viewing items during the second presentation that were repeated without manipulation ($N = 711$) or replacements of an item from the first presentation ($N = 711$). Only scenes where the repeated or replaced item was fixated during the first presentation were included. For panels A, C & D, colored shading represents SEM and gray shading indicates periods of significant differences between repeated and replaced items, calculated using a cluster-based non-parametric permutation test ($p < 0.05$, corrected for multiple comparisons). (B) Time spent viewing repeated and replacement monkeys and objects. Stars represent significant differences (both $p < .001$). (C) Same as in (A) but for monkeys only (Repeated: $N = 424$, Replaced: $N = 415$). (D) Same as in (C) but for objects only (Repeated: $N = 287$, Replaced: $N = 296$).

Figure 3.4 Saliency Does Not Account for Social Viewing Preference



(A) Percent of fixation time spent viewing monkeys, objects or the background. (B) Percent of fixation time normalized by the area occupied and the mean saliency of all pixels in the region. (C) Correlation between the average percent of fixation time spent looking at each of the different monkeys and objects when they appeared in novel scenes and the average salience of those items.

Next we wanted to determine whether salience accounted for viewing behavior, by first measuring whether image categories differed in salience, and whether subjects fixated more salient locations relative to the mean salience of the area (Table 3.1). A 2-way ANOVA with region category (monkeys, objects or background) and presentation number as factors and mean salience of the region as the dependent variable yielded main effects of region category, $F(2,9137) = 2752.53$, $p < .0001$, presentation, $F(1,8808) = 35.09$, $p < .0001$ and a significant interaction between region and presentation, $F(2,8808) = 38.69$, $p < .0001$. Post-hoc tests showed that monkeys were more salient than objects, which were more salient than the background. In addition, the background was more salient during the second presentation compared to the first.

We next conducted a 2-way ANOVA with region category (monkeys, objects or background) and presentation number as factors, and salience at fixation location as the dependent variable. This analysis uncovered a main effect of region category, $F(2,8808) = 1000.24$, $p < .0001$, and post-hoc comparisons showed that the salience of fixations on monkeys was greater than objects, which was also greater than those on the background. The means and differences between mean salience and the salience at fixated regions are reported in Table 3.1.

Table 3.1 Mean Salience of Categories and Salience at Fixation Location

		Monkeys	Objects	Background
Mean Salience of ROI	*P1*	.386 ± .001	.375 ± .001	.263 ± .001
	P2	.386 ± .001	.386 ± .001	.288 ± .001
Saliency at Fixation Location	*P1*	.396 ± .002	.374 ± .002	.300 ± .002
	P2	.401 ± .002	.379 ± .003	.293 ± .002
Difference from Mean Salience at Fixated Locations	*P1*	.009 ± .001	-.001 ± .002	.036 ± .002
	P2	.015 ± .001	.005 ± .003	.005 ± .002

Table 3.1 Salience of the image was computed in MATLAB by summing feature maps for color, edge orientation, and intensity contrast over multiple spatial scales. The resulting salience map was normalized from 0 to 1, ranging from the least salient pixel to the most salient.

Given these difference in salience and the larger size of the background compared to monkeys and objects, we compared time spent viewing these categories normalized by the area they occupied and the mean saliency of the region (Figure 3.4B). Normalization was done by dividing the percent of time spent viewing the category by the percent of the image occupied by category, and then dividing this value by the mean salience that area. Plotting the data in this way shows that even when accounting for these variables, monkeys are still viewed for longer than objects, and objects longer than the background. To further examine whether time spent viewing an item was related to saliency we calculated the average percent of fixation time that was spent looking at each of the 635 different monkey and object images when they appeared throughout the 540 scenes and correlated this value with the mean salience of those images. We found no significant correlation between salience and time spent viewing monkeys (Pearson's R = -.05, p = .19), and a weak but significant relationship for objects (R = -.08, p = .04), such that objects viewed longer tended to be less salient (Figure 3.4C). Together, these results demonstrate that subjects preferred to view objects of social relevance and that salience did not account for this preference.

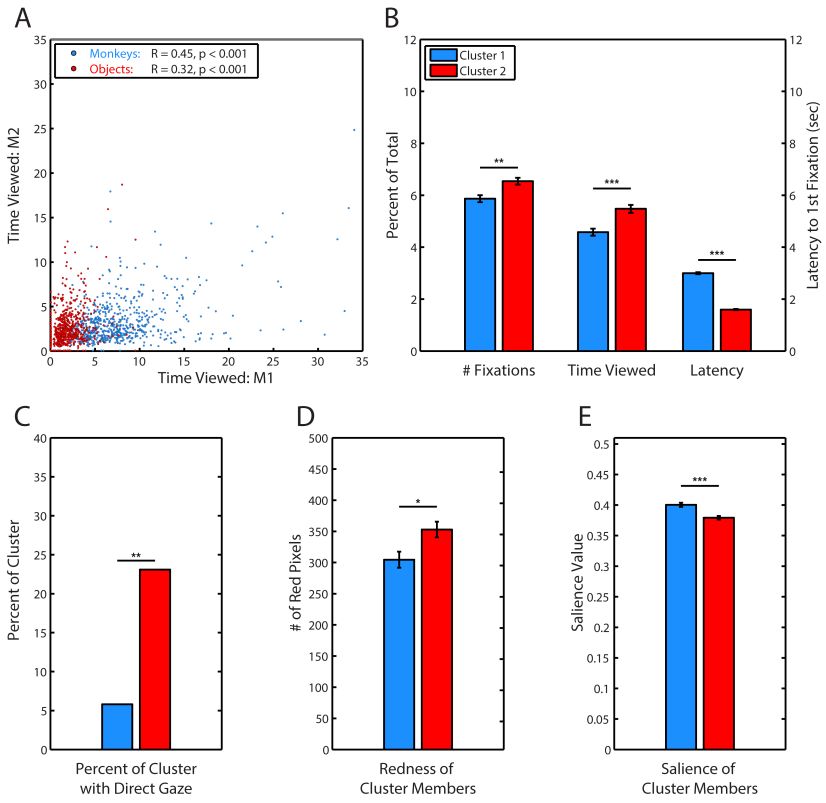
3.3.4 Social relevance drives viewing behavior

After identifying monkeys as a highly viewed stimulus category we examined whether specific characteristics of individual monkeys could explain viewing behavior. We first calculated each subject's preference for specific monkeys and objects appearing in the scenes and then measured how correlated the subjects were in their preferences. During the first presentation of a scene, pairs of subjects were strongly correlated (Figure 3.5A) in the time they spent viewing specific monkeys (M1-M2: R = .45, M1-M3: R =

.24, M2-M3: $R = .33$, all $p < .0001$), but were significantly less correlated in the time they spent viewing objects (M1-M2: $R = .32$, M1-M3: $R = .13$, M2-M3: $R = .24$, all $p < .0001$). Differences in the between-subject correlations for monkeys and objects were evaluated for significance using Fisher's z transformation (M1-M2: $z = 2.55$, M1-M3, $z = 2.03$, M2-M3, $z = 1.75$, all $p < .05$).

Next we used k-means clustering analysis to determine if specific monkeys formed discriminable groups based on viewing statistics. We limited our analysis to the first presentation and took the average of all 3 subjects because they showed a strong correlation in their preferences during this period. For each of the 635 monkey images we calculated the percent of total fixations that were made on the monkey, the percent of trial time spent fixating the monkey and the latency to fixate the monkey after the trial began. Measures calculated as a percent of total (fixations & time viewed) were normalized by the percent of the image occupied by the monkey. To determine the optimal number of clusters for the data we conducted a silhouette analysis that plotted the mean distance between each data point (each monkey) for each cluster in the 3 dimensional data space. Taking the mean of these distances revealed that clustering the data into two clusters (C1 & C2) resulted in the highest separation between clusters (2 clusters: $M = .73$, 3: $M = .69$, 4: $M = .70$, 5: $M = .70$).

Figure 3.5 Social Relevance Drives Viewing Behavior



(A) Correlation between subjects M1 & M2 in the average percent of fixation time spent looking at each of the different monkeys and objects when they appeared in novel scenes. (B) K-means clustering analysis of viewing statistics during the first presentation for each of the 635 different monkeys revealed two distinct clusters. Members of Cluster 2 (C2) were fixated significantly longer, and earlier than members of Cluster 1 (C1). Stars represent significant differences between the clusters (1 star: $p < .05$, 2: $p < .005$, 3: $p < .0005$). (C) Percent of cluster members with direct gaze. (D) Mean number of red pixels in cluster members. (E) Mean salience of cluster members.

Compared to C1 (N = 242), the monkeys in C2 (N = 393) were viewed earlier, $t(633) = 33.91$, $p < .0001$, (C1: $M = 2.99 \pm .04$ sec, C2: $M = 1.59 \pm .02$ sec), longer, $t(633) = 4.10$, $p < .0001$, (C1: $M = 4.58 \pm .14$ % of trial, C2: $M = 5.48 \pm .15$ %) and with more fixations, $t(633) = 3.36$, $p < .0001$ (C1: $M = 5.87 \pm .13$ % of fixations, C2: $M = 6.54 \pm .13$ %) (Figure 3.5B).

To determine the characteristics of the monkeys in C2 that were viewed earlier and longer, we compared the prevalence of different characteristics between each cluster. Before the experiment began, each monkey image was categorized according to the visibility of the eyes (0, 1 or 2 eyes visible), age (infant & juvenile or adult), sex (male, female, or undetermined), and gaze direction (direct or averted from subject). A significantly greater proportion of monkeys in C2 had direct gaze (Figure 3.5C), $\chi^2(17.49,1)$, $p < .0001$, (C1: 21 out of 242 (8.68%), C2: 84 out of 393 (21.37%)). There were no significant differences between clusters in regards to visibility of the eyes, age or sex.

In male and female rhesus macaques, the redness of sex skin around the face and rump increases during the mating season (Baulu, 1976), and adult females spend more time looking at red faces and rumps (Waitt, Gerald, Little, & Kraiselburd, 2006). We compared the mean number of red pixels in category members in each cluster and found that monkeys in C2 ($M = 304.56 \pm 12.96$ red pixels) were significantly redder than those in C1 ($M = 352.96 \pm 12.57$), $t(633) = 2.55$, $p = .01$ (Figure 3.5D).

Finally, we found that monkeys in C2 were significantly less salient than those in C1, $t(633) = 4.75$, $p < .0001$, (C1: $M = .393 \pm .003$, C2: $M = .372 \pm .003$) (Figure 3.5E).

3.4 Discussion

To date, experiments using social scenes have been limited by potentially confounding variability present in uncontrolled stimuli as well as the extensive time and effort required to draw regions of interest around scene items and analyze the resulting data. As a result, low numbers of stimuli have been used and scene content has been characterized at relatively superficial levels, if at all. Inspired by studies using composed scenes (Birmingham et al., 2008c; Henderson & Hollingworth, 2003;Melcher & Kowler, 2001; Underwood, Foulsham, van Loon, Humphreys, & Bloyce, 2006;Unema, Pannasch, Joos, & Velichkovsky, 2005), we developed a semi-automated system for constructing hundreds of novel scenes from an image library of background contexts, objects and rhesus monkeys. This novel method permits more rigorous control and characterization of scene content, and opens up new avenues for investigating memory and the role of scene content through manipulation of scene items.

Using this approach, we found that subjects shifted their viewing strategy with experience and demonstrated memory for scene content. Consistent with previous reports in humans, during the initial viewing, monkeys made fixations that steadily increased in duration and saccades that steadily decreased in amplitude (Antes, 1974; Buswell, 1935; Irwin & Zelinsky, 2002;Melcher, 2006; Pannasch, Helmert, Roth, & Walter, 2008). Interestingly, when a scene was viewed a second time, this change occurred much more rapidly. Only 2 seconds after the beginning of the second viewing, fixation duration and saccade amplitude reached levels similar to what was observed 5 seconds into the first trial. This increase in fixation duration with repeated viewing is in agreement with findings of a “repetition effect” in humans showing that fixation durations are longer

when viewing previously viewed images (Althoff & Cohen, 1999; Ryan, Hannula, & Cohen, 2007).

Because we delineated each item that we added to the composed scene, we were able to investigate how subjects viewed particular items and whether this changed upon repeated viewing. We found that compared to the first viewing, subjects fixated on average about 2 fewer of the total 12 items, which is analogous to the sampling of fewer image regions (Ryan et al., 2000). This change was accompanied by an increase in the time spent viewing each fixated item, a decrease in the number of fixations per item and a decrease in the latency to revisit previously viewed items. Together with the observed increase in fixation duration and decrease in saccade amplitude, these changes suggest a shift in viewing strategy from an orientation to scene contents at a global level to a more elaborative focus on local detail. This shift may reflect a narrowing of focus onto items of high interest, which is consistent with a recent study finding that locations that are fixated by a high proportion of human observers are also viewed with longer fixations and shorter saccades (Dorr, Martinetz, Gegenfurtner, & Barth, 2010).

We also found that items that were replaced by new items in the repeated viewing were viewed longer than those that were repeated without manipulation, replicating an effect observed in humans (Ryan et al., 2000;Smith et al., 2006). These data suggest that subjects remembered the contents of the scene across repeated encounters, confirming previous work showing that memory for scene items persists across time (Melcher, 2001; Melcher & Kowler, 2001;Melcher, 2006).

What remains poorly described are the characteristics of scene contents that are viewed by humans and monkeys during free viewing. One prominent theory argues that

simple low-level features of an image determine fixation location, with these salient locations being viewed more than would be predicted by chance during free viewing (Parkhurst et al., 2002). However, this hypothesis does not account for the existing priors and preferences of an organism that are developed over many interactions with its environment as it searches for food and mates. Encapsulating this alternative viewpoint is the cognitive relevance hypothesis, a theory which proposes that visual features are given specific weights based on the needs of the organism (Henderson et al., 2009). Indeed, objects in scenes are better predictors of fixation location than saliency, and the saliency of objects contributes little extra information despite the finding that memorable objects are often highly salient (Einhäuser, Spain, & Perona, 2008). Perhaps one of the most important object categories for any organism, and especially group-living primates, are conspecifics.

Rhesus monkeys find social stimuli highly rewarding (Butler, 1954; Humphrey, 1974) and will even sacrifice juice reward to view the faces of high-status males and female perinea (Deaner et al., 2005). When viewing a social scene, humans and monkeys spend most of the time viewing conspecifics, and faces in particular (Bindemann et al., 2010; Birmingham, Bischof, & Kingstone, 2008b; Birmingham et al., 2008d, 2009; McFarland et al., 2013; Smilek et al., 2006). In humans, the saliency model fails to account for fixations to faces and saliency values of the locations fixated first are no different than chance (Birmingham et al., 2009). By adding information about the location of faces or text, the saliency model's predictive power is significantly enhanced (Cerf, Frady, & Koch, 2009).

Our results support these findings, demonstrating that rhesus macaques spend most of their time viewing objects of social relevance when viewing a social scene and that saliency does not account for this preference. Further, we found that the three subjects were more correlated in their preference for specific monkeys than objects. Similarly, Deaner, Khera and Platt found that two males were strongly correlated in their ranked preference for specific faces (Deaner et al., 2005). To understand what social characteristics were most important, we used a model-free, cluster-based approach that separated monkey images by viewing time, number of fixations and latency to first fixation. We found that monkeys who were viewed earlier and longer were more likely to have direct gaze and had redder sex skin, both of which are important visual cues for guiding social behavior (Gerald, Waitt, Little, & Kraiselburd, 2007; Higham, Pfefferle, Heistermann, Maestripieri, & Stevens, 2013; Maestripieri, 1997, 2005; Nunn, 1999; Vandenbergh, 1965; Waitt et al., 2003, 2006).

It is important to note that further experiments with additional subjects, including females, will be necessary in order to generalize across rhesus monkeys as a group.

Another important consideration is that the images used in the present experiment were not photographs of real scenes. However, digitally composed scenes offer far greater control over stimulus features and have been used extensively to study attention and memory (Gajewski & Henderson, 2005; Henderson & Hollingworth, 2003; Loftus & Mackworth, 1978; Melcher, 2001; Melcher & Kowler, 2001; Pannasch et al., 2008; Unema, Pannasch, Joos, & Velichkovsky, 2005).

Because this task requires minimal training (~1 month), allows for the collection of a large amount of data in a short period, and uses stimuli that can be easily altered to

manipulate specific factors, it can readily be used to address a variety of questions about social cognition as well as the neural and hormonal systems regulating it. Oxytocin and vasopressin have long been known to regulate social behavior in rodent species (Donaldson & Young, 2008; Ferguson et al., 2000; Young, Lim, Gingrich, & Insel, 2001), but the role of oxytocin in primate social behavior is less well known (Boccia, Goursaud, Bachevalier, Anderson, & Pedersen, 2007; Chang et al., 2012; Ebitz et al., 2013; Parr, Modi, Siebert, & Young, 2013; Simpson et al., 2014; Smith, Agmo, Birnie, & French, 2010; Winslow & Insel, 1991). Because of the importance of maintaining high ecological relevance when studying attention to social stimuli, it will be important going forward to use tasks that elicit social behaviors that are similar to those observed in natural settings (Bindemann et al., 2009, 2010; Birmingham et al., 2008a, 2008c, 2012; Birmingham & Kingstone, 2009; Kingstone et al., 2003; Neisser, 1967; Riby & Hancock, 2008b; Smilek et al., 2006). Future experiments using this and other tasks in the rhesus monkey model have the potential to advance our understanding of the neural mechanisms of social behaviors that are disrupted in psychopathologies such as autism spectrum disorder and schizophrenia (Chang & Platt, 2013).

Chapter 4. Oxytocin increases attention selectively to social stimuli independent of low-level salience

4.1 Abstract

Reduced attention towards socially relevant stimuli is a hallmark of several psychiatric disorders, particularly autism spectrum disorders (Dawson et al., 1998). Eye tracking methodologies have proved to be a sensitive way to assess these alterations in attention, and the time spent viewing faces compared to objects in natural scenes is well-correlated with social competency in autistic individuals (Jones, Carr, & Klin, 2008). By using similar tasks in rhesus monkeys, we can assess the effects of novel therapeutics on social behaviors that are altered in autism. One such therapeutic is oxytocin (OT), a neurohypophyseal peptide that is currently being tested in clinical trials as a treatment for social impairments in autism and schizophrenia. Acute doses of intranasally delivered OT in healthy and autistic humans increases the time spent viewing the eye region of faces (Guastella, Mitchell & Dadds, 2008; Andari et al., 2010), but evidence for increased attention to social stimuli has been mixed in rhesus macaques, an important model for understanding the neural mechanisms of OT's effects on social behavior. Using a novel scene-viewing task, we monitored the gaze of three rhesus macaques while they freely viewed over 500 well-controlled composed social scenes and analyzed the time spent viewing objects and monkeys in the scene. In alternating sessions, either saline or 48 IU of OT was administered intranasally through a pediatric nebulizer 40 minutes prior to scene presentation. In each of twelve behavioral sessions, the monkey viewed a set of 90 images (540 unique scenes) with each image presented twice in a session. The image remained on the screen until the monkey accumulated 10s of viewing time for novel

images and 6s of viewing time for repeated images. In two-thirds of the repeated scenes, either a monkey or an object was replaced with a novel item (manipulated scenes). Eye movements were recorded using a noninvasive infrared eye-tracking system (ISCAN) and were sampled at 200 Hz. The monkey was not rewarded during the scene presentation, but received rewarded trials on an unrelated task between scene viewing trials. Treatment with OT amplified an existing shift in viewing strategy from a rapid orienting to global scene contents to a more local analysis with longer fixations and shorter saccades. Upon first fixation of a face in this repeated viewing, subjects treated with oxytocin held their gaze longer, and this effect was not observed for objects at the first fixation. Also during this period, we found that OT increased the time spent viewing monkeys and that this effect was strongest for infant and juveniles and faces with direct gaze. Importantly, these effects were not related to image salience in terms of low-level image features. These data support previous research showing that OT promotes attention to social stimuli, possibly by reducing the social anxiety typically exhibited by rhesus monkeys when faced with unfamiliar monkeys.

4.2 Introduction

Reduced attention towards socially relevant stimuli is a hallmark of several psychiatric disorders, including schizophrenia and autism spectrum disorders (ASD) (Corden et al., 2008; Falck-Ytter, 2008; Hernandez et al., 2009; Jones et al., 2008b; Klin, Jones, Schultz, Volkmar, & Cohen, 2002a; Klin & Jones, 2008; McPartland et al., 2011; Mueser, Penn, Blanchard, & Bellack, 1997; Ochsner, 2008; Pelphrey et al., 2002; Trepagnier et al., 2002). Eye tracking methodologies have proved to be a sensitive way to assess these alterations in attention, and the time spent viewing faces compared to objects

in natural scenes is well-correlated with social competency in autistic individuals (Jones et al., 2008b). This relationship emerges very early in life, with 2-6 month old infants later diagnosed with ASD spending less time looking at eyes (Jones & Klin, 2013). Critically, these infants begin life with normal levels of attention to the eyes, suggesting that early intervention or therapeutics that enhance attention to social stimuli could improve developmental outcomes (Jones & Klin, 2013).

One such potential therapeutic is oxytocin (OT), a neurohypophyseal peptide that is currently being tested in clinical trials as a treatment for social impairments in ASD and schizophrenia (Macdonald & Feifel, 2013; Meyer-Lindenberg et al., 2011). Acute doses of intranasally delivered OT in healthy and autistic individuals increases the time spent viewing faces (Andari et al., 2010; Guastella, Mitchell, & Dadds, 2008), and enhances recognition memory for faces, but not nonsocial stimuli (Guastella, Mitchell, & Mathews, 2008; Hurlemann et al., 2010; Rimmele, Hediger, Heinrichs, & Klaver, 2009; Savaskan et al., 2008).

Rhesus monkeys provide an ideal model for understanding the neural mechanisms by which oxytocin alters attention to and memory for faces, but little is known about how oxytocin administration affects social processing. The first study to investigate the effects of OT on social behavior in this species found that while OT made monkeys more likely to choose to reward themselves over another monkey in the first 2 hours after treatment, from this point on they made more prosocial choices to reward the other monkey. During this period, OT increased the frequency of looking towards the other monkey when the subject chose to give them reward (Chang et al., 2012).

Supporting this finding of Chang et al. (2012), a subsequent student found that OT increased the time spent viewing images of familiar cagemates' faces, particularly the eye region (Ebitz et al., 2013). However, a different experiment from this study found that OT reduced subjects' existing preference to choose to view dominant monkeys, and increased the time they spent viewing them when they were chosen. The authors interpreted this effect as a decrease in the typically high vigilance that monkeys have for potential social threats in their environment. In line with this interpretation, subjects making saccades to a target were less distracted by faces that briefly flashed on the screen when they were given OT. However, this effect only occurred when expressive, but not non-expressive faces with direct or averted gaze were presented (Ebitz et al., 2013). A lack of attentional capture by expressive faces is in agreement with a previous study, which found that subjects given OT were slower to touch a target that appeared in the location of faces with negative facial expressions, but not neutral social or nonsocial images (Parr et al., 2013). The conclusion of Ebitz et al. (2013) that OT reduces social vigilance is difficult to square with their finding that OT increased time spent viewing faces, including dominant monkeys and monkeys with direct gaze. Prolonged direct gaze is a threatening gesture in rhesus macaques (Hauser, 1996; Van Hooff, 1967), and Parr (2013) found that subjects given OT were faster to respond to direct gaze faces. Ebitz et al. (2013) suggested that OT might have increased gaze to faces and eyes because these regions are salient in terms of low-level perceptual features. They noted that future studies could address this issue by using nonsocial control stimuli with high contrast features like those present in the eyes of faces. Another possibility suggested by Ebitz et al. (2013) was that OT might promote eye gaze by reducing social anxiety. This explains

their findings that OT reduced distraction by briefly flashed expressive faces, and increased viewing of dominant faces and faces with direct gaze.

Our current experiment aimed to directly compare the effect of OT on viewing social and nonsocial stimuli by showing complex scenes containing monkeys and objects. Because the objects in the scenes had high contrast and were presented simultaneously with monkeys, we were able to directly test the hypothesis suggested by Ebitz et al. (2013) that OT treatment results in fixations on regions of the scene that are more salient. This approach also addresses another gap, in that all previous studies measuring OT's effect on viewing social stimuli have presented faces cropped from the body one at a time. However, in natural settings, faces are rarely seen in isolation from bodies and other individuals and objects. Several groups have emphasized the importance of maintaining high ecological relevance when studying attention to social stimuli (Bindemann et al., 2009, 2010; Birmingham et al., 2008a, 2008c, 2012; Birmingham & Kingstone, 2009; Kingstone et al., 2003; Neisser, 1967; Riby & Hancock, 2008b; Smilek et al., 2006). While isolated faces direct attention to the face by design, faces embedded in complex scenes demand that the viewer select among many stimuli the ones that are most relevant.

It has been suggested that this difference in stimulus complexity (Riby & Hancock, 2008b) might explain why some studies have found that attention to faces is reduced in autism spectrum disorders (ASD) (Jones et al., 2008b; Klin et al., 2002b; Nacewicz et al., 2006; Pelphrey et al., 2002; Riby & Hancock, 2008a; Spezio et al., 2007; Sterling et al., 2008; Trepagnier et al., 2002) while other studies report no difference from neurotypical individuals (Bar-Haim et al., 2006; de Wit et al., 2008; Rutherford & Towns, 2008; van der Geest, Kemner, Camfferman, et al., 2002; van der Geest, Kemner,

Verbaten, et al., 2002). A direct comparison of isolated faces and social scenes revealed that individuals with Asperger syndrome looked less at the eyes when faces were embedded in social scenes but were no different than neurotypical individuals when faces were presented in isolation (Hanley et al., 2012).

However, experiments using social scenes have been limited by potentially confounding variability present in uncontrolled stimuli as well as the extensive time and effort required to draw regions of interest around scene items and analyze the resulting data. As a result, low numbers of stimuli have been used and scene content has been characterized at relatively superficial levels, if at all. Inspired by studies using composed scenes (Birmingham et al., 2008c; Henderson & Hollingworth, 2003; Melcher & Kowler, 2001; Underwood et al., 2006; Unema et al., 2005), we developed a semi-automated system for constructing hundreds of novel scenes from an image library of background contexts, objects and rhesus monkeys. This method enabled more control over and detailed characterization of social content as well as the ability to easily replace items with new ones to test memory. Using this task we were able to identify how OT altered attention to specific social characteristics of monkeys and evaluate OT's impact on memory.

4.3 Methods

4.3.1 Data Collection

A more detailed description of the methods can be found in the Materials and Methods section of Chapter 3. Three adult male rhesus monkeys (*Macaca mulatta*) were obtained from the breeding colony at the Yerkes National Primate Research Center Field

Station where they were mother-reared in large, multi-family social groups for the first three years of life.

At the beginning of each behavioral session, the monkey was administered 2 mL of aerosolized saline or oxytocin solution (24 IU/mL) through a Pari Baby^{TM} pediatric mask placed over the nose (Pari Respiratory Equipment Inc., Midlothian, VA) using a Drive Pacifica Elite nebulizer (Drive Medical Design & Manufacturing, Port Washington, NY).

Forty minutes after nebulization ended, the monkey was tested on the Social Scene Viewing Task (Figure 4.1A). Eye movements were recorded using a noninvasive infrared eye-tracking system (ISCAN) that measured the position of the pupil and corneal reflection of the right eye. Eye movements were sampled at 200 Hz and saccades were detected offline using a velocity threshold of 30°/s and measured in degrees of visual angle (dva).

The monkey initiated each trial by fixating a white cross (the fixation target, 1°) at the center of the computer screen. After maintaining fixation on this target for 1 s, the target disappeared and a Novel picture of a social scene measuring 25° by 33° was presented (see *Scene Creation* in Chapter 3 for details about scenes). The image remained on the screen until the monkey accumulated 10 s of viewing time, and any fixations made outside of the image bounds were not counted towards this viewing requirement and were not analyzed. After a 1 s inter-trial interval, the monkey initiated a second presentation of the scene by fixating a white cross (1°) at the center of the screen for 1 s. The second presentation of the scene remained onscreen until the monkey accumulated 6 s of viewing time on the scene.

The monkey was not rewarded during the scene presentation. Between each block of two scene presentations, the monkey was able to obtain reward by completing 3 trials of the 9-point calibration task. This procedure enabled us to maintain motivation and verify calibration throughout the session. In each session lasting approximately 60 minutes, 90 novel scenes were each presented twice for a total of 180 scene viewing trials. Each subject completed 12 sessions, viewing each of the six different sets of 90 scenes once after saline and once after oxytocin, with at least a month separating repeated viewings of the same set. Oxytocin and saline sessions alternated each day and the order of conditions was counterbalanced across subjects.

4.3.2 Data Analysis

To investigate the effects of OT treatment on general viewing strategy we measured fixation duration (average duration of a fixation) and saccade amplitude (distance between fixations) for all fixations made during a scene viewing trial that were within image bounds. To evaluate the effect of OT on attention to and memory for social and non-social stimuli we calculated the time spent viewing fixated items as a percent of total fixation time. Because time spent viewing fixated items could depend upon how many items were fixated, we also calculated how many of the 6 monkeys and 6 objects were viewed during a scene viewing trial as an additional measure of OT's effect on social viewing. To address whether OT altered early processing of faces, we calculated the average duration of the first fixation when this fixation was made on a face. The eye data measures were then averaged across all applicable ROIs within a scene presentation (e.g. all fixations that landed on monkeys). Only scenes that contained at least one instance of each level of a given category (e.g. only scenes with at least one male and one

female when examining sex) were included in the analyses. All estimates of error are expressed as standard error of the mean across trials for all 3 subjects combined. With the exception of analysis of memory for replaced items, viewing strategy and total items fixated, fixations on the replacements were excluded from analysis to avoid any influence of memory on social attention.

The data were analyzed using ANOVAs, including subject, drug condition, presentation number and, when appropriate, stimulus category as within-subjects factors. We conducted post-hoc comparisons of the ANOVA results using independent samples t-tests that were corrected for multiple comparisons using a false discovery rate (FDR) correction of *p*-values. To analyze viewing across time, we used a cluster-based, nonparametric permutation test to compare viewing behavior at separate time-points throughout the trial, correcting for multiple comparisons (Maris & Oostenveld, 2007). Effect sizes of post-hoc comparisons were calculated using Hedges' *g*, an estimate similar to Cohen's *d* in that the differences between means are divided by pooled variances, but Hedges' *g* corrects for small sample sizes.

Salience of each image was computed in MATLAB by summing feature maps for color, edge orientation, and intensity contrast over multiple spatial scales (Itti et al., 1998). The resulting salience map was normalized from 0 to 1, ranging from the least salient pixel in the image to the most salient. This produced an 800 x 600 pixel saliency map, which was used to calculate the salience at every fixated location.

Redness of the image was computed in MATLAB by first converting the RGB color map to a hue-saturation-value map. Then, within each ROI, we calculated the total number of pixels with a red hue (hue value > .9). To determine if this was an accurate

quantification of the redness of the sex skin on faces and rumps in our set of 635 monkey images, we selected 48 (8%) faces and 77 (12%) rumps that had strong red coloration in the sex skin in those regions and calculated the mean number of red pixels in the ROI across every appearance of the monkey across different scenes.

The mean number of red pixels was significantly higher in both red faces, $t(633) = 3.66$, $p < .0001$, (Non-Red: $M = 89.28 \pm 3.43$, Red: 147.92 ± 17.65) and rumps, $t(633) = 3.66$, $p < .0001$, (Non-Red: $M = 88.42 \pm 3.67$, Red: 221.49 ± 21.59) compared to the rest of the image pool. We took these results as a proof of concept that our method accurately quantified redness of the monkey images. Monkeys were classified as red if they had over 100 red pixels in the face or rump.

Likely due to a strong preference for novel stimuli, subjects sometimes looked away from repeated images. To limit our analysis to trials where the subject was sufficiently engaged, we excluded a trial if more than 1085 ms was spent looking outside of the image (95^{th} percentile of all saline trials).

Subjects varied significantly in the time they spent outside per trial under saline, $F(2,3233) = 121.45$, $p < .0001$ (M1: $M = 38.09 \pm 16.79$ ms, M2: $M = 150.17 \pm 16.79$ ms, M3: $M = 416.73 \pm 20.99$ ms). Subjects spent more time looking outside during the second presentation (P2) than the first (P1), $F(1,3233) = 8.87$, $p = .0029$ (P1: $M = 171.13 \pm 11.79$ ms, P2: $M = 232.18 \pm 17.56$ ms) and this novelty preference effect was stronger for M3, who spent the most time outside. Out of the 6480 trials collected, 331 in total were excluded based on time outside and the following proportion of all trials were excluded for each subject: M1: 0.25%, M2: 1.06%, M3: 3.79%.

4.4 Results

4.4.1 Oxytocin alters viewing strategy

We first tested the hypothesis that OT alters attention by modulating basic viewing behavior as a function of experience with the scene from the first presentation to the second. To test this hypothesis, we conducted a 3-way ANOVA, including drug treatment (Saline (SL) vs. OT), presentation number (first vs. second) and subjects (M1, M2 & M3) as factors with fixation duration as the dependent variable. Post-hoc comparisons were made using independent samples t-tests that were corrected for multiple comparisons using a false discovery rate (FDR) correction of *p*-values.

This analysis revealed significant main effects of presentation number, $F(1,6105) = 350.21$, $p < .0001$, drug treatment, $F(1,6105) = 4.27$, $p = .0388$, and subject, $F(2,6105) = 496.47$, $p < .0001$.

Post-hoc analysis of the main effect of presentation number revealed that fixations lasted significantly longer during the second presentation ($M = 228.65 \pm .96$ms) compared with the first ($M = 218.51 \pm .95$ms), $t(6104) = 7.47$, $p < .0001$, $g = .19$. Post-hoc analysis of the main effect of drug treatment condition revealed that compared with SL treatment ($M = 222.19 \pm .95$ms), there was a trend towards longer fixations after OT treatment, ($M = 224.97 \pm .95$ms), $t(6104) = 1.96$, $p = .06$, $g = .05$. Finally, post-hoc analysis of the main effect of subject found that M1 ($M = 242.48 \pm 1.14$ms) made longer fixations than M2 ($M = 234.84 \pm 1.15$ms), $t(4202) = 4.09$, $p < .0001$, $g = .13$, and M3 ($M = 193.43 \pm 1.21$ms), $t(4208) = 28.37$, $p < .0001$, $g = .89$, and M2 made longer fixations than M3, $t(3976) = 31.16$, $p < .0001$, $g = .99$.

This analysis also revealed significant interactions between drug treatment and presentation, $F(1,6105) = 7.55$, $p < .01$, drug treatment and subject, $F(1,6105) = 4.42$, $p =$

.01, and presentation and subject, $F(1,6105) = 24.2$, $p < .0001$. There was no significant 3-way interaction between drug treatment, subject and presentation, $F(2,6105) = 1.48$, $p = .23$.

Post-hoc analysis of the interaction between drug treatment and presentation showed that while fixation duration did not differ between drug treatment conditions during the first presentation (SL: $M = 218.97 \pm 1.34$ms, OT: $M = 218.05 \pm 1.34$ms), $t(3087) = .64$, $p = .56$, $g = .02$, during the second presentation fixations were significantly longer after treatment with OT compared to SL (SL: $M = 225.41 \pm 1.36$ms, OT: $M = 231.89 \pm 1.35$ms), $t(3015) = 2.64$, $p = .01$, $g = .09$.

Post-hoc analysis of the interaction between drug treatment and subject showed that while M1 made significantly longer fixations after treatment with OT compared to SL (SL: $M = 239.1 \pm 1.61$ms, OT: $M = 245.86 \pm 1.61$ms), $t(2126) = 2.23$, $p = .03$, $g = .1$, and M2 exhibited a trend in the same direction (SL: $M = 232.64 \pm 1.63$ms, OT: $M = 237.03 \pm 1.63$ms), $t(2074) = 2.01$, $p = .054$, $g = .09$, M3 exhibited a trend in the opposite direction (SL: $M = 194.82 \pm 1.71$ms, OT: $M = 192.03 \pm 1.7$ms), $t(1900) = 1.96$, $p = .06$, $g = .09$. Follow-up tests for other interactions with fixation duration as the dependent variable are given in Appendix 1.

We next continued our test of the hypothesis that OT modulates basic viewing behavior by examining the effects of OT on saccade amplitude. To this end, we conducted a 3-way ANOVA, including drug treatment (Saline vs. OT), presentation number (first vs. second) and subject (M1, M2 & M3) as factors with saccade amplitude as the dependent variable. Saccade amplitude was measured as the distance in degrees of visual angle between fixations, excluding fixations made outside of the image bounds.

Post-hoc comparisons were made using independent samples t-tests that were corrected for multiple comparisons using a false discovery rate (FDR) correction of *p*-values.

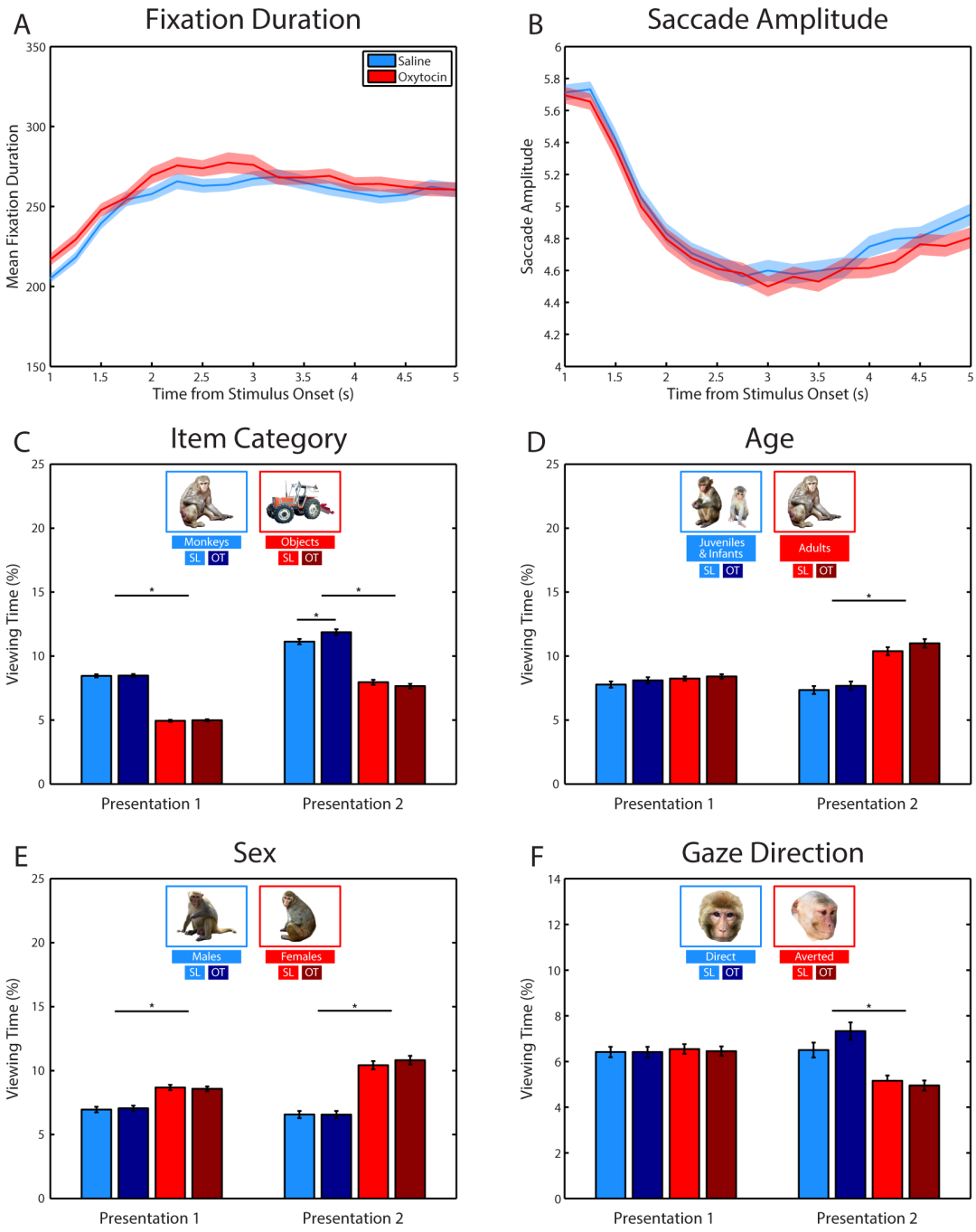
This analysis revealed significant main effects of presentation number, $F(1,6105) = 10.3$, $p < .0001$, drug treatment, $F(1,6105) = 5.3$, $p = .02$, and subject, $F(2,6105) = 884.7$, $p < .0001$.

Post-hoc analysis of the main effect of presentation number revealed that saccades were significantly shorter during the second presentation ($M = 5.14 \pm .02$ dva) compared with the first ($M = 5.22 \pm .02$ dva), $t(6104) = 3.99$, $p < .0001$, $g = .1$. Post-hoc analysis of the main effect of drug treatment condition revealed that compared with SL treatment ($M = 5.21 \pm .02$ dva), there was a trend towards shorter saccades after OT treatment, ($M = 5.15 \pm .02$ dva), $t(6104) = 1.94$, $p = .06$, $g = .05$. Finally, post-hoc analysis of the main effect of subject found that M1 ($M = 4.62 \pm .02$ dva) made shorter saccades than M2 ($M = 5.01 \pm .02$ dva), $t(4202) = 13.6$, $p < .0001$, $g = .42$, and M3 ($M = 5.92 \pm .02$ dva), $t(4028) = 39.09$, $p < .0001$, $g = 1.23$, and M2 made shorter saccades than M3, $t(3976) = 24.93$, $p < .0001$, $g = .79$.

This analysis also revealed a significant interaction between subject and presentation, $F(2,6105) = 224.76$, $p < .0001$, but no significant interaction between drug treatment and subject, $F(2,6105) = 2.63$, $p = .07$, and no significant interaction between drug treatment and presentation, $F(1,6105) = 2.58$, $p = .11$. There was no significant 3-way interaction between drug treatment, subject and presentation, $F(2,6105) = .41$, $p = .67$.

Follow-up tests for the interaction between subject and presentation are given in Appendix 1.

Figure 4.1 Oxytocin Alters Viewing Strategy and Increases Attention to Monkeys



(A) Mean duration of fixations across the 2nd presentation. Data are plotted in 1s bins stepped in 250ms increments, with fixations included in a bin if the fixation was initiated during that time. Colored shading represents SEM. The 2nd presentation lasted 6s but only the first 5s are plotted due to edge effects on fixation duration. (B) Saccade amplitude plotted in same fashion as A. (C-F) Percent of fixation time spent looking at each fixated item across the entire presentation. Only scenes with at least one item from each category level are included. Data in F is limited to the face region, while C-E include the whole item. Error bars represent SEM. Line with stars indicate significant differences.

4.4.2 Oxytocin does not alter memory for manipulated items

Next we examined whether OT altered memory for scene items that were manipulated after the first presentation. A 3-way ANOVA, including trial type (scene repeated without manipulation or replaced an item), item category (monkey or object) and drug treatment (saline or oxytocin) as factors revealed a significant main effect of trial type, $F(1,2824) = 85.74$, $p < .0001$, with subjects spending more time viewing an item that was replaced ($M = 463.65 \pm 17.97$ ms) than repeated without manipulation ($M = 252.65 \pm 11.87$ ms). However, there was no main effect of drug or any interactions between drug and category or trial type.

4.4.3 Oxytocin increases time spent viewing monkeys

We next tested the hypothesis that OT selectively altered the time spent viewing monkeys using the percent of fixation time spent viewing each fixated item as the dependent measure. We performed a 4-way ANOVA with drug treatment (saline or oxytocin), item category (monkeys or objects), presentation (first or second), and subject as factors and the percent of time spent looking at each item as the dependent variable. We followed this ANOVA with post-hoc comparisons, when appropriate, using independent samples *t*-tests that were FDR-corrected for multiple comparisons. See Table 4.1 for means & standard error. There were significant main effects of item category, $F(1,12211) = 1134.22$, $p < .0001$, presentation, $F(1,12211) = 796.86$, $p < .0001$, subject, $F(2,12211) = 387.46$, $p < .0001$, but no significant main effect of drug, $F(1,12211) = 1.41$, $p = .24$.

As a follow-up to the main effect of item category, a post-hoc *t*-test revealed that monkeys were viewed longer than objects, $t(12210) = 30.69$, $p < .0001$, $g = .56$. As a follow-up to the main effect of presentation, a post-hoc *t*-test revealed that items were

viewed longer during the second presentation, compared to the first, $t(12210) = 24.73$, $p < .0001$, $g = .45$. As a follow-up to the main effect of subject, post-hoc t-tests revealed that M1 viewed items longer than M2, $t(8406) = 16.44$, $p < .0001$, $g = .36$, and M3, $t(8058) = 22.95$, $p < .0001$, $g = .51$. Finally, M2 viewed items longer than M3, $t(7954) = 5.8$, $p < .0001$, $g = .13$. See Table 4.1 for means & standard error.

We hypothesized that OT would not have an effect on viewing items overall, but would have a selective effect on the viewing of monkeys compared to objects (a predicted interaction between drug treatment and item category). Supporting this hypothesis, while there was no main effect of drug treatment on time spent viewing items, there was a significant drug treatment x item category interaction, $F(1,12211) = 6.28$, $p = .01$. Post-hoc analyses using independent-samples *t*-tests with FDR-corrected p-values revealed that, compared to treatment with saline, subjects given OT viewed monkeys significantly longer, $t(6104) = 2.04$, $p < .05$, $g = .052$, and that viewing of objects did significantly differ across drug treatment conditions, $t(6104) = .88$, $p = .4$, $g = .02$. See Table 4.1 for means & standard error.

With time spent viewing as the dependent variable, there were no significant interactions between drug treatment and subject, $F(2,12211) = .95$, $p = .39$, or drug treatment and presentation, $F(1,12211) = .71$, $p = .4$. However, there was a significant 3-way interaction between drug treatment, item category and presentation, $F(1,12211) = 6.58$, $p = .01$. Post-hoc comparisons using independent-samples *t*-tests with FDR-corrected p-values revealed that when treated with OT, subjects looked longer at monkeys, but not objects (data given above), and that this effect was significant in the second presentation, $t(3015) = 2.33$, $p = .02$, $g = .085$, but not the first, $t(3087) = .15$, $p =$

.89, g = .01, Figure 4.1C. See Table 4.1 for means & standard error. Follow-up tests for other interactions with time spent viewing items as the dependent variable are given in Appendix 1.

4.4.4 Oxytocin does not affect the number of items viewed

These results suggest that OT increased the time spent viewing monkeys. There are two possibilities that could account for this finding. OT could have increased the amount of time individual monkeys were viewed or OT could have increased the number of monkeys that were viewed. In order to distinguish between these two possibilities, we next tested the hypothesis that OT affects the number of items viewed. To test this hypothesis, we performed an ANOVA that included 4 independent variables: (1) item category (monkey or object), (2) drug treatment (saline or oxytocin), (3) presentation (first or second) and (4) subject, with the number of items fixated as the dependent variable. We followed this ANOVA with post-hoc comparisons, when appropriate, using independent samples t-tests that were FDR-corrected for multiple comparisons. See Table 4.1 for means & standard error.

This analysis revealed significant main effects of item category, $F(1,12211)$ = 5100.13, $p < .0001$, presentation, $F(1,12211) = 2684.84$, $p < .0001$, subject, $F(2,12211)$ = 734.49, $p < .0001$, but no significant main effect of drug treatment, $F(2,12211) = .16$, p = .69. Because there was no significant main effect of drug treatment, and no significant interactions between drug treatment and item category $F(1,12211) = .42$, $p = .52$, drug treatment and presentation $F(1,12211) = 1.65$, $p = .2$, or drug treatment and subject $F(2,12211) = 1.32$, $p = .27$, these data suggest that OT does not alter the number of items

viewed. Follow-up tests for other interactions with number of items viewed as the dependent variable are given in Appendix 1.

4.4.5 Time-course of the effects of oxytocin on viewing behavior

We next considered whether oxytocin's effect on viewing monkeys was consistent across the entire scene presentation or if it was restricted to a particular time period. To address this question, we used a sensitive cluster-based nonparametric permutation test that compares viewing across conditions throughout the trial while correcting for multiple comparisons (Maris & Oostenveld, 2007). Comparing signals between two conditions across time requires many tests, and the high number of comparisons inflates the family-wise error rate (FWER). One way to address this problem is to apply a Bonferroni correction to the *p*-values obtained from each test, but this approach is highly conservative given a large number of samples. The Maris & Oostenveld (2007) method computes a test statistic that is based on clustering samples from adjacent time-points that exhibit a similar difference and then testing only those clusters. This method first (1) compares the values of two conditions across time using a *t*-value, then (2) selects time-points whose *t*-value crosses a threshold (which does not affect the FWER), then (3) clusters these time-points according to distance in the time dimension and then (4) performs cluster-level statistics using the sum of the *t*-values within a cluster and finally (5) performs a nonparametric statistical test by comparing the *p*-value from cluster-level statistics to a *p*-value obtained by performing hundreds of tests on random partitions of the data. This method is highly sensitive to time-dependent differences and corrects for multiple comparisons, but can only be performed on two

conditions at a time. A more detailed explanation of the method and its implementation in MATLAB can be found in Maris & Oostenveld (2007).

We used this method to compare the probability of viewing items between the two drug treatment conditions (SL & OT), performing this test for each item category (monkeys or objects) and each presentation (first or second), resulting in 4 tests. To measure viewing of items across the duration of a given trial, we first included only items that were fixated at least once during the trial. Then for each fixated item, we represented the time-points when the item was being fixated with a "1", and all other time-points with a "0". Then we took the average across all fixated items at each time-point, resulting in a millisecond-by-millisecond measure of the probability of viewing fixated items. This procedure was performed for each scene that contained at least one member of each item category, and trials meeting this criterion were combined from each subject. Each test used a cluster threshold $p = .5$ (used in Step 2 listed above, this does not affect the FWER) and compared the *p*-values obtained from tests between conditions within these clusters to a distribution of *p*-values obtained from 1000 comparisons of random partitions of the data.

Consistent with the results from the ANOVA presented above, viewing of monkeys or objects did not differ by drug treatment condition in the first presentation, all $p > .1$. In the second presentation, viewing of objects did not differ by drug treatment condition ($p > .1$), but when treated with OT, subjects viewed monkeys more during the first half of the 6-second trial, $p < .05$ (Figure 4.2A).

4.4.6 Oxytocin affects the duration of the first fixation to faces

The duration of the first fixation has been used to measure processing of faces in rhesus macaques (Gibboni, Zimmerman, & Gothard, 2009; T. K. Leonard et al., 2012), patients with ASD (Santos et al., 2012), or social anxiety disorder (Garner, Mogg, & Bradley, 2006) as well as neurotypicals (Cerf et al., 2009). We hypothesized that in addition to increasing time spent viewing monkeys, OT would increase the duration of the first fixation on faces. To test this hypothesis, we ran a 3-way ANOVA with drug treatment condition (saline or OT), presentation (first or second) and subject as factors. For the dependent variable, we used the duration of the first fixation, limited to first fixations that were made on faces.

This analysis revealed significant main effects of drug treatment condition, $F(1,3088) = 4.33$, $p = .03$, and subject, $F(2,3088) = 85.56$, $p < .0001$, but no significant main effect of presentation, $F(1,3088) = .34$, $p = .56$. Post-hoc comparisons were conducted using independent-samples *t*-tests with FDR-corrected p-values. As a follow-up to the main effect of drug treatment, a post-hoc *t*-test revealed that the duration of the first fixation on faces was longer during OT treatment ($M = 169.88 \pm 2.7$ms) compared to saline treatment ($M = 162.09 \pm 2.6$ ms), $t(3087) = 2.07$, $p < .05$, $g = .07$. As a follow-up to the main effect of subject, post-hoc *t*-tests revealed that M1's first fixation on faces ($M = 162.09 \pm 2.6$ms), lasted longer than those of M2, $t(2389) = 10.23$, $p < .0001$, $g = .42$ and M3, $t(2079) = 8.83$, $p < .0001$, $g = .41$, with no difference between M2 and M3, $t(1704) = .4$, $p = .74$, $g = .02$.

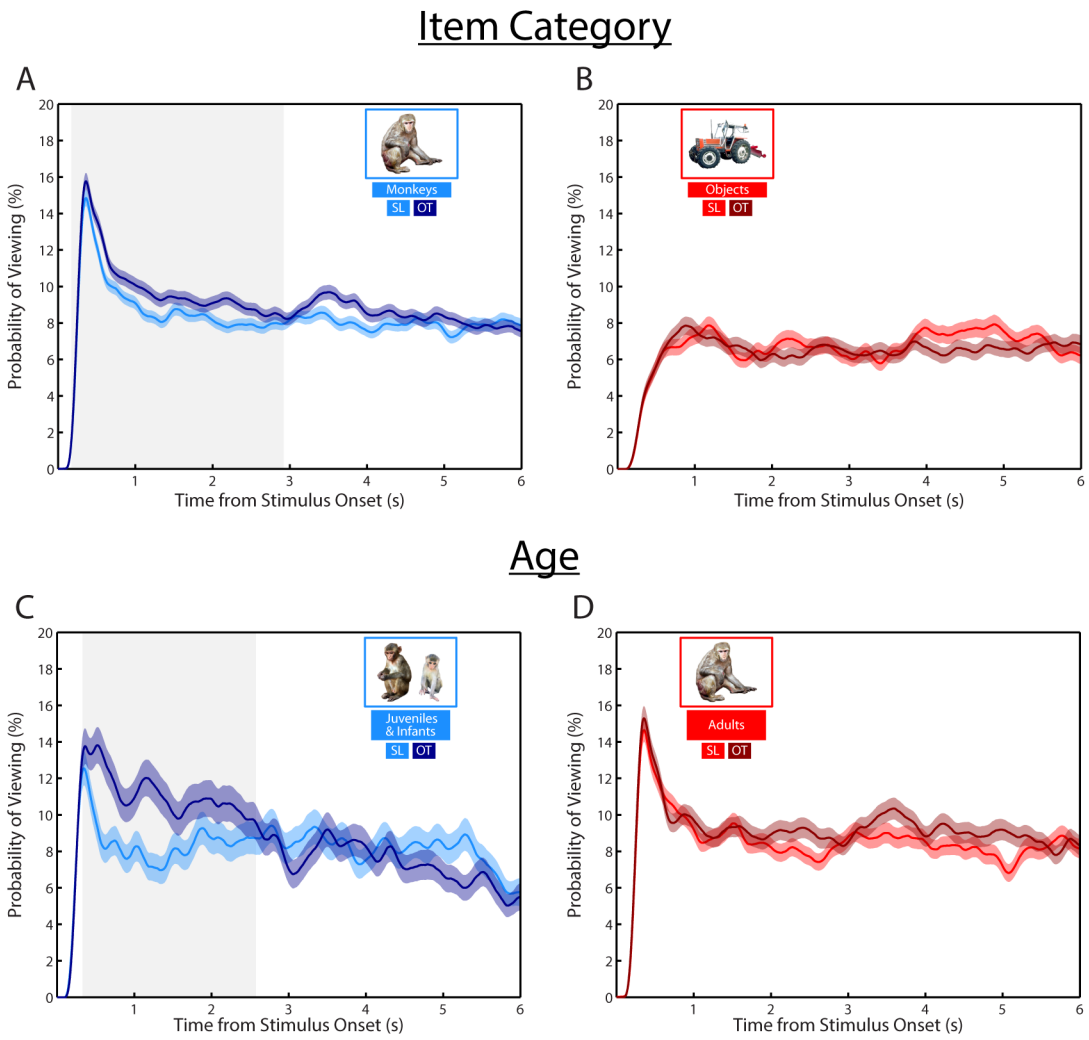
This analysis also revealed some significant interaction effects. There was a significant drug treatment x presentation interaction, $F(1,3088) = 4.72$, $p < .05$, a

significant subject x presentation interaction, $F(2,3088) = 5.34$, $p < .01$, but no significant interaction between subject and drug treatment, $F(2,3088) = .13$, $p = .88$.

The significant interaction between the factors drug treatment and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected *p*-values. These analyses revealed no effect of drug treatment on first fixation duration in the first presentation (*SL*: $M = 165.06 \pm 3.4$ms, *OT*: $M = 164.72 \pm 3.5$ms, $t(1737) = .24$, $p = .83$, $g = .01$). By contrast, in the second presentation, the duration of first fixations were significantly longer after treatment with OT ($M = 175.04 \pm 4$ms) compared to saline ($M = 159.12 \pm 4$ms), $t(1348) = 2.42$, $p < .05$, $g = .13$.

Follow-up tests for the subject x presentation interaction are given in Appendix 1.

Figure 4.2 Oxytocin Increases Time Spent Viewing Monkeys



(A) Probability of looking at fixated monkeys averaged across all scenes where a monkey was fixated. Saline trials plotted in light color & oxytocin treatment in darker color. Colored shading represents the standard error of the mean probability of fixation across scenes. Gray shading indicate periods of significant differences between OT and SL, calculated using a cluster-based non-parametric permutation test ($p < 0.05$, corrected for multiple comparisons) (B-D). Same as in A but for the respective categories. Only scenes with at least one item from each category level are included.

4.4.7 Oxytocin alters social interest in specific characteristics

In Chapter 3, a model-free, k-means cluster analysis found that monkeys that were viewed earlier and longer were more likely to have direct gaze and had more red sex skin. In preliminary analyses (using more clusters than the optimal fit), we observed that clusters which were viewed longer and earlier had greater proportions of infant and juvenile monkeys, in addition to the previously reported relationship of more red sex skin and more monkeys with direct gaze. Our overriding hypothesis is that OT enhances existing social preferences. Accordingly, based on these observations, we hypothesized that treatment with OT would increase the time spent viewing monkeys with these preferred characteristics (red sex skin, direct gaze and young age).

To test these hypotheses, we used the cluster-based nonparametric permutation tests of viewing across time to examine the time-course of any drug effect on viewing behavior. We restricted our analyses to the second presentation, based on the results from the ANOVAs reported above, and we examined the effects of drug treatment on the viewing of monkeys of different ages, sex, gaze direction, and redness of skin. Only scenes that contained at least one instance of each category level (e.g. at least one male and one female) were included in the analysis. Only scenes that contained at least one monkey with red sex skin and one without were used to evaluate the effect of redness. Analysis of gaze direction included only the time spent viewing the face ROI, while all other analyses included any fixation made within the whole-item ROI. See Tables 4.2, 4.3 and 4.4 for means & standard error.

The nonparametric permutation test for the effects of drug treatment on the viewing of monkeys of different ages revealed that, compared to treatment with saline, OT significantly increased viewing of infants and juveniles during the first 2.5 seconds of

the trial (Figure 4.2C), but there were no differences between saline and OT treatment conditions in the viewing of adults (all $p > .1$) (Figure 4.2D).

The nonparametric permutation tests for the effects of drug treatment on the viewing of monkeys of different sex revealed no significant differences between saline and OT treatment conditions in the viewing of males or females (all $p > .1$).

The nonparametric permutation test for the effects of drug treatment on the viewing of monkeys with averted or direct gaze revealed that, compared to treatment with saline, OT significantly increased viewing of faces with direct gaze from 3.5 – 5.5 seconds after the start of the trial (Figure 4.6). There were no differences between saline and OT treatment conditions in the viewing of averted gaze faces $p > .1$ (Figure 4.6D).

The nonparametric permutation tests for the effects of drug treatment on the viewing of monkeys different levels of redness of sex skin around the face and rump revealed that there were no differences between saline and OT treatment conditions in the viewing of red or non-red monkeys (all $p > .1$).

4.4.8 Oxytocin does not alter viewing of low-level salience

In Chapter 3 we found that the time spent viewing monkeys and objects could not be accounted for by the salience of the low-level features of those items. From this we predicted that treatment with OT would not alter the salience of fixated locations and thus an increase in the viewing of salient regions would not explain the observed increase in viewing monkeys due to OT treatment.

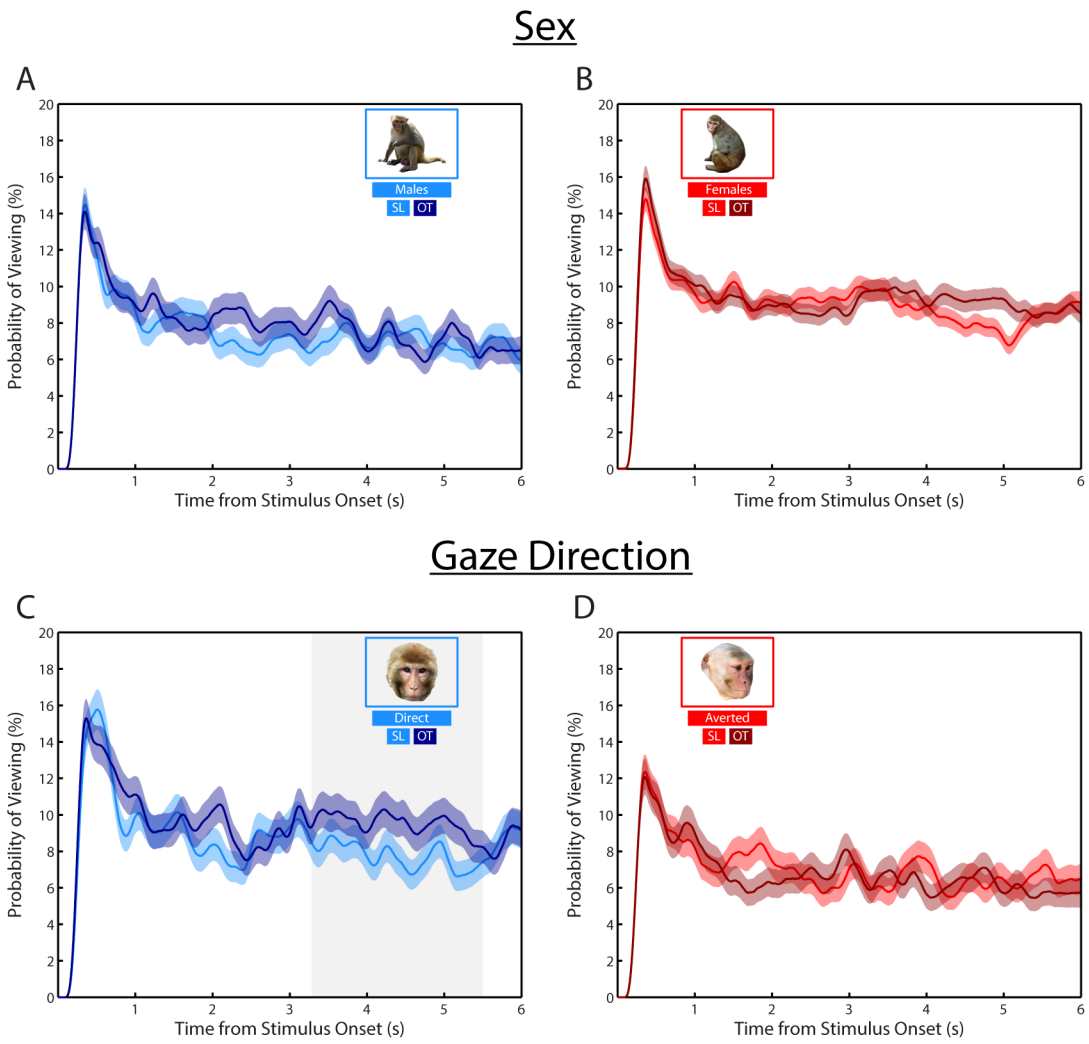
To test this hypothesis we conducted a 3-way ANOVA with drug treatment (SL or OT), presentation (first or second), and subject as factors. For the dependent variable we took the salience value at the location of each fixation made during a scene viewing

trial. We predicted that the salience of fixated locations would not differ by drug treatment, thus indicating that OT did not increase viewing of low-level image features that were more salient. The ANOVA revealed no main effect of drug treatment on the salience of fixated locations, $F(1,6105) = 1.08$, $p = .3$, indicating that salient low-level image features did not account for the effects of OT on viewing behavior. There was no significant main effect of presentation, $F(1,6105) = .02$, $p = .88$, but there was a significant main effect of subject, $F(2,6105) = 570.61$, $p < .0001$.

The significant main effect of subject was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected *p*-values. These tests showed that the regions that M1 fixated were more salient than those fixated by M2, $t(1045) = 11.46$, $p < .0001$, $g = .71$, and M3, $t(989) = 15.66$, $p < .0001$, $g = .99$, and that M2 fixated more salient regions that M3, $t(980) = 4.25$, $p < .0001$, $g = .27$.

There were no significant interactions between subject and drug treatment, $F(2,6105) = 2.55$, $p = .08$, subject and presentation, $F(2,6105) = 2.4$, $p = .09$, drug treatment and presentation, $F(1,6105) = .09$, $p = .76$, or between subject, drug treatment and presentation, $F(2,6105) = .25$, $p = .78$.

Figure 4.3 Oxytocin Increases Looking at Faces with Direct Gaze



(A) Probability of looking at fixated male monkeys averaged across all scenes where a male monkey was fixated. Saline trials plotted in light color & oxytocin treatment in darker color. Colored shading represents the standard error of the mean probability of fixation across scenes. Only scenes with at least one item from each category level are included. (B-D). Same as in A but for the respective categories. Gray shading indicate periods of significant differences between OT and SL, calculated using a cluster-based non-parametric permutation test ($p < 0.05$, corrected for multiple comparisons).

Tables 4.1 & 4.2 Means and SEM for Viewing Time by Item Category and Monkey Age

Table 4.1: Viewing Time by Item Category

		Presentation 1			Presentation 2		
		M1	M2	M3	M1	M2	M3
Monkeys	SL	13.2 ± .2 *	5.9 ± .2	5.9 ± .3	16.5 ± .2 *	8.5 ± .2	7.9 ± .3
	OT	13.1 ± .2 *	6.1 ± .2	5.9 ± .3	17.7 ± .2 *	9.4 ± .2 *	8 ± .3
		M1	M2	M3	M1	M2	M3
Objects	SL	3.8 ± .2 *	5.7 ± .2	5.4 ± .3	6.5 ± .2 *	9.4 ± .2 *	8 ± .3
	OT	3.9 ± .2 *	5.6 ± .2	5.4 ± .3	5.9 ± .2 *	9.5 ± .2 *	7.5 ± .3

* = significant difference or interaction with item

Item		* Drug		Presentation		* Subject		
	Mean	SL	OT	Pres. 1	Pres. 2	M1	M2	M3
Monkeys	9.8 ± .1 *	9.6 ± .1 *	10 ± .1 *	8.4 ± .1 *	11.3 ± .1 *	15.1 ± .1 *	7.5 ± .1 *	6.9 ± .1
Objects	6.4 ± .1	6.5 ± .1	6.3 ± .1	5 ± .1 *	7.8 ± .1	5 ± .1 *	7.6 ± .1 *	6.6 ± .1

Table 4.2: Viewing Time by Monkey Age

		Presentation 1			Presentation 1		
		M1	M2	M3	M1	M2	M3
Infants & Juveniles	SL	12 ± .4 *	6.2 ± .4	4.8 ± .4	11.2 ± .4 *	6.6 ± .4 *	4 ± .4
	OT	12.3 ± .4 *	6.9 ± .4	4.8 ± .4	12 ± .4 *	6.1 ± .4	4.6 ± .4
		M1	M2	M3	M1	M2	M3
Adults	SL	13.7 ± .4 *	5.2 ± .4	5.5 ± .4	17.4 ± .4 *	7.3 ± .4	6.1 ± .4
	OT	13.5 ± .4 *	5.7 ± .4	5.9 ± .4	17.6 ± .4 *	8.5 ± .4	6.5 ± .4

* = significant difference or interaction with age

Age		Drug		* Presentation		* Subject		
	Mean	SL	OT	Pres. 1	Pres. 2	M1	M2	M3
Infants & Juveniles	7.6 ± .1 *	7.5 ± .2 *	7.8 ± .2 *	7.9 ± .2 *	8.2 ± .2 *	11.9 ± .2 *	6.5 ± .2 *	4.6 ± .2 *
Adults	9.4 ± .1	9.2 ± .2	9.6 ± .2	7.4 ± .2 *	10.6 ± .2	15.6 ± .2 *	6.7 ± .2	6 ± .2

Tables 4.1 and 4.2 Means and SEM broken down by category level, presentation number, drug treatment and subject in the top half and arranged by combinations between category level and drug, presentation or subject in the bottom half. Stars denote significant differences between apposing means and significant interactions between level and the factor with star next to its label.

Tables 4.3 & 4.4 Means and SEM for Viewing Time by Monkey Sex and Gaze Direction

Table 4.4: Viewing Time by Monkey Sex

		Presentation 1			Presentation 2		
		M1	M2	M3	M1	M2	M3
Male	SL	9.9 ± .4 *	5.5 ± .4	5.3 ± .4	10 ± .4 *	5.6 ± .4	3.8 ± .4
	OT	10.7 ± .4 *	5.2 ± .4	5 ± .4	10.5 ± .4 *	5.2 ± .4	3.8 ± .4
		M1	M2	M3	M1	M2	M3
Female	SL	15 ± .4 *	5.4 ± .4	5.2 ± .4	18.5 ± .4 *	6.9 ± .4	5.4 ± .4
	OT	14.4 ± .4 *	5.5 ± .4	5.6 ± .4	18.4 ± .4 *	7.5 ± .4	6 ± .4

* = significant difference or interaction with sex

Sex		Drug		* Presentation		* Subject		
	Mean	SL	OT	Pres. 1	Pres. 2	M1	M2	M3
Male	6.7 ± .1 *	6.7 ± .2 *	6.7 ± .2 *	6.9 ± .2 *	6.5 ± .2 *	10.3 ± .2 *	5.4 ± .2 *	4.5 ± .2 *
Female	9.5 ± .1	9.4 ± .2	9.6 ± .2	8.5 ± .2 *	10.4 ± .2	16.6 ± .2 *	6.3 ± .2 *	5.6 ± .2

Table 4.3: Viewing Time by Monkey Gaze Direction

		Presentation 1			Presentation 2		
		M1	M2	M3	M1	M2	M3
Direct	SL	13 ± .4 *	3.5 ± .4	2.3 ± .4	14 ± .4 *	3.1 ± .4	1.9 ± .4
	OT	13 ± .4 *	3.5 ± .4	2.3 ± .4	16.3 ± .4 *	2.7 ± .4	2.4 ± .4
		M1	M2	M3	M1	M2	M3
Averted	SL	12.5 ± .4 *	3.8 ± .4	3 ± .4	9.6 ± .4 *	3.2 ± .4	2.3 ± .4
	OT	12.1 ± .4 *	3.5 ± .4	3.5 ± .4	9 ± .4 *	2.9 ± .4	2.8 ± .4

* = significant difference or interaction with gaze

Gaze		Drug		* Presentation		* Subject		
	Mean	SL	OT	Pres. 1	Pres. 2	M1	M2	M3
Direct	6.5 ± .1 *	6.3 ± .2	6.7 ± .2 *	6.3 ± .2	6.7 ± .2 *	14.1 ± .2 *	3.2 ± .2 *	2.3 ± .2
Averted	5.7 ± .1	5.7 ± .2	5.6 ± .2	6.4 ± .2 *	5 ± .2	10.8 ± .2 *	3.3 ± .2	2.9 ± .2

Tables 4.3 and 4.4 Means and SEM broken down by category level, presentation number, drug treatment and subject in the top half and arranged by combinations between category level and drug, presentation or subject in the bottom half. Stars denote significant differences between apposing means and significant interactions between level and the factor with star next to its label.

4.5 Discussion

In agreement with previous findings in humans and rhesus macaques that OT increases attention to social, but not nonsocial stimuli, rhesus treated with OT looked longer at monkeys, but not objects (Andari et al., 2010; Chang et al., 2012; Ebitz et al., 2013; Gamer et al., 2010; Guastella, Mitchell, & Dadds, 2008). Our results extend previous research by showing that this effect occurs when social and nonsocial are viewed simultaneously in a social scene, and that OT increases attention to specific characteristics of monkeys. When viewing a scene for the second time, subjects treated with OT held their gaze for longer when viewing a face in their first fixation. During this repeated viewing under OT, they looked more at infants and juveniles in the first half of the viewing period, and more at faces gazing directly at them in the second half. When viewing a repeated scene, subjects made longer fixations and shorter saccades, shifting from a rapid orienting to global scene contents to a more local analysis of fewer items. Treatment with OT amplified this shift in viewing strategy. Furthermore, we demonstrate that OT's enhancement of attention to social stimuli is not due to low-level image salience.

From these data we conclude that OT promotes attention to social stimuli, possibly by reducing the social anxiety typically exhibited by rhesus monkeys when faced with unfamiliar monkeys. Humans with higher social anxiety make shorter fixations when viewing faces (Garner et al., 2006), and we observed that after OT treatment subjects made longer fixations on faces when viewing them with their first fixation. Overall, fixations were longer and saccades were shorter on OT, suggesting that subjects may have been less anxious when exploring the scenes for a second time. Further supporting the notion that subjects were less anxious on OT, we found that OT

increased viewing of faces whose gaze was directed at the viewer, a threatening gesture in rhesus macaques. This is in agreement with a previously observed trend towards increased attention to direct gaze faces presented for 500 ms (Parr et al., 2013). Adult male rhesus emit more affiliative lipsmacking expressions towards young monkeys than adults when they are seen alone, but young monkeys are typically found in close proximity to, and fiercely protected by, their mother and her close female relatives (Berman, 1980; Mosher, Zimmerman, & Gothard, 2011a). We found that treatment with OT increased viewing of infants and juveniles, who were seen in proximity to adult females. It is possible that this increase in attention may have been brought on through an OT-mediated reduction in anxiety related to the threat of staring at the offspring of an unfamiliar and possibly high-ranking female.

A role for OT in the reduction of social anxiety is well-supported by the literature (Averbeck, 2010; Bartz & Hollander, 2006; Carter et al., 2008). In rodents, OT attenuates HPA activity, reducing anxiety-related behavior and promoting social behavior (Amico et al., 2004; Neumann et al., 2000; Neumann, 2002; Uvnäs-Moberg, 1998; Windle et al., 2004). In humans, exogenous OT suppresses cortisol in response to stressful social situations, especially in combination with social support (Heinrichs et al., 2003). Oxytocin also reduces social anxiety in those with social phobia, normalizing a hyperreactive amygdala response to threatening faces (Labuschagne et al., 2010). In healthy individuals, OT increases trust and decreases amygdala reactivity to threatening faces and neutral faces that become aversive through fear-conditioning (Domes et al., 2007; Kirsch et al., 2005; Kosfeld et al., 2005; Petrovic et al., 2008). In monkeys, administration of OT reduces ACTH and salivary cortisol (Parker et al., 2005; Simpson et

al., 2014). Our results are in agreement with this extensive body of research, showing that OT increases viewing of social stimuli, possibly through a reduction in social anxiety.

Contrary to a small number of studies in humans finding that OT treatment increases recognition memory for faces when delivered before the task, we did not observe an effect of OT on subjects' memory for monkeys or objects that were replaced in the second presentation (Guastella, Mitchell, & Mathews, 2008; Rimmele et al., 2009). In our experiment, OT increased viewing of monkeys during the second presentation, and this may have overridden any effects on our viewing-time based measure of memory. Future experiments examining OT's effects on memory should use measures that are not dependent upon viewing time.

The magnitude of OT's effects in our experiment were reliable, but modest. Previous studies showing increases in looking at faces after OT have also reported modest effects (Andari et al., 2010; Guastella, Mitchell, & Dadds, 2008, Dal Monte et al., 2014). While these studies used large images of faces and found that OT only increased viewing of the eyes, our analysis included the entire animal and the relatively small size of the face region precluded an accurate assessment of attention to the eye region specifically.

Studies in humans also have the advantage of using many more participants, not all of whom exhibit significant effects of OT treatment (A. Guastella, personal communication, October 24, 2011). Others have emphasized the importance of individual differences and contextual factors (Bartz et al., 2011). Our experiment included 3 animals, a typical number for studies with monkeys. With the addition of more subjects, we hope to increase our power to detect effects of OT and examine how potential

differences between subjects with particular temperaments may interact with OT treatment. For example, the subject who showed the strongest and most reliable effects of OT in our experiment, M1, is highly dominant, showed the most interest in the monkeys in the images and regularly lipsmacked at the images. The subject who showed the weakest effects of OT, M3, is submissive, showed the least interest in the monkeys and frequently looked away from the images. This positive relationship between sociability and the magnitude of OT's effects supports a recent finding that infant macaques with greater imitative capacity show greater increases in lipsmacking after treatment with OT compared to those with a lower propensity for imitation (Simpson et al., 2014).

Despite these subject differences, we observed reliable group effects in response to OT treatment. Importantly, these effects were not due to fixating features with greater low-level salience, arguing against a previous hypothesis that salience drives increased viewing of faces after OT administration (Ebitz et al., 2013). Instead, our data provide additional support for the hypothesis that OT increases the motivational salience to seek out highly rewarding social information, and that this may be related to a concurrent decrease in anxiety. Oxytocin is necessary for social reward in mice, and decreases amygdala-mediated anxiety while increasing functional connectivity between the amygdala and the superior colliculus in humans during gaze shifts to the eyes (Dölen, Darvishzadeh, Huang, & Malenka, 2013; Gamer et al., 2010). It is currently unknown whether similar mechanisms underlie OT's effects in rhesus monkeys. Future experiments combining site-specific manipulation of OT within the brain, recording of single neurons tuned to social information and measures of autonomic stress responses will begin to address these questions.

Chapter 5. Discussion

5.1 Interpretation

Disorders impairing social behavior including autism and schizophrenia collectively affect over 2% of the population, and our limited understanding of the neurobiological mechanisms underlying these impairments has hindered the development of treatment strategies targeting these symptoms. The goal of the present experiments was to advance our understanding of the neuronal and hormonal mechanisms mediating attention to and memory for social information. In doing so, I aimed to identify candidate mechanisms to be used in the development of optimal treatments for social impairments.

In this thesis, I presented 3 investigations into the mechanisms underlying social behavior. I first demonstrated that neurons in the macaque hippocampus discriminate both the social content and novelty of images through selective changes in firing rate for the preferred stimulus category. Then, using methods informed by screening tools for autism, I found that experience shifts exploration strategy, and that visual social cues drive the allocation of attention independent of the salience of low-level image features. Treatment with oxytocin amplifies this shift in exploration strategy and selectively increases attention towards social stimuli independent of low-level salience.

5.1.1 Face-selective neurons in the macaque hippocampus

My finding that neurons in the anterior portion of the hippocampus carry information about the category of visual stimuli contrasts with existing notions that the hippocampus provides domain-general signals of the novelty or familiarity of relations between item and context (Davachi, 2006; Manns & Eichenbaum, 2006; Strange et al., 1999). Previous experiments have reported that neurons in the monkey hippocampus do

not respond selectively to individual stimuli (Naya & Suzuki, 2011) or exhibit stimulus-selective recognition signals (Suzuki & Eichenbaum, 2000). I also did not find neurons that selectively responded to individual stimuli, instead I found that responses that were selective for a specific category of stimuli.

Importantly, category-specific neurons that were modulated by stimulus novelty did so in a category-specific manner that was dependent upon a strong response during encoding. These data fit with previous demonstrations in humans that the anterior portion of the hippocampus where our recordings were performed exhibit stronger representations of item category and stronger signals related to item novelty (Liang et al., 2013; Litman et al., 2009; Sperling et al., 2003). The category-specificity of the novelty-related responses I observed has been found to be important for coordinating memory-related processing within category-specific networks in the neocortex, suggesting that category-specificity may be a mechanism by which disparate networks are connected (Gordon et al., 2013; Mundy et al., 2013; Nichols et al., 2006; Polyn et al., 2005; Prince et al., 2009; Ranganath et al., 2004).

However, the interpretation of my results is limited by the inability to rule out other untested stimulus categories as factors, and future experiments should aim to examine the role of category-specificity with a stimulus set designed to test this hypothesis.

5.1.2 Social relevance drives the allocation of attention independent of low-level salience

A prominent theory of viewing behavior argues that simple low-level features of an image determine fixation location, with these salient locations being viewed more than would be predicted by chance during free viewing (Parkhurst et al., 2002). However, this

hypothesis does not account for the existing priors and preferences of an organism that are developed over many interactions with its environment as it searches for food and mates. While viewing scenes containing objects of social and non-social relevance, rhesus macaques strongly preferred to view conspecifics, and these preferences were not accounted for by the salience of low-level image features. Moreover, conspecifics that were viewed earlier and longer displayed highly relevant social cues of direct gaze and red sex skin (Gerald et al., 2007; Higham et al., 2013; Maestripieri, 1997, 2005; Nunn, 1999; Vandenbergh, 1965; Waitt et al., 2003, 2006).

Consistent with a previously observed "repetition effect", I found that when viewing a scene that had been previously explored, subjects made longer fixations and shorter saccades, shifting from a rapid orienting to global scene contents to a more local analysis of fewer items (Althoff & Cohen, 1999; Ryan et al., 2007).

Previous experiments examining attention to social information have almost exclusively presented single faces cropped from the body against a neutral background, but these conditions eliminate the important demand that the viewer select among many stimuli the ones that are most relevant. In order to more closely approximate natural social situations while controlling for confounding factors, I developed a semi-automated system for constructing hundreds of novel social scenes from an image library of background contexts, objects and rhesus monkeys. This novel method permits more rigorous control and characterization of scene content, and opens up new avenues for investigating social cognition through the direct manipulation of social content.

5.1.3 Oxytocin increases attention selectively to social stimuli independent of low-level salience

Using my novel social scene-viewing task, I addressed three outstanding questions in rhesus macaques: (1) Does oxytocin increase attention specifically for social compared to non-social stimuli? (2) Does oxytocin alter memory specifically for social compared to non-social stimuli? (3) Does oxytocin increase viewing of salient low-level image features? In a limited sample that is typical for the field, I found that oxytocin increases the time spent viewing conspecifics independent of low-level salience, and did not find any evidence supporting an effect of oxytocin on memory.

In addition, a detailed analysis of the characteristics of monkeys shown in the social scenes revealed that oxytocin specifically increased early viewing of infant and juvenile monkeys and late viewing of faces whose gaze was directed at the subject. These novel findings are in agreement with previous work showing that adult male rhesus emit more affiliative lipsmacking expressions towards young monkeys and that oxytocin increases eye movements towards the eye region of monkeys with direct gaze (Dal Monte, Noble, Costa, & Averbeck, 2014; Mosher, Zimmerman, & Gothard, 2011b).

I also found that concurrent with increased attention to conspecifics, oxytocin amplified an existing shift in viewing strategy from a rapid orienting to global scene contents to a more local analysis with longer fixations and shorter saccades. Upon first fixation of a face in this repeated viewing, subjects treated with oxytocin held their gaze longer, and this effect was not observed for objects. This increase in fixation duration may be due to an OT-mediated reduction anxiety, as humans with higher social anxiety make shorter fixations when viewing faces (Garner et al., 2006).

A role for OT in the reduction of social anxiety is well-supported by the literature (Averbeck, 2010; Bartz & Hollander, 2006; Carter et al., 2008), and the pattern of results observed further support this hypothesis. I found that OT increased viewing of young monkeys, who are typically found in close proximity to, and fiercely protected by, their mother and her close female relatives (Berman, 1980). Furthermore, I found that the faces of monkeys with direct gaze were viewed longer on OT, despite the fact that staring at a monkey with direct gaze is a threatening gesture (Maestripieri, 1997, 2005).

Together, these data provide evidence for a role of oxytocin in directing attention to social stimuli in rhesus macaque males, potentially through a reduction in social anxiety. This hypothesis is strongly supported by oxytocin's long history of anxiolytic effects and increases in social approach and social information seeking (Amico et al., 2004; Averbeck, 2010; Chang & Platt, 2013; Heinrichs et al., 2009; Neumann et al., 2000; Riem et al., 2011; Ring et al., 2006; Uvnäs-Moberg, 1998; Young, 2002).

However, caution must be exercised in the interpretation of my data due to my limited sample of subjects and subject differences in drug response magnitude. My study currently includes 3 adult males, and though this is average for the field, it limits extrapolation to macaques as a population. One interpretation of subject differences is that the effect of OT may be related to baseline levels of social interest. In line with this hypothesis, I found that the magnitude of OT's increase in viewing monkeys followed the same rank order of baseline levels of time spent viewing monkeys. The subject who exhibited the most robust and reliable effects of OT, M1, spent ~70% of trial time viewing monkeys, while M2 spent ~25% and exhibited smaller effects of OT and M3 spent ~15% and showed slightly smaller effects of OT than M2.

It has recently been suggested that endogenous levels of OT might moderate the response to exogenous OT, proposing that those with higher endogenous OT levels may be a biomarker of social motivation (Bartz et al., 2011). Bartz et al. (2011) note that blood plasma levels of OT are lower in individuals with autism (Modahl et al., 1998), and that plasma OT correlates with symptom severity (Rubin et al., 2010) and poorer emotion identification in those with schizophrenia (McCarthy et al., 1996). Conversely, high levels of plasma OT are associated with positive parenting behaviors (Feldman, Gordon, & Zagoory-Sharon, 2011; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a, 2010b) and trustworthy behavior in reciprocal interactions (Kosfeld et al., 2005). Other studies have found that plasma OT interacts with an individual's interpersonal characteristics (Taylor et al., 2006; Taylor, Saphire-Bernstein, & Seeman, 2010; Turner, Altemus, Enos, Cooper, & McGuinness, 1999). Because my scene viewing task is sensitive to individual differences in preference for particular stimulus categories, with additional subjects I will be able to more closely examine how varying degrees of social interest, differences in stimulus preference, endogenous OT and drug dosage interact to predict response to OT.

5.2 Open questions and future directions

5.2.1 Social salience, social anxiety, or both?

Several groups have suggested that oxytocin increases attention to socially salient stimuli through a reduction in social anxiety (Bartz et al., 2011; Chang & Platt, 2013; Churchland & Winkielman, 2012). Although both phenomena have been thoroughly demonstrated, a convincing link between the two has not yet been found. A potential link may lie in oxytocin's regulation of the amygdala's distinct subregions. In rats, OT

decreases fear by increasing inhibition of projections from the central amygdala to the brainstem, without altering the cardiovascular response that typically occurs during fear (Viviani et al., 2011). In line with these data, oxytocin reduces amygdala reactivity to threatening faces in humans and reduces coupling with brainstem regions involved in the generation of fear (Domes et al., 2007; Kirsch et al., 2005; Petrovic et al., 2008). However, it has also been found oxytocin increases gaze to the eyes and that the likelihood of this effect is positively correlated with amygdala activation (Gamer et al., 2010). Because the directionality of the BOLD signal can be problematic to interpret in terms of excitation and inhibition at the neuronal level (Logothetis, 2008), it is difficult to reconcile how OT can both increase and decrease amygdala activation. One method of addressing this question is by recording single neurons in the amygdala of rhesus macaque monkeys while they view social stimuli.

In order to dissociate the effects of OT on social salience and anxiety, future experiments could compare how diazepam alone, oxytocin, and oxytocin combined with an anxiogenic like carbon dioxide treatment alters social behavior and anxiety. Because oxytocin has been found to reduce fear but not heart rate or heart rate variability, this and another measure of autonomic function like skin conductance response may be able to provide important outcome measures.

5.2.2 Interaction between endogenous and exogenous oxytocin and individual differences

As mentioned previously, endogenous and exogenous oxytocin may interact with individual differences between subjects to produce different degrees, or even directions of response. This is an important question to address going forward, especially in the translation of effects found in healthy subjects to impaired populations. In order to

address these questions, future experiments will need to use more subjects, variable doses, and measure basal levels of OT. Because release of oxytocin into the peripheral system via the bloodstream is not tied to central levels of oxytocin, measures of basal OT should be taken via CSF taps and not from saliva or blood plasma (Ludwig & Leng, 2006; Neumann, 2007). Collaboration between labs would help to increase the number of subjects, as well as the interpretation of data if standard practices are used across labs. By using variable dosages, we can determine if OT's effects follow a linear or an inverted-U-shaped dose-response curve. Initial reports have found that a lower dose of OT results in a weaker effect, but a higher dose is needed in order to test the descending arm of a putative inverted-U-shaped dose-response curve.

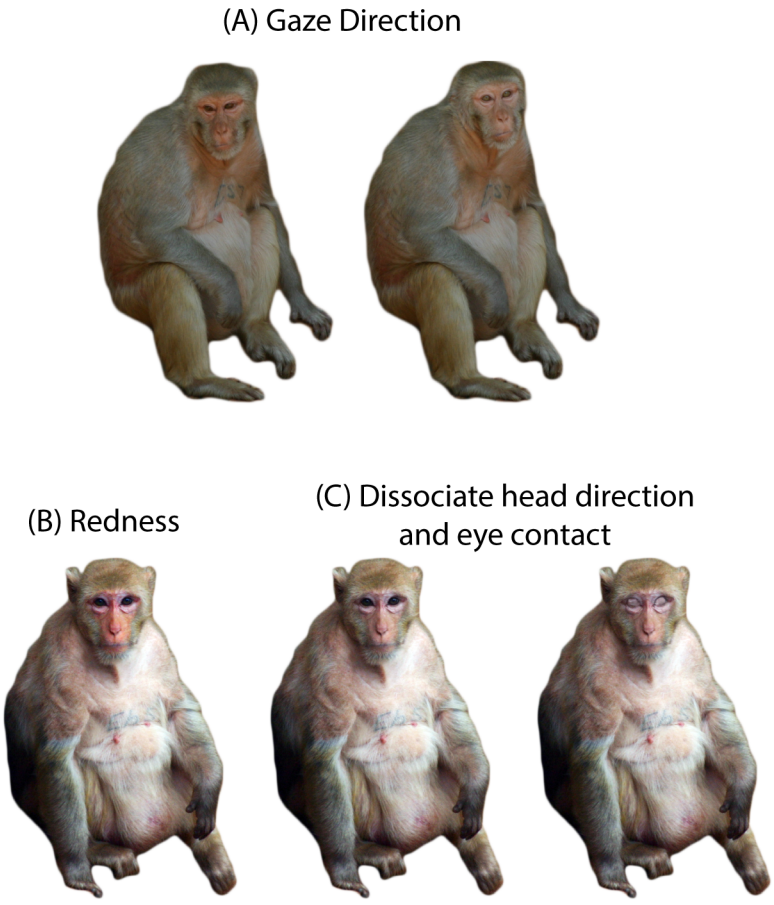
5.2.3 Manipulating social content with static scenes

Because my novel social scene viewing task was developed using a large stimulus set and programmatic methods at almost every level, new scenes with different parameters can be created quickly with almost unlimited possibilities for exact specifications. While the scenes used in the present experiments aimed for a distribution of sex and age that mimicked natural conditions, we can also construct scenes with, for example, all adult males with direct gaze. Another possibility is digitally manipulating the redness of the face or rump, or the gaze direction of a face to explicitly test specific factors while keeping all other factors constant. This level of control allows a number of questions about social cognition to be addressed in a controlled manner while retaining a high level of ecological relevance. For example, we can dissociate head direction and eye contact by digitally manipulating an image to make it look like the monkey's eyelids are closed (Figure 5.1).

5.2.4 Developing controlled tasks with high ecological relevance

Central to understanding the mechanisms of social behavior is measuring social behavior that accurately reflects what an animal does in its natural environment. The requirements of laboratory research and the need to reduce the impact of confounding variables impose certain restrictions, but the goal should be to maximize ecological relevance because this has been shown to be important for revealing impairments in social behavior (Hanley et al., 2012; Riby & Hancock, 2008b). Using videotaped social behavior as a stimulus elicits robust social behavior from subjects and most closely approximates what would be seen in a monkey's natural environment (Mosher et al., 2011;Zimmerman et al., 2012), but it is extremely time-consuming to acquire and process the stimuli, analyze the resulting data, control for potential confounds and manipulate stimulus features. On the other end of the spectrum, static images are relatively easier to control, acquire, process and analyze associated data, but are much less realistic.

Figure 5.1 Manipulating social factors through digital editing



(A) Digitally manipulating gaze direction maintaining body posture constant. Monkey on the right is the same as the left but with a face of a different gaze direction.

(B) Manipulating redness by increasing saturation of the skin within the face.

(C) Dissociating head direction and eye contact by editing the eye region so that the eyelids appear to be closed.

Recently a middle ground has been found whereby participants can "interact" with a visual stimulus through gaze-contingent changes in the stimulus display (Wilms et al., 2010). In this experiment, an anthropomorphic virtual face appeared centrally on a monitor, surrounded by three targets. In the contingent condition, the character's gaze followed the participant's gaze when they fixated one of the three surrounding objects, thereby experimentally controlling joint attention.

Recent experiments in the macaque amygdala have found "eye cells" that respond specifically when the subject fixates the eyes of a monkey in a video, and a subset of these cells were modulated by moments of eye contact between the subject and the stimulus monkey (Zimmerman et al., 2012).

By using a gaze-contingent paradigm and static images, we can more precisely control the parameters of a pseudo-interaction by triggering changes in the stimulus monkey's gaze direction, eye visibility or expression off of a number of factors. For example, programming an interaction such that when the subject views the face of a monkey with averted gaze, the face then directs its gaze at the subject. Because the stimulus is under experimental control, we can then program specific stimulus monkeys to vary in the time that they stare at the subject before looking away.

Directly staring at another monkey is a threatening gesture, and by varying the time that stimulus monkeys stare we can manipulate the reputation of specific individuals. For example, when the subject views monkey A, A stares at the subject for 4 seconds before looking away, whereas monkey B looks at the subject for only 1 second before looking away. Moreover, we can design even more interesting scenarios where fixations by the

subject of a food item near monkey A result in joint attention to the item, followed by a open-mouth threat expression towards the subject.

This level of controls allows us to ask several questions that would be difficult or less precise with videos, and opens the door for investigating social cognition in a more realistic context that remains under experimental control. For example, do subjects differentiate between monkeys that stare at them and those that look away quickly? Are eye cells modulated by the expression of the face, duration of eye contact or perhaps the responsiveness of the stimulus monkey to the subject's eye movements? Because these factors are under experimental control, parameters can be easily varied and control conditions can be created where the monkey is not responsive to the subject's gaze or has a long lag in response.

Future experiments utilizing this approach would benefit from enhanced ecological relevance, increased experimental control, and a broader array of tractable experimental questions. This could prove to be extremely valuable for understanding the mechanisms of specific social behaviors and the evaluation of potential treatments for social impairments.

5.3 Summary of findings

The present experiments have examined in the rhesus macaque how neurons in the hippocampus encode faces into memory, and how social scenes are viewed under the influence of saline and oxytocin. I demonstrated that neurons in the macaque hippocampus discriminate both the social content and novelty of images through selective changes in firing rate for the preferred stimulus category. Using methods informed by screening tools for autism, I found that experience shifts exploration

strategy, and that visual social cues drive the allocation of attention independent of the salience of low-level image features. Treatment with oxytocin amplifies this shift in exploration strategy and selectively increases attention towards social stimuli independent of low-level salience.

Overall, these data support previous work showing that the encoding of social information occurs within networks specific for social content and that the peptide oxytocin specifically regulates attention towards social information. In doing so, my experiments have advanced our understanding of how social information is encoded in the brain and how social attention is regulated by hormone systems. These advances fill critical gaps in our knowledge of how social behavior is mediated through neurobiological mechanisms, and informs an ongoing movement towards optimizing treatment strategies for disorders impairing social function.

Appendix 1

Oxytocin alters viewing strategy

We first tested the hypothesis that OT alters attention by modulating basic viewing behavior as a function of experience with the scene from the first presentation to the second. To test this hypothesis, we conducted a 3-way ANOVA, including drug treatment (Saline vs. OT), presentation number (first vs. second) and subjects (M1, M2 & M3) as factors with fixation duration as the dependent variable. Post-hoc comparisons were made using independent samples t-tests that were corrected for multiple comparisons using a false discovery rate (FDR) correction of *p*-values.

This analysis revealed significant main effects of presentation number, $F(1,6105) = 350.21$, $p < .0001$, drug treatment, $F(1,6105) = 4.27$, $p = .0388$, and subject, $F(2,6105) = 496.47$, $p < .0001$.

Post-hoc analysis of the main effect of presentation number revealed that fixations lasted significantly longer when viewing a scene for the second time ($M = 228.65 \pm .96$ms) compared with the first ($M = 218.51 \pm .95$ms), $t(6104) = 7.47$, $p < .0001$, $g = .19$. Post-hoc analysis of the main effect of drug treatment condition revealed that compared with SL treatment ($M = 222.19 \pm .95$ms), there was a trend towards longer fixations after OT treatment, ($M = 224.97 \pm .95$ms), $t(6104) = 1.96$, $p = .06$, $g = .05$. Finally, post-hoc analysis of the main effect of subject found that M1 ($M = 242.48 \pm 1.14$ms) made longer fixations than M2 ($M = 234.84 \pm 1.15$ms), $t(4202) = 4.09$, $p < .0001$, $g = .13$, and M3 ($M = 193.43 \pm 1.21$ms), $t(4208) = 28.37$, $p < .0001$, $g = .89$, and M2 made longer fixations than M3, $t(3976) = 31.16$, $p < .0001$, $g = .99$.

We also found significant interactions between drug treatment and presentation, $F(1,6105) = 7.55$, $p < .01$, drug treatment and subject, $F(1,6105) = 4.42$, $p = .01$, and presentation and subject, $F(1,6105) = 24.2$, $p < .0001$. There was no significant 3-way interaction between drug treatment, subject and presentation, $F(2,6105) = 1.48$, $p = .23$.

Post-hoc analysis of the interaction between drug treatment and presentation showed that while fixation duration did not differ between drug treatment conditions during the first presentation (SL: $M = 218.97 \pm 1.34$ms, OT: $M = 218.05 \pm 1.34$ms), $t(3087) = .64$, $p = .56$, $g = .02$, during the second presentation fixations were significantly longer after treatment with OT compared to SL (SL: $M = 225.41 \pm 1.36$ms, OT: $M = 231.89 \pm 1.35$ms), $t(3015) = 2.64$, $p = .01$, $g = .09$.

Post-hoc analysis of the interaction between drug treatment and subject showed that while M1 made significantly longer fixations after treatment with OT compared to SL (SL: M = 239.1 ± 1.61ms, OT: M = 245.86 ± 1.61ms), $t(2126) = 2.23$, $p = .03$, $g = .1$, and M2 exhibited a trend in the same direction (SL: M = 232.64 ± 1.63ms, OT: M = 237.03 ± 1.63ms), $t(2074) = 2.01$, $p = .054$, $g = .09$, M3 exhibited a trend in the opposite direction (SL: M = 194.82 ± 1.71ms, OT: M = 192.03 ± 1.7ms), $t(1900) = 1.96$, $p = .06$, $g = .09$.

Post-hoc analysis of the interaction between subject and presentation showed that M1 exhibited a trend towards longer fixations in the second presentation compared to the first (P1: M = 239.41 ± 1.61ms, P2: M = 245.55 ± 1.62ms), $t(2126) = 2.03$, $p = .05$, $g = .09$, M2 made significantly longer fixations in the second presentation (P1: M = 223.28 ± 1.63ms, P2: M = 246.39 ± 1.63ms), $t(2074) = 10.91$, $p < .0001$, $g = .48$, and M3 showed no difference in fixation duration between presentations (P1: M = 192.83 ± 1.68ms, P2: M = 194.02 ± 1.73ms), $t(1900) = .83$, $p = .44$, $g = .04$.

During the first presentation, M1 made longer fixations than M2, $t(1900) = .83$, $p = .44$, $g = .04$, and M3 (M1: M = 239.41 ± 1.61ms, M2: M = 223.28 ± 1.63ms, M3: M = 192.83 ± 1.68ms), $t(1900) = .83$, $p = .44$, $g = .04$, and M2 made longer fixations that M3, $t(1900) = .83$, $p = .44$, $g = .04$. However, during the second presentation, M1 and M2 did not differ in the duration of their fixations, $t(1900) = .83$, $p = .44$, $g = .04$, and M3 made shorter fixations than both M1, $t(1900) = .83$, $p = .44$, $g = .04$ and M2, $t(1900) = .83$, $p = .44$, $g = .04$, (M1: M = 245.55 ± 1.62ms, M2: M = 246.39 ± 1.63ms, M3: M = 194.02 ± 1.73ms).

We next continued our test of the hypothesis that OT alters attention by modulating basic viewing behavior as a function of experience with the scene from the first presentation to the second. To test this hypothesis, we conducted a 3-way ANOVA, including drug treatment (Saline vs. OT), presentation number (first vs. second) and subject (M1, M2 & M3) as factors with saccade amplitude as the dependent variable. Saccade amplitude was measured as the distance in degrees of visual angle between fixations, excluding fixations made outside of the image bounds. Post-hoc comparisons were made using independent samples t-tests that were corrected for multiple comparisons using a false discovery rate (FDR) correction of *p*-values.

This analysis revealed significant main effects of presentation number, $F(1,6105) = 10.3$, $p < .0001$, drug treatment, $F(1,6105) = 5.3$, $p = .02$, and subject, $F(2,6105) = 884.7$, $p < .0001$.

Post-hoc analysis of the main effect of presentation number revealed that saccades were significantly shorter when viewing a scene for the second time ($M = 5.14 \pm .02$ dva) compared with the first ($M = 5.22 \pm .02$ dva), $t(6104) = 3.99$, $p < .0001$, $g = .1$. Post-hoc analysis of the main effect of drug treatment condition revealed that compared with SL treatment ($M = 5.21 \pm .02$ dva), there was a trend towards shorter saccades after OT treatment, ($M = 5.15 \pm .02$ dva), $t(6104) = 1.94$, $p = .06$, $g = .05$. Finally, post-hoc analysis of the main effect of subject found that M1 ($M = 4.62 \pm .02$ dva) made shorter saccades than M2 ($M = 5.01 \pm .02$ dva), $t(4202) = 13.6$, $p < .0001$, $g = .42$, and M3 ($M = 5.92 \pm .02$ dva), $t(4028) = 39.09$, $p < .0001$, $g = 1.23$, and M2 made shorter saccades than M3, $t(3976) = 24.93$, $p < .0001$, $g = .79$.

We also found a significant interaction between subject and presentation, $F(2,6105) = 224.76$, $p < .0001$, and no significant interaction between drug treatment and subject, $F(2,6105) = 2.63$, $p = .07$, and drug treatment and presentation, $F(1,6105) = 2.58$, $p = .11$. There was no significant 3-way interaction between drug treatment, subject and presentation, $F(2,6105) = .41$, $p = .67$.

Post-hoc analysis of the interaction between subject and presentation showed that while saccades were shorter in the second presentation compared to the first for subjects M1 (P1: $M = 4.79 \pm .03$ dva, P2: $M = 4.46 \pm .03$ dva), $t(2126) = 9.71$, $p < .0001$, $g = .42$, and M2 (P1: $M = 5.3 \pm .03$ dva, P2: $M = 4.71 \pm .03$ dva), $t(2074) = 13.91$, $p < .0001$, $g = .61$, subject M3 made significantly longer saccades in the second presentation (P1: $M = 5.58 \pm .03$ dva, P2: $M = 6.26 \pm .03$ dva), $t(1900) = 12.31$, $p < .0001$, $g = .56$.

Time spent viewing items

In chapter 4, we examined the effects of four variables on the time spent viewing items by running a 4-way ANOVA with drug treatment (saline or oxytocin), item category (monkeys or objects), presentation (first or second), and subject as factors and the percent of time spent looking at each item as the dependent variable. There were significant main effects of item category, $F(1,12211) = 1134.22$, $p < .0001$, presentation, $F(1,12211) = 796.86$, $p < .0001$, subject, $F(2,12211) = 387.46$, $p < .0001$, and no significant main effect of drug, $F(1,12211) = 1.41$, $p = .24$. See Table 4.1 for means & standard error.

As a follow-up to the main effect of item category, a post-hoc *t*-test revealed that monkeys were viewed longer than objects, $t(12210) = 30.69$, $p < .0001$, $g = .56$. As a follow-up to the main effect of presentation, a post-hoc *t*-test revealed that items were viewed longer during the second presentation, compared to the first, $t(12210) = 24.73$, $p < .0001$, $g = .45$. As a follow-up to the main effect of subject, post-hoc *t*-tests revealed that M1 viewed items longer than M2, $t(8406) = 16.44$, $p < .0001$, $g = .36$, and M3, $t(8058) = 22.95$, $p < .0001$, $g = .51$. Finally, M2 viewed items longer than M3, $t(7954) = 5.8$, $p < .0001$, $g = .13$. See Table 4.1 for means & standard error.

We hypothesized that OT would not have an effect on viewing items overall, instead selectively increasing viewing of monkeys compared to objects. Supporting this hypothesis, while there was no main effect of drug treatment on time spent viewing items, there was a significant drug treatment x item category interaction, $F(1,12211) = 6.28$, $p = .01$. Post-hoc comparisons between the factors drug treatment and item category using independent-samples *t*-tests with FDR-corrected p-values showed that compared to treatment with saline, subjects given OT viewed monkeys significantly longer, $t(6104) = 2.04$, $p < .05$, $g = .052$, and that viewing of objects did significantly differ across drug treatment conditions, $t(6104) = .88$, $p = .4$, $g = .02$. See Table 4.1 for means & standard error.

With time spent viewing as the dependent variable, there were significant interactions between the factors subject and item category, $F(2,12211) = 1082.41$, $p < .0001$, and the factors subject and presentation, $F(2,12211) = 11.9$, $p < .0001$. There were no significant interactions between drug treatment and subject, $F(2,12211) = .95$, $p = .39$,

drug treatment and presentation, $F(1,12211) = .71$, $p = .4$, or item category and presentation, $F(1,12211) = .37$, $p = .55$.

Post-hoc comparisons between the factors subject and item category using independent-samples *t*-tests with FDR-corrected p-values showed that M1 viewed monkeys longer than M2, $t(4202) = 38.47$, $p < .0001$, $g = 1.19$, and M3, $t(4028) = 44.38$, $p < .0001$, $g = 1.4$, and that M2 viewed monkeys longer than M3, $t(3976) = 3.05$, $p < .01$, $g = .16$. Post-hoc tests also revealed that M2 spent more time viewing objects than M1, $t(4202) = 13.99$, $p < .0001$, $g = .43$ and M3, $t(3976) = 5.06$, $p < .01$, $g = .16$, and that M3 viewed objects longer than M1, $t(4028) = 9.97$, $p < .0001$, $g = .31$. See Table 4.1 for means & standard error.

The significant interaction between the factors subject and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected p-values. These tests showed that while M2 & M3 did not differ in the time spent viewing items during the first presentation, $t(4038) = 1.39$, $p = .19$, $g = .04$, M2 spent more time viewing items than M3 in the second presentation, $t(3914) = 5.62$, $p < .0001$, $g = .18$.

The was also a significant 3-way interactions between subject, item category, and presentation, $F(2,12211) = 12.65$, $p < .0001$ as well as drug treatment, item category and presentation, $F(1,12211) = 6.58$, $p = .01$.

The significant interaction between the factors subject, item category and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected p-values. These tests showed that while during the first presentation M2 and M3 did not differ in the time spent viewing monkeys, $t(2018) = .18$,

p = .87, g = .01, or objects, $t(2018) = 1.81$, p = .08, g = .08, during the second presentation M2 viewed monkeys, $t(1956) = 3.2$, $p < .01$, g = .15 and objects longer than M3, $t(1956) = 4.66$, $p < .0001$, g = .21.

The significant interaction between the factors drug treatment, item category and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected p-values. These tests showed that when treated with OT, subjects looked longer at monkeys, but not objects, and that this effect was significant in the second presentation, $t(3015) = 2.33$, p = .02, g = .085, but not the first, $t(3087) = .15$, p = .89, g = .01, Figure 4.1C.

Number of items viewed

In Chapter 4, we tested the hypothesis that OT affects the number of items viewed. To test this hypothesis, we performed an ANOVA that included 4 independent variables: (1) item category (monkey or object), (2) drug treatment (saline or oxytocin), (3) presentation (first or second) and (4) subject, with the number of items fixated as the dependent variable. We followed this ANOVA with post-hoc comparisons, when appropriate, using independent samples *t*-tests that were FDR-corrected for multiple comparisons. See Table 4.1 for means & standard error.

This analysis revealed significant main effects of item category, $F(1,12211) = 5100.13$, $p < .0001$, presentation, $F(1,12211) = 2684.84$, $p < .0001$, subject, $F(2,12211) = 734.49$, $p < .0001$, but no significant main effect of drug, $F(2,12211) = .16$, p = .69. Because there was no significant main effect of drug, and no significant interactions

between drug and item category, drug and presentation, or drug and subject, these data suggest that OT does not alter the number of items viewed.

As a follow-up to the main effect of item category, a post-hoc *t*-test revealed that more monkeys (M = 4.12 ± .02) were viewed than objects (M = 2.6 ± .02), $t(12210) = 59.97$, $p < .0001$, $g = 1.09$. As a follow-up to the main effect of presentation, a post-hoc *t*-test revealed that fewer items were viewed in the second presentation (M = 2.78 ± .02) compared to the first (M = 3.91 ± .02), $t(12210) = 39.72$, $p < .0001$, $g = .72$. Finally, as a follow-up to the main effect of subject, post-hoc *t*-tests revealed that M1 (M = 3.9 ± .02) viewed more items than M2 (M =3.1 ± .02), $t(8406) = 20.75$, $p < .0001$, $g = .45$ and M3 (M = 2.9 ± .02), $t(8058) = 25.9$, $p < .0001$, $g = .58$, and M2 viewed more items than M3, $t(7954) = 5.06$, $p < .0001$, $g = .11$.

Next we tested interactions between factors and found that there were significant interactions between item category and presentation, $F(1,12211) = 49.61$, $p < .0001$, item category and subject, $F(1,12211) = 798.83$, $p < .0001$, and subject and presentation, $F(1,12211) = 75.13$, $p < .0001$. There were no significant interactions between drug treatment and presentation, $F(1,12211) = 1.65$, $p = .2$, drug treatment and item category, $F(1,12211) = .42$, $p = .52$, or subject and drug treatment, $F(1,12211) = 1.32$, $p = .27$.

Post-hoc comparisons between the factors item category and presentation using independent-samples *t*-tests with FDR-corrected p-values showed that more monkeys were viewed than objects during both the first, $t(6176) = 52.62$, $p < .0001$, $g = 1.34$ and second presentation, $t(6104) = 12.64$, $p < .0001$, $g = .32$, (**P1**: *Monkeys*: M = 4.76 ± .02, *Objects*: M = 3.05 ± .02; **P2**: *Monkeys*: M = 3.48 ± .02; *Objects*: M = 2.08 ± .02).

Post-hoc comparisons between the factors item category and subject using independent-samples *t*-tests with FDR-corrected p-values showed that while subjects did not differ in the number of objects they viewed, (M1-M2: $t(4202) = .69$, $p = .53$, $g = .02$, M1-M3: $t(4028) = 1.18$, $p = .27$, $g = .04$, M2-M3: $t(3976) = .46$, $p = .67$, $g = .01$), M1 viewed more monkeys than M2, $t(4202) = 39.37$, $p < .0001$, $g = 1.21$, and M3, $t(4028) = 51.82$, $p < .0001$, $g = 1.63$ and M2 viewed more monkeys than M3, $t(3976) = 7.75$, $p < .0001$, $g = .25$ (Monkeys: M1: $M = 5.30 \pm .03$, M2: $M = 3.72 \pm .03$, M3: $M = 3.35 \pm .03$; Objects: M1: $M = 2.54 \pm .03$, M2: $M = 2.57 \pm .03$, M3: $M = 2.58 \pm .03$)

Post-hoc comparisons between the factors presentation and subject using independent-samples t-tests with FDR-corrected p-values showed that during the first presentation, M1 ($M = 4.42 \pm .03$) viewed more items than M2 ($M = 3.89 \pm .03$), $t(4216) = 10.95$, $p < .0001$, $g = .34$, and M3 ($M = 3.41 \pm .03$), $t(4096) = 20.89$, $p < .0001$, $g = .65$, and M2 viewed more items than M3, $t(4038) = 11.29$, $p < .0001$, $g = .36$. During the second presentation, M1 ($M = 3.42 \pm .03$) viewed more items than M2 ($M = 2.39 \pm .03$), $t(4188) = 20.42$, $p < .0001$, $g = .63$, and M3 ($M = 2.52 \pm .03$), $t(3960) = 17.85$, $p < .0001$, $g = .57$, but M2 viewed less items than M3, $t(3914) = 3.04$, $p < .01$, $g = .1$.

Next we tested for 3-way interactions between factors and found that there was a significant interaction between the factors subject, item category and presentation, $F(1,12211) = 7.57$, $p < .001$, and no other significant 3-way interactions. Post-hoc comparisons between the factors subject, item category and presentation using independent-samples *t*-tests with FDR-corrected p-values showed that during the first presentation, M1 viewed more monkeys than M2, $t(2107) = 32.09$, $p < .0001$, $g = 1.39$ and M3, $t(2047) = 47.17$, $p < .0001$, $g = 2.09$ and M2 viewed more monkeys than M3,

$t(2018) = 11.37$, $p < .0001$, $g = .51$, and more objects than M1, $t(2097) = 29.13$, $p < .0001$, $g = 1.27$ and M3, $t(2018) = 6.35$, $p < .0001$, $g = .28$. (**P1**: *Monkeys*: M1: $M = 5.83 \pm .04$, M2: $M = 4.54 \pm .04$, M3: $M = 3.92 \pm .04$; *Objects*: M1: $M = 3.01 \pm .04$, M2: $M = 3.25 \pm .04$, M3: $M = 2.89 \pm .04$; **P2**: *Monkeys*: M1: $M = 4.77 \pm .04$, M2: $M = 2.89 \pm .04$, M3: $M = 2.77 \pm .04$; *Objects*: M1: $M = 2.07 \pm .04$, M2: $M = 1.89 \pm .04$, M3: $M = 2.27 \pm .04$).

Oxytocin affects the duration of the first fixation to faces

The duration of the first fixation has been used to measure processing of faces in rhesus macaques (Gibboni et al., 2009; T. K. Leonard et al., 2012), patients with ASD (Santos et al., 2012), or social anxiety disorder (Garner et al., 2006) as well as neurotypicals (Cerf et al., 2009). We hypothesized that in addition to increasing time spent viewing monkeys, OT would increase the duration of the first fixation on faces. To test this hypothesis, we ran a 3-way ANOVA with drug treatment condition (saline or OT), presentation (first or second) and subject as factors. For the dependent variable, we used the duration of the first fixation, limited to first fixations that were made on faces.

As presented in Chapter 4, this analysis revealed significant main effects of drug treatment condition, $F(1,3088) = 4.33$, $p = .03$, and subject, $F(2,3088) = 85.56$, $p < .0001$, but no significant main effect of presentation, $F(1,3088) = .34$, $p = .56$. Post-hoc comparisons were conducted using independent-samples *t*-tests with FDR-corrected p-values. As a follow-up to the main effect of drug treatment, a post-hoc *t*-test revealed that the duration of the first fixation on faces was longer during OT treatment ($M = 169.88 \pm 2.7$ms) compared to saline treatment ($M = 162.09 \pm 2.6$ ms), $t(3087) = 2.07$, $p < .05$, $g =$

.07. As a follow-up to the main effect of subject, post-hoc *t*-tests revealed that M1's first fixation on faces (M = 162.09 ± 2.6ms), lasted longer than those of M2, $t(2389) = 10.23$, $p < .0001$, $g = .42$ and M3, $t(2079) = 8.83$, $p < .0001$, $g = .41$, with no difference between M2 and M3, $t(1704) = .4$, $p = .74$, $g = .02$.

This analysis also revealed some significant interaction effects. There was a significant drug treatment x presentation interaction, $F(1,3088) = 4.72$, $p < .05$, a significant subject x presentation interaction, $F(2,3088) = 5.34$, $p < .01$, but no significant interaction between subject and drug treatment, $F(2,3088) = .13$, $p = .88$.

The significant interaction between the factors drug treatment and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected *p*-values. These analyses revealed no effect of drug treatment on first fixation duration in the first presentation (*SL*: M = 165.06 ± 3.4ms, *OT*: M = 164.72 ± 3.5ms, $t(1737) = .24$, $p = .83$, $g = .01$). By contrast, in the second presentation, the duration of first fixations were significantly longer after treatment with OT (M = 175.04 ± 4ms) compared to saline (M = 159.12 ± 4ms), $t(1348) = 2.42$, $p < .05$, $g = .13$.

The significant interaction between the factors subject and presentation was followed up with post-hoc comparisons using independent-samples *t*-tests with FDR-corrected p-values. These tests showed that while first fixation duration in M2 did not differ by presentation (M2: *P1*: M = 151.41 ± 4.2ms, *P2*: M = 148.78 ± 4.5ms, $t(1006) = .53$, $p = .66$, $g = .03$), M1 made longer first fixations on faces during the second presentation (M = 188.31 ± 3.6ms) compared to the first (M = 206.32 ± 3.9ms), $t(1381) = 2.6$, $p < .05$, $g = .14$, and M3 made shorter first fixations on faces during the second

presentation (M = 146.14 ± 6.1ms) compared to the first (M = 154.94 ± 4.7ms), $t(696)$ = 2.29, $p < .05$, $g = .18$.

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