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# Sexual Differentiation of the Prefrontal Cortex in Humans: Examining Behavioural Sex Differences and the Modulatory Role of Androgens

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SEXUAL DIFFERENTIATION OF THE PREFRONTAL CORTEX IN HUMANS:

EXAMINING BEHAVIOURAL SEX DIFFERENCES

AND THE MODULATORY ROLE OF ANDROGENS

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by

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**ABSTRACT**

Sex hormones are important factors in the establishment of sex differences in the brain and behaviour during the prenatal developmental period and during adulthood. One brain area that has received little attention with respect to the study of sex differences is the prefrontal cortex (PFC). The PFC is involved in cognitive functions not limited to working memory, reinforcement learning, and inhibitory control. Currently, our understanding of the hormonal modulation of the PFC by sex steroids is also limited. The overall objectives of the present thesis were: to test the hypothesis that select cognitive functions known to depend on the PFC exhibit sex differences, to investigate whether some of these functions are influenced by developmental and/or adult androgens, and to begin to determine the functional components of PFC-dependent cognitive tasks that are responsible for eliciting sex differences. In Study 1, there was no evidence for a sex difference on two working memory tasks (Self-Ordered Pointing and the *n*-back), but males selected more advantageous cards than females on the Iowa Gambling Task (IGT) and were more accurate during the reversal phase of a probabilistic reversal learning task. In Study 2, the relationship between current and developmental androgens and performance on the IGT was investigated. Financial risk-taking was assessed as a potential mediator of the relationships. Circulating testosterone was found to be negatively correlated with the number of good card selections on the IGT, but there was no evidence to suggest that risk-taking was a mediator. On the other hand, there was evidence that developmental levels of androgens (using digit ratio as a proxy measure) may influence IGT performance in adulthood indirectly through an effect on risk-taking. In Study 3, females were more accurate than males on a reinforcement learning task under conditions where learning was based on positive feedback, whereas males were faster on an interference inhibition task than females. Taken together, the set of studies described in the present dissertation advance our knowledge regarding the sexual differentiation of the PFC and add to our current understanding of the modulatory role played by sex steroids on certain cognitive functions dependent on the PFC.

**Key words:** sex differences; prefrontal cortex; working memory; decision-making; reversal learning; reward processing; inhibitory control; risk-taking; androgen; digit ratio

**CO-AUTHORSHIP STATEMENT**

All research described in the current thesis was carried out solely by Kelly L. Evans with the exception of the radioimmunoassays which were conducted by Bavani Rajakumar under the supervision of Dr. Elizabeth Hampson and the digit ratio reliability measurements performed by Janani Sankar. Dr. Elizabeth Hampson supervised and contributed to all aspects of the studies described within the current dissertation including experimental design, data analysis, interpretation, and revision of manuscripts.

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| | |
|---|---|
| 2D:4D | ratio of the second to fourth digit lengths |
| $5\text{-HT}_{1A}$ | serotonin 1A receptor |
| $5\text{-HT}_{2A}$ | serotonin 2A receptor |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| AR | androgen receptor |
| BA | Brodmann's area |
| CNS | central nervous system |
| CWT | California weather task |
| DHT | dihydrotestosterone |
| DLPFC | dorsolateral prefrontal cortex |
| $E_2$ | estradiol |
| ERα | estrogen receptor alpha |
| ERβ | estrogen receptor beta |
| fMRI | functional magnetic resonance imaging |
| IGT | Iowa Gambling Task |
| JPI-R | Jackson Personality Inventory - Revised |
| L-DOPA | L-3,4-dihydroxyphenylalanine |
| MANOVA | multivariate analysis of variance |
| mRNA | messenger ribonucleic acid |
| MRI | magnetic resonance imaging |
| OFC | orbitofrontal cortex |
| OVX | ovariectomized |
| PANAS | Positive and Negative Affect Schedule |
| PET | positron emission tomography |
| PFC | prefrontal cortex |
| POMS | Profile of Mood States |
| PRL | probabilistic reversal learning |
| PST | probabilistic selection task |
| SD | standard deviation |
| SEM | standard error of the mean |
| SOP | Self-Ordered Pointing |
| SSD | stop-signal delay |
| SSRT | stop-signal reaction time |
| T | testosterone |
| VMPFC/OFC | ventromedial prefrontal cortex/orbitofrontal cortex |

**CHAPTER 1**

**GENERAL INTRODUCTION**

During embryonic development, the brain starts out as a sexually indifferent structure, morphologically identical in male and female mammals.  Through the influence of genetics and sex hormones, the brain differentiates into a sexually dimorphic organ which can ultimately lead to observable sex differences in behaviour.  In humans, sexual differentiation begins at about 6 weeks gestational age, when the genes determine whether the indifferent gonad differentiates into a testis or ovary; phenotypic sex thereafter is determined primarily by gonadal secretions, specifically the production of sex steroid hormones (Breedlove & Hampson, 2002; Grumbach et al., 2003; McCarthy & Arnold, 2011).  Sex hormones such as androgens and estrogens (classes of sex steroids secreted primarily from the testes and ovaries, respectively) are important for the initiation and/or maintenance of sex differences in the brain and behaviour not merely during early fetal development, but throughout the lifespan including postpubertal adult life.  Currently, it is generally accepted that sex differences in the body, brain and behaviour arise due to genetic, hormonal, and environmental factors (McCarthy & Arnold, 2011).  While many sex differences exist in brain areas and behaviours related to reproduction, differences between males and females in non-reproductive functions have also been discovered (see Hampson, 2002; 2008 for reviews).

The purpose of the current dissertation is to investigate cognitive functions known to depend on the prefrontal cortex (PFC), a region of the brain that has received only limited study in the context of sex differences.  The objective was to determine whether discernible sex differences exist in several candidate cognitive functions mediated by the PFC, to investigate whether these functions are influenced by either developmental or current androgen levels, and to further break down any complex differences observed to understand sex differences at a simpler level of function.  If any of the cognitive functions under study shows a behavioural sex difference and/or is related to developmental or adult hormone levels, this will provide empirical support to the idea that the PFC is sexually differentiated at the functional level in humans and that sex steroids can modulate the functioning of sites in the human PFC.  Such a demonstration would be a significant theoretical advance, in view of the

limited understanding of the hormonal modulation of the frontal cortex that is currently available in the neuroendocrine literature.

To begin, the principles of sexual differentiation and organizational and activational effects of hormones will be reviewed. The focus of the present work is sex differences at the functional level, however the possibility of differences in function is bolstered by evidence of sex differences in the anatomy or physiology of the frontal cortex. Evidence supporting the idea that the PFC is a site of steroid activity will be presented in sections addressing estrogen and androgen actions in the PFC. Next, evidence of anatomical sex differences in the PFC will be examined. Preliminary evidence also will be reviewed showing behavioural sex differences in PFC-dependent functions including working memory, and reinforcement learning, although to date, such studies are limited in number and systematic investigations devoted to sex differences are lacking. The influence of gonadal hormones on PFC-dependent tasks will also be discussed. Finally, the specific objectives for the current thesis and how these address the current gaps in the literature will be presented.

## 1.1 BASIC PRINCIPLES OF SEXUAL DIFFERENTIATION IN HUMANS

The primary sex difference, as described in the classical model of sexual differentiation, is the sex of the gonads which is directly determined by the presence or absence of the Y chromosome (McCarthy & Arnold, 2008; 2011). Initially, during embryonic development, humans develop in a bipotential fashion with both sexes having reproductive organs that are identical. The female developmental trajectory is considered to be the default. The process of sexual differentiation begins when the presence of a Y chromosome in the cells of the gonad leads to the development of a testis in normal males (XY individuals) via a gene called the sex-determining region of the Y (*SRY*) (Berta et al., 1990). In normal females (individuals with an XX karyotype), the gonad develops into an ovary in the absence of the *SRY* gene. After the establishment of the primary sex difference in the gonads, and the onset of hormone synthesis, gonadal hormones play the major role in the process of sexual differentiation. Given that the default developmental trajectory is female, hormones secreted by the ovary do not play a primary role in many aspects of early female development (but feminizing effects of ovarian hormones may be important in the central nervous system (CNS) during adolescence; see Berenbaum & Beltz, 2011). Rather, it is hormones secreted

by the testes that direct sexual differentiation (specifically, the processes of masculinization and defeminization). The testes produce both testosterone and anti-Müllerian hormone which lead to masculine development of the internal genitalia (e.g., vas deferens, epididymis, and seminal vesicles); the lack of these hormones in the female leaves the Müllerian ducts to develop into the female reproductive structures (fallopian tubes, uterus, cervix, and inner vagina; Breedlove & Hampson, 2002), while the Wolffian duct system regresses. Testosterone is also involved in the formation of the penis and scrotum in males, but acts via a metabolite, dihydrotestosterone (DHT; a potent androgen that results from conversion of testosterone by the enzyme 5-α-reductase), whereas the external genitalia of the female (i.e., clitoris, labia) form in the absence of testosterone and its metabolites (Breedlove & Hampson, 2002).

## 1.2 ORGANIZATIONAL AND ACTIVATIONAL EFFECTS OF HORMONES

Although genes alone can play a direct role in the establishment of certain sex differences (sex chromosome effects; see Arnold, 2009 and McCarthy & Arnold, 2011 for reviews), notably in avian species, most established sex differences in physiology and behaviour have been shown to result from the actions of gonadal hormones in humans and other primates. These hormones can have effects at many time points across the lifespan, from early gestational development to adulthood. The influence of hormones on the brain and behaviour during development (prenatal, perinatal and possibly pubertal; Berenbaum & Beltz, 2011; Schulz et al., 2009) are called *organizational* effects, whereas the effects of hormones during adulthood are considered to be *activational*. Sex differences can arise as a result of organizational effects, activational effects, or a combination of the two types of effects. The distinction between organizational and activational effects was first made by Phoenix and colleagues in 1959. In a classic study, pregnant guinea pigs were injected with testosterone propionate and the mating behaviour of their offspring was examined during adulthood. In gonadectomized female offspring who had been exposed to testosterone, female-typical mating behaviour (i.e., lordosis) was greatly reduced, whereas male-typical mating behaviour (i.e., mounting) was elicited instead (Phoenix et al., 1959). These findings led to the organizational-activational framework. Organizational effects are permanent changes in the brain that occur in response to exposure to a particular steroid, take place before the brain has matured, and can only be induced during a specific sensitive period or

defined temporal window in development (Arnold & Breedlove, 1985; Phoenix et al., 1959). These permanent changes can involve alterations in neural structure, changes in metabolism of steroids, or changes in the responsiveness of neurons to steroids (Arnold & Breedlove, 1985). On the other hand, activational effects are transient or impermanent, are elicited by adult gonadal steroids, and can occur at any time in response to the steroid hormone levels currently available in the circulation (Arnold & Breedlove, 1985; McCarthy & Arnold, 2011; Phoenix et al., 1959). Activational effects may or may not interact with, or be constrained by, earlier organizational effects (McCarthy & Arnold, 2011). They involve temporary alterations in neurotransmitter production, release, or sensitivity, or reversible changes in the structure of the neuron, synapse, or receptor (Arnold & Breedlove, 1985; McEwen & Alves, 1999).

In humans, sex differences in several cognitive abilities have been identified that appear to result largely from the organizational or activational effects of gonadal steroids (although experiential variables may also play some role). For example, one consistent sex difference that has been extensively studied is the male advantage in mental rotation (i.e., imagining the rotation of a depicted object; Hampson, 2002). Studies suggest both an organizational and activational role. With respect to organizational influences, it is thought that prenatal or early postnatal androgen exposure may play a role in mental rotation ability as the sex difference is established by 3-5 months of age (Moore & Johnson, 2008; Quinn & Liben, 2008). Androgen levels in amniotic fluid correlate with mental rotation abilities measured at the age of 7, whereby better mental rotation performance was related to higher prenatal testosterone levels (Grimshaw et al., 1995). Females with congenital adrenal hyperplasia, who experience atypically elevated androgen levels *in utero* due to a defect in adrenal hormone synthesis, have been found to have better mental rotation skill than unaffected females (Berenbaum et al., 2012). With respect to activational effects, many studies have found that females perform better on mental rotation tests at the menstrual phase of the ovarian cycle (when estradiol levels are low) compared to the midluteal phase (when estradiol levels are higher) (e.g., Hausman et al., 2000; Maki et al., 2002; Phillips & Silverman, 1997; but see Epting & Overman, 1998). Testosterone may also exert activational influences over spatial cognition as circulating testosterone levels have been found to predict performance on tests of spatial visualization (e.g., Moffat & Hampson, 1996; Neave et al., 1999; Vuoksimaa et al., 2012; but

see Puts et al., 2010). Thus, given the evidence above, and accumulating evidence in other cognitive domains, it is clear that sex steroids can affect human behaviour beyond basic reproductive functions, opening up the possibility that in addition to spatial cognition, other aspects of cognition may be both sexually differentiated and influenced by sex steroids.

## 1.3 SEXUAL DIFFERENTIATION OF THE PREFRONTAL CORTEX

A vast literature in nonhuman species, using a variety of hormonal manipulations, shows that sex differences can develop in the brain and in behavior as the result of organizational or activational hormone effects. One brain region where preliminary evidence is beginning to emerge for sexual differentiation is the PFC. In primates, the PFC is involved in a wide range of so-called 'executive' functions which are defined as control processes that help to optimize performance during complex cognitive tasks (Robbins & Arnsten, 2009). Of particular interest for the current thesis is the idea that there may be sex differences in executive functions thought to depend on the PFC. The next few sections will provide an overview of the current evidence that supports the idea that the PFC is a sexually differentiated brain region. To begin, the basic mechanisms of steroid action in the brain will be reviewed.

### 1.3.1 Basic mechanisms of estrogen and androgen action in the brain

Estrogenic and androgenic effects occur primarily when the steroid diffuses through the plasma membrane, binds to intracellular receptors in the cytoplasm or nucleus, and alters gene expression and subsequent protein synthesis in the target cell (Michels & Hoppe, 2008). These are referred to as genomic effects and are slow, more prolonged effects thought to occur on the order of minutes to hours (Foradori et al., 2008; Michels & Hoppe, 2008). Androgens and estrogens exert genomic effects by binding to a class of intracellular receptors (in the nuclear receptor superfamily) that includes estrogen receptor sub-types ERα and ERβ, and the androgen receptor (AR) (Li & Al-Azzawi, 2009). Depending on the type of protein being synthesized in the target cell, regulatory effects of steroids on gene expression can lead to a variety of alterations in cell structure and function including the remodeling of synapses or the regulation of neurotransmitter systems (McEwen, 1991). In recent years, rapid, non-genomic effects also have been identified that involve estrogens or androgens binding to membrane receptors that modulate voltage- or ligand-gated ion

channels (Michels & Hoppe, 2008). Non-genomic effects can lead to changes in neuronal excitability, activate second messenger pathways, and protect neurons from toxins and free radicals (McEwen, 1999). Non-genomic effects occur on the order of milliseconds to minutes (Mermelstein et al., 1996; Michels & Hoppe, 2008).

*1.3.2 Estrogens, androgens and their receptors are present in the PFC*

Markers for the presence of estrogens and androgens have been located in the PFC of developing rodents, monkeys, and humans. ERα mRNA has been discovered during the first days of postnatal life in the PFC of male and female rats. However, a sex difference in the timing of expression may exist whereby males have a decline and females have an increase in ERα mRNA expression on postnatal day 10, which disappears by postnatal day 18 (Wilson et al., 2011). MacLusky, Naftolin, and Goldman-Rakic (1986) found evidence for the presence of estrogen receptors in the PFC of prenatal and postnatal rhesus monkey brain specimens. In addition, androgen receptors have been identified in the frontal lobes of fetal rhesus monkeys (Handa et al., 1988; Pomerantz et al., 1985; Pomerantz & Sholl, 1987), but there may be a sex difference in the distribution of AR across the left and right hemispheres. For example, Sholl and Kim (1990) observed that male fetal rhesus monkeys had higher levels of AR in the right frontal lobe compared to the left, whereas the distribution of AR was more equalized between the hemispheres in females. In the developing rhesus monkey, evidence of androgen binding sites in specific areas of the PFC, namely dorsolateral (DLPFC) and orbitofrontal cortex (OFC), has also been discovered (Clark et al., 1988) and aromatase (the enzyme responsible for the conversion of testosterone to estradiol) has been found in the PFC, with the DLPFC and OFC having the highest levels among the frontal and non-frontal cortical regions examined (Clark et al., 1988; MacLusky et al., 1986). The presence of sex steroid receptors suggests that steroids are able to exert activity in regions of prefrontal cortex during early brain development.

There is also evidence for the presence of estrogens and androgens in the PFC during adulthood. In adult rats and rhesus monkeys, ERα and ERβ messenger RNA has been identified in the cerebral cortex (Shughrue et al., 1997; 1998) and in the PFC (Pau et al., 1998; Wang et al., 2004). In young and aged rhesus monkeys, ERα is present in excitatory synapses of the DLPFC (Wang et al., 2010). Evidence for the presence of AR also has been

found in the DLPFC and OFC in adult rhesus monkeys (Clark et al., 1988; Finley & Kritzer, 1999). Data from humans are limited because of the technical difficulties of mapping receptors in human brains. With respect to humans, ERα mRNA has been found post-mortem in the DLPFC in brain specimens from both sexes ranging from infants to adults (Perlman et al., 2005). Both testosterone and estradiol have been detected in the PFC of brain specimens from adult human females, with the PFC having one of the highest concentrations of estradiol among the brain regions examined (Bixo et al., 1995). In adult human females, high levels of the enzyme that converts the major conjugated estrogen in the plasma of females into more biologically active forms such as estrone (i.e., estrone sulfatase) also have been found in the frontal cortex (Platia et al., 1984).

*1.3.3 Estrogens and androgens alter neuronal morphology within the PFC*

There is some evidence to suggest that estrogens and androgens produce alterations in neuronal morphology within the PFC. In adult male rats, both androgens and estradiol have been shown to induce spine synapse formation in the PFC (Hajszan et al., 2007). Hajszan et al. (2008) found that spine density in the PFC was 70% higher in gonadally intact male vervet monkeys compared to castrated males and found that testosterone treatment increased spine density in the PFC of ovariectomized (OVX) females by 80%. Reports in OVX adult female rats also suggest that treatment with estradiol can increase the number of dendritic spines in the PFC (Inagaki et al., 2012; Khan et al., 2013). Studies in OVX young female rhesus monkeys have also shown that treatment with estradiol increases the number of spines in the DLPFC compared to vehicle treatment (Hao et al., 2007; Tang et al., 2004). Regions of the visual cortex did not show any change in spine density after estradiol treatment indicating that there is regional specificity (Tang et al., 2004).

These effects are reminiscent of estradiol-induced changes in dendritic spine densities reported over the estrous cycle of the rat in a now classic study by Woolley, McEwen and others (Gould et al., 1990).

*1.3.4 Estrogens and androgens modulate neurotransmitter systems of the PFC*

Androgens and estrogens can influence activity in neurotransmitter systems within the PFC, which is especially important as evidence suggests that the dopaminergic and serotonergic

systems in particular play a key role in several PFC-dependent cognitive functions including working memory, reinforcement learning, and inhibitory control (e.g., Calaminus & Hauber, 2008; Cools & D'Esposito, 2011; Krugel et al., 2009; Mehta et al., 2001; Rogers, 2011). Many studies have used animal models to examine the effects of gonadectomy and subsequent estrogen or androgen replacement on neurotransmitters, their metabolites, and their receptors in the PFC.  For example, in the rat, estradiol treatment after gonadectomy increases the density of 5-HT$_{2A}$ binding sites in the male and female frontal cortex (Sumner & Fink, 1995; 1998).  Treatment with estradiol or an ERβ-selective agonist also increased levels of metabolites of serotonin, dopamine, and norepinephrine in the PFC of OVX rats (Inagaki et al., 2010; Jacome et al., 2010).  In a rodent study that employed immunohistochemistry to examine dopaminergic and non-dopaminergic mesocortical neurons projecting to the medial PFC, dopaminergic neurons showed the most immunoreactivity for the androgen receptor (AR) in both male and female animals (Kritzer & Creutz, 2008).  Androgens may also modulate PFC dopaminergic systems indirectly via an influence on glutamate (Aubele & Kritzer, 2012).  In the rhesus monkey, OVX monkeys had a lower density of cholinergic fibers in the DLPFC compared to intact controls and OVX monkeys receiving estrogen replacement therapy (Tinkler et al., 2004).  A decreased density of DLPFC fibers immunoreactive for tyrosine hydroxylase (the enzyme involved in the formation of the dopamine precursor, L-DOPA) and choline acetyltransferase (the enzyme involved in the formation of acetylcholine) and an increased density of DLPFC fibers immunoreactive for dopamine ß-hydroxylase (the enzyme that converts dopamine to norepinephrine) and serotonin has also been found in OVX monkeys (Kritzer & Kohama, 1998; 1999).  Taken together, these studies suggest that modulation of neurotransmitter systems within the PFC may be a mechanism by which steroid hormones can influence PFC-dependent cognitive functions.

*1.3.5  Anatomical sex differences exist in regions of the PFC*

Most neuroanatomical sex differences are due to the actions of androgens during critical periods of development, and tend to be markers for brain regions that might potentially retain responsiveness to steroids in adulthood.  Thus, evidence indicating anatomical differences between males and females in the PFC is further support for the idea that sex steroids are active in this region.  In young rhesus monkeys, the ventromedial PFC/orbitofrontal cortex

(VMPFC/OFC) may develop at a faster rate in males compared to females (Goldman et al., 1974), although this early finding has yet to be replicated.  In humans, recent evidence suggests that fetal testosterone plays a role in OFC development as testosterone measured by amniocentesis between 13 and 20 weeks gestation was found to negatively predict gray matter volume in the lateral OFC, as judged from magnetic resonance imaging (MRI), in prepubertal boys (Lombardo et al., 2012).  In adults, some studies have reported larger relative cortical volumes for females in certain areas of the VMPFC/OFC compared to males (Gur et al., 2002; Lunders et al., 2009; Raine et al., 2011; Welborn et al., 2009; Wood et al., 2008; but see Goldstein et al., 2001; 2002).  With respect to other areas of the PFC, women also may have larger gray matter volume in the DLPFC compared to men relative to total brain volume (Goldstein et al., 2001; Lunders et al., 2009; Schlaepfer et al., 1995).  In addition, gray matter volumes of the inferior frontal cortex may be sexually dimorphic with one study finding that females had larger relative gray matter volume in the left inferior frontal cortex (triangular region), whereas males had larger volumes in the left inferior frontal cortex (opercular region) (Witte et al., 2010).  In the same study, circulating testosterone was inversely related to gray matter volume in the left opercular inferior frontal cortex only (Witte et al., 2010).  Note that the above findings should be interpreted with great caution as it can be difficult to make inferences about function based on differences in anatomy because sex differences also have been identified in the packing density of neurons in some cortical areas (Witelson et al., 1995). This, however, does not negate the fact that sex differences have been observed in the PFC and if they are confirmed, are likely to reflect the actions of sex steroids during the early developmental period of brain organization.

*1.3.6  Do PFC-dependent cognitive functions show sex differences?*

The PFC is responsible for a range of cognitive functions, as well as important aspects of motor control.  Functions involved in working memory, response inhibition, and reinforcement learning are relevant to the current set of studies.  These functions were singled out for further investigation based on the evidence reviewed above.  It should be noted that while preliminary reports of sex differences do exist within these functional domains, existing reports are limited, sporadic, and mostly unreplicated, and thus have received little research attention.  Systematic and dedicated studies of sexual differentiation in the PFC have not been conducted to date.  The reports of sex differences that do exist have

typically been incidental findings encountered in the context of doing research to address a different theoretical question.

### 1.3.6.1 Working memory

Internalizing and holding information "in mind" temporarily with the possibility of using that information to guide behavior without the assistance of external cues is a common definition of working memory (Goldman-Rakic, 1987; 1993). It is generally agreed that working memory represents a system that is involved in the storage, maintenance, and processing of information important to cognition on a moment to moment basis (Baddeley, 1996). Much progress has been made in understanding the neural correlates of working memory and one of the main findings from a variety of methodologies is that the PFC (and in particular the DLPFC) is one of the areas critical for working memory (see Goldman-Rakic, 1987; Owen et al., 2005 for reviews).

The exact role played by the PFC is still debated. One issue is whether the DLPFC is specialized for spatial working memory or mediates all forms of working memory. There are two competing hypotheses. For example, Goldman-Rakic and colleagues (e.g., Goldman-Rakic, 1995; Levy & Goldman-Rakic, 1999; 2000) have suggested a domain-specificity model in which there are separate systems for various modalities of information (object or spatial) mapped out across different brain regions. For example, the cortex surrounding the principal sulcus in the monkey is thought to be responsible for the storage and processing of information in visuospatial working memory, whereas the inferior convexity (just ventral to the principal sulcus) is thought to be involved in the storage and processing of objects and faces (Levy & Goldman-Rakic, 2000). Other researchers have suggested a domain-general model whereby the brain is organized according to the type of processing required rather than the type of information to be processed (e.g., D'Esposito et al., 1999; Owen et al., 1999; Petrides, 1995). In this model, it is thought that the DLPFC plays a role in certain active control processes required for working memory (such as active manipulation and monitoring) regardless of the modality of the information to be held in mind. Imaging work using functional MRI (fMRI) has found evidence for increased activation in the DLPFC during a variety of working memory tasks that include both spatial and non-spatial stimuli (e.g., D'Esposito et al., 1998; Smith & Jonides, 1999). Data from patients with DLPFC lesions

also indicates impairment on working memory tasks that involve the manipulation of either verbal or spatial information (Barbey et al., 2013).

Another issue is whether the PFC is involved in mnemonic (storage) or non-mnemonic (executive control) aspects of working memory. Current evidence suggests the PFC is involved in the executive control, but not the storage processes of working memory. For example, impaired performance is seen on working memory tasks that place demands on both storage and executive components of working memory in patients with damage to the DLPFC (Barbey et al., 2013; Petrides, 1995). However, these same patients show normal performance on span tasks that involve repeating a sequence of numbers and that only place demands on working memory storage (Barbey et al., 2013; Petrides, 1995). Conversely, patients with damage to posterior cortical regions (parietal and perisylvian cortices) display impairments on working memory tasks that emphasize the passive short-term recall of either verbal or spatial information (D'Esposito & Postle, 1999; Milner, 1971). A large body of imaging work corroborates the idea that the PFC is involved in various active control processes required by the working memory system and that more posterior cortical areas mediate storage. For example, the DLPFC is said to be involved in active maintenance (e.g., Funahashi et al., 1993; Goldman-Rakic, 1987; Owen et al., 1999), manipulation (e.g., D'Esposito et al., 1999; Postle et al., 1999; 2006; Owen et al., 1999) and monitoring of the contents of working memory (e.g., Champod & Petrides, 2010; Owen et al., 2005; Rowe et al., 2000), whereas parietal and perisylvian cortex is activated when only the passive storage of information related to working memory is required (Paulesu et al., 1993; Postle et al., 1999; Wager & Smith, 2003).

Limited evidence suggests that sex differences may exist on tasks assessing the frontally-dependent executive processes of working memory. On working memory tasks that depend heavily on executive processes such as monitoring and updating (which recruit the DLPFC), females make fewer errors and take less time to complete a spatial working memory task (Duff & Hampson, 2001; Lejbak et al., 2009) and display more accurate performance on a digit ordering task compared to males (Duff & Hampson, 2001). Two studies in children and adults have found that females perform more accurately than males on the *n*-back task, although other studies using the *n*-back have reported no differences (Speck et al., 2000; Vuontela et al., 2003; but see Lejbak et al., 2011; Nagel et al. 2007; Schmidt et al., 2009).

No sex difference has been found on span tasks (Duff & Hampson, 2001; Farrell Pagulayan et al., 2006; Robert & Savioe, 2006).

### 1.3.6.2 Reinforcement learning

Decision making is a complex cognitive process that involves evaluating the value of multiple options to choose one that is optimal (Fellows, 2007; 2011). Decision making is also viewed as consisting of multiple component processes and some of these processes can include reversal learning and value assessment (Fellows & Farah, 2003; 2005; 2007). A common task used to assess decision making in the laboratory and clinical setting is the Iowa Gambling Task (IGT; Bechara et al., 1994), which is a complex task that involves learning payoffs associated with different decks of cards over time. The IGT is considered a valid model of decision making as it involves many of the component processes mentioned above (Lawrence et al., 2009) and predicts poor decision making in real life (Bechara, 2007). The original study by Bechara and colleagues (1994) showed that patients with damage to the ventromedial PFC were impaired on the IGT compared to neurologically intact controls and brain damaged controls with lesions in occipital, temporal, or dorsolateral cortex. Subsequent patient studies have confirmed the importance of the VMPFC in IGT performance (e.g., Bechara et al., 2000; Fellows & Farah, 2005), along with studies in healthy volunteers using neuroimaging techniques (e.g., Christakou et al., 2009a; Lawrence et al., 2009). However, the exact role of the VMPFC is still debated because, even though the IGT is predictive of real life decision making, the task is complex and it is hard to determine what component(s) is/are affected when performance is impaired.

Many studies have attempted to further tease apart the hypothetical components of IGT performance, including reversal learning which can be defined as the ability to alter previously learned stimulus-reward associations when the reward and punishment contingencies of stimuli reverse (Fellows & Farah, 2003). There is an extensive literature showing that lesions to the OFC in a variety of species lead to impairment on object reversal learning tasks (e.g., Dias et al., 1996; Jones & Mishkin, 1972; Kazama & Bachevalier, 2012; Rygula et al., 2010). Patients with lesions of the VMPFC/OFC are also impaired on simple object reversal tasks (Fellows & Farah, 2003; 2005) and on reversal learning tasks that involve probabilistic feedback, in which the feedback given is incorrect on some proportion

of trials (e.g., Berlin et al., 2004; Hornak et al., 2004). Neuroimaging studies in healthy subjects have confirmed that switching a response following a contingency reversal elicits activation in the VMPFC/OFC, in addition to more variable activations in several other areas of the PFC including the ventrolateral PFC, dorsolateral PFC, dorsomedial PFC, and anterior cingulate cortex (e.g., Budhani et al., 2007; Cools et al., 2002; Greening et al., 2011; Hampshire et al., 2012; O'Doherty et al., 2003). Currently, the involvement of each region in the cognitive processes and behaviours needed during reversal learning are still debated, much like the working memory literature. However, the critical region that may be the most associated with the actual reversal of a response is the VMPFC/OFC. The role of the VMPFC/OFC in reversal learning may be related to the prediction error signaling necessary to detect contingency change and that may be the key to reversing one`s behavioural response (Budhani et al., 2007; Mitchell, 2011; O`Doherty et al., 2003). It is proposed that the VMPFC/OFC is involved in processing rewarding and punishing feedback as it maintains representations of the relative value of stimuli and re-evaluates these representations as contingencies change to flexibly guide behaviour (Fellows & Farah, 2007; Hampshire et al., 2012; Plassmann et al., 2010; Tsuchida et al., 2010).

Here too, limited data have begun to suggest that sex differences exist on reinforcement learning tasks. Behavioural studies using the IGT have consistently shown a sex difference with males choosing more cards from the advantageous decks than females (e.g., Bolla et al., 2004; Overman et al., 2006; 2011; Reavis & Overman, 2001; Weller et al., 2009). Differences in brain activation have also been found with males showing greater activation of the right and left lateral OFC, and females showing greater activation in the left medial OFC, during IGT performance (Bolla et al., 2004). With respect to reversal learning, a male advantage has been reported by one study on a basic object reversal task in young children (15 to 30 months of age; Overman et al., 1996) and this is similar to a report in infant monkeys (Clark & Goldman-Rakic, 1989), though neither report has been confirmed. On the other hand, adult males and females in the same study (Overman et al., 1996) were similar in their level of performance. This may be related to the fact that the basic object reversal task is not sufficiently challenging to a young healthy adult population and produced a ceiling effect. A subsequent study using a more complex task found no evidence for a sex difference in probabilistic reversal learning in either children or adults (Overman, 2004), but the sample

sizes used were small and there was evidence that participants found the task to be too difficult.

*1.3.6.3  Inhibitory control*

Inhibitory control (or response inhibition) involves the suppression of behaviours that are no longer optimal (inappropriate, unsafe, or no longer required) due to changing environmental demands (Chambers et al., 2009).  As with other executive functions such as working memory and reinforcement learning, inhibitory control can also be broken down into finer component processes.  Subtypes of inhibitory control described in current literature include interference inhibition (suppressing interfering, involuntary response tendencies due to the presentation of incompatible stimulus dimensions), withholding a prepotent action (action withholding), and stopping an already initiated action (action cancellation) (Sebastian et al., 2013a).  Common laboratory tasks used to assess inhibitory control include the Simon, the Flanker, and the Stroop tasks (interference inhibition), the Go/no-go task (action withholding), and the stop-signal task (action cancellation) (Sebastian et al., 2013a).

With respect to neural correlates, inhibitory control is thought to involve a network of regions including the right inferior frontal cortex, the DLPFC, the medial PFC including the supplementary motor area and the pre-supplementary motor area, the left parietal lobe, and the basal ganglia (Aron, 2011; Chambers et al., 2009; Nee et al., 2007; Sebastian et al., 2013b).  However, cortical regions appear to be differentially activated depending upon the components of inhibitory control under study (Sebastian et al., 2013a; 2013b).  For example, imaging studies suggest interference inhibition relies more heavily on fronto-parietal-pre-motor regions, whereas action cancellation relies more heavily on fronto-striatal regions (Sebastian et al., 2013b).  While both the inferior frontal cortex and the medial PFC appear to play a key role in response inhibition, it is likely that they make functionally separate contributions; it has been proposed that inferior frontal cortex is involved in restraining an inappropriate response during response execution, whereas the medial PFC is involved in response selection by switching from inappropriate to appropriate response sets (Nee et al., 2007; Sebastian et al., 2013b).

Whether sex differences exist in the various components of inhibitory control remains unclear.  It is possible there are differences among the different subtypes of response

inhibition. In terms of action withholding tasks, females in one study were found to be better at inhibiting a response than males on a go/no-go-like task (Hansen, 2011), but sex differences have not been found in many other studies (Cross et al., 2011; Garavan et al., 2006; Liu et al., 2012). For tasks that involve interference, sex differences have not been found with the Stroop paradigm (Cross et al., 2011; MacLeod, 1991; Veroude et al., 2013; but see Van der Elst et al., 2006), but a male advantage has been reported on a novel task that involved inhibiting responses to obvious stimuli in favor of less obvious stimuli (Halari & Kumari, 2005; Halari et al., 2005). Two studies using the Flanker task found that males were faster and less error-prone than females (Clayson et al., 2011; Stoet, 2010). One additional study using a Simon task found no evidence of behavioural sex differences, but did find differences in brain activation with females showing increased left prefrontal and temporal activation and with males showing increased right inferior prefrontal and parietal activation (Christakou et al., 2009b). Behavioural sex differences have not been found in adult samples on action cancellation tasks such as the stop-signal (Cross et al., 2011; Li et al., 2006; 2009; Rubia et al., 2013; Williams et al., 1999; Yu et al., 2012), though a report by Rubia and colleagues (2013) showed that brain activation during task performance may differ between the sexes with females showing increased left prefrontal activation and males showing increased right inferior parietal activation on a stop-signal task. Since alternate routes can exist to the same behavioural outcome, sex differences in brain activation do not necessarily signify that any sex difference will be present at the behavioural level.

*1.3.7 Sex steroid levels predict performance on PFC-dependent cognitive tasks*

Clearer support for the possibility of sex differences in function has come from recent reports in which variation in sex steroid levels has been discovered to correlate with variation in performance on PFC-dependent tasks. Specifically, reports are beginning to appear suggesting that tasks known to depend on the PFC are influenced by estrogen and androgen levels, implying activational effects may be present. Postmenopausal women taking estrogens performed better on working memory tasks that had an active manipulation component than postmenopausal women not on hormone replacement therapy (Duff & Hampson, 2000; Krug et al., 2006). Young women having ovarian function suppressed through treatment with an inhibitor of gonadotropin releasing hormone had worse performance on an *n*-back task of working memory compared to not receiving treatment and

to controls (Grigorova et al., 2006). Treatment suppressed estradiol to the postmenopausal range. Studies comparing young women at different points during the menstrual cycle indicate that working memory performance is optimal when estradiol is higher compared to menses when estradiol is low (Hampson & Moffat, 2004; Hampson & Morley, 2013).

Regarding reinforcement learning, androgen levels may be correlated with performance, although existing studies are few. A study that manipulated testosterone levels by administering testosterone to healthy females in a double-blind placebo-controlled crossover design found that IGT performance was impaired after testosterone compared to placebo (van Honk et al., 2004; but see Goudriaan et al., 2010), and two studies have now suggested that IGT performance may be inversely related to testosterone levels in young males and females (Reavis & Overman, 2001; Stanton et al., 2011). It has been proposed that a link between current testosterone levels and IGT performance could reflect a link between risk-taking and testosterone (Stanton et al., 2011). To date, no studies have examined the relationship between testosterone and reversal learning in humans, but early work in rhesus monkeys by Clark and Goldman-Rakic (1989) indicates that testosterone may be important to the development of the OFC and to the cognitive functions that rely on it. In this study, male monkeys outperformed female monkeys on an object reversal task. The sex difference disappeared by 18 months of age (Goldman et al., 1974). Female monkeys who received injections of testosterone propionate were similar to males in their performance indicating that exposure to testosterone during the prenatal or early postnatal period may cause the OFC to mature faster in males than in females (Clark & Goldman-Rakic, 1989).

A few studies have examined the influence of sex steroids on inhibitory control, but the findings have been inconsistent. No effect of menstrual cycle phase on the go/no-go task was found by Amin and colleagues (2006) or Bannbers and colleagues (2012), but effects on stop-signal reaction times (Colzato et al., 2010) and the Stroop interference task (Hatta & Nagaya, 2009) were seen in two separate studies. In older populations, higher estradiol levels have been associated with less interference on the Stroop task in females (Wolf & Kirschbaum, 2002) and higher testosterone has been associated with more interference on the Flanker task in males (Van Strien et al., 2009). Halari and colleagues (2005) found no significant correlations between performance on a task that involved inhibiting responses to

obvious stimuli and either estradiol or testosterone measures in young adult males and females.

## 1.4  OBJECTIVES OF THE CURRENT THESIS

To date, there is some evidence that the PFC is sexually differentiated at a physiological level based on the findings that estrogens and androgens and their receptors are present in the PFC, can alter neuronal structure in the PFC, and can modulate various neurotransmitter systems within the PFC.  In addition, in intermittent reports, performance on tasks that depend upon the PFC (like working memory, reinforcement learning, and inhibitory control) has been shown to correlate with levels of estrogens and androgens.  Thus, it may be the case that certain *cognitive* functions known to depend on the PFC are sexually differentiated in humans and are affected by sex steroid levels.  As many cognitive functions potentially rely on the PFC, it is not yet known which may be sexually differentiated.  PFC-dependent functions that are potential candidates for exhibiting sex differences based on past literature are the active control processes of working memory, reversal learning in its purest form, and interference-related inhibitory control.

Currently, there is a small body of evidence suggesting a female advantage might exist on working memory tasks with PFC-dependent control components and a male advantage may exist on tasks emphasizing reinforcement learning like the IGT, but sex differences on cognitive tasks dependent on the PFC have not been systematically investigated.  Existing findings are few and far from conclusive, particularly in light of methodological issues that complicate interpretation.  For example, a female advantage in working memory has been claimed, but evidence to date is based primarily on newly developed tasks whose anatomical basis is not well established.  No study to date has found a male advantage in reversal learning in an adult sample, leaving open the possibility that the sex difference seen by Overman and colleagues (1996) in children may be nothing more than a transient developmental phenomenon.  Thus, the objective of Study 1 in the present thesis was to investigate whether there are sex differences on classic working memory tasks with support from patient and imaging work for their anatomical basis and that involve active control processes like monitoring and updating, and to investigate whether there are sex differences

on reinforcement learning tasks that involve decision making and reversal learning that are optimized for healthy adult participants.

In addition, given that androgens are known to have early organizing effects that predict later expression of adult sex differences in the brain and behaviour (Lombardo et al., 2012), the association between developmental and current androgen levels and decision-making as assessed by the IGT was investigated in Study 2. Preliminary evidence suggests that performance on the IGT may correlate with testosterone levels in adults, but it is not known whether this signifies an activational effect of the hormone, whether organizational effects of androgens also could be important, or whether the function that mediates any association with testosterone is risk-taking as some have suggested. The objective of Study 2 was to begin to tease apart these associations.

Finally, PFC-dependent tasks tend to be complex in nature, making it difficult to pinpoint the exact function that underlies observed sex differences in behaviour. If a sex difference exists on a complex task, more basic tasks can be useful to further elucidate the cognitive functions that are important. Some of the shared task components that could underlie a male advantage on the IGT or reversal learning include inhibitory control, the ability to flexibly reverse an established behavioral pattern, and/or sensitivity to reward/punishment. Therefore, in Study 3 of the current thesis the performance of males and females was examined on tasks specifically designed to assess inhibitory control, reversal learning, and learning based on reward and/or punishment in an effort to understand the sex differences in performance at a simpler functional level.

Together these studies will test the hypothesis that certain cognitive functions dependent upon the PFC are sexually differentiated, are influenced by both organizational and activational effects of androgens, and will attempt to provide further insight into the latent task components that are important for eliciting the observed sex differences in behaviour. Collectively, this work will advance our knowledge of the sexual differentiation and hormonal modulation of the cognitive functions dependent on the PFC, which has potential implications for basic research design/interpretation and clinical assessment.

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**CHAPTER 2**

**SEX DIFFERENCES ON PREFRONTALLY-DEPENDENT COGNITIVE TASKS**

Kelly L. Evans and Elizabeth Hampson

## 2.1 ABSTRACT

Preliminary evidence suggests the prefrontal cortex (PFC) may be modulated by sex steroids in humans and other primates.  Estrogen receptors have been found in the dorsolateral prefrontal cortex and androgen receptors in the orbitofrontal cortex, among other regions. The objective of the current study was to examine whether there are discernible sex differences in humans on classic working memory tasks that emphasize active control processes like monitoring and updating, and/or on tasks that involve decision-making and reversal learning (processes known to engage the ventromedial PFC/orbitofrontal cortex; VMPFC/OFC).  Healthy, young adults (48 females; 45 males) completed the *n*-back, Self-Ordered Pointing (SOP), the Iowa Gambling Task (IGT), and a probabilistic reversal learning task.  The sexes were matched in general intelligence.  As predicted, males selected fewer cards from the disadvantageous decks than females on the IGT.  On the reversal learning task, there was no significant sex difference in acquisition of the reinforcement contingencies, but males made fewer errors than females during the reversal phase. However, contrary to prediction, the sexes did not differ on the *n*-back task or SOP.  These findings provide tentative support for the hypothesis that functions carried out by the VMPFC/OFC are sexually differentiated in humans.

**Key words:**    sex difference, decision-making, reversal learning, working memory, prefrontal cortex

## 2.2 INTRODUCTION

The prefrontal cortex (PFC) plays an important role in cognitive processes involved in working memory, cognitive flexibility, and decision-making.  Over the past three decades, a significant body of work has been devoted to understanding the diverse functions of the PFC, while over the same period, advances have been made in our understanding of sex steroids and their sites of action in the central nervous system (CNS).  Growing evidence suggests that these sites might include the PFC.  In spite of a potential to be mutually informative, there has been remarkably little cross-talk between these two disciplines.  The purpose of the present study was to open a dialogue by exploring whether four neuropsychological tasks widely used to study the PFC in clinical or experimental settings--the *n*-back task, self-ordered pointing, probabilistic reversal learning, and the Iowa Gambling Task--exhibit evidence of sexual differentiation at the behavioural level.

### 2.2.1  Role of the PFC in Working Memory and Reversal Learning

Working memory can be defined as holding information "in mind" temporarily with the possibility of using that information to guide behavior in the absence of external cues (Goldman-Rakic, 1987; 1993).  The working memory system includes passive storage processes that depend upon posterior perisylvian regions (e.g., D'Esposito and Postle, 1999; Paulesu et al., 1993; Postle et al., 1999; Wager and Smith, 2003), but the PFC is required for a number of executive processes that can be performed on the contents of working memory (D'Esposito et al., 2006).  It has been shown that the dorsolateral PFC (DLPFC) (e.g., Funahashi et al., 1993; Goldman-Rakic, 1987; Owen et al., 1999) and ventrolateral PFC (e.g., Awh et al., 1996; Postle et al., 1999; Owen et al., 1999; 2005) are involved in the active maintenance of items in working memory, as well as, for DLPFC, the manipulation of items in short-term store (e.g., D'Esposito et al., 1999; Postle et al., 1999; 2006; Owen et al., 1999).  In addition, monitoring, updating, the use of mnemonic strategies, temporal ordering and selection among the contents of working memory are functions that have been attributed to dorsolateral cortex (e.g., Champod and Petrides, 2010; Chase et al., 2008; Owen et al., 2005; Provost et al., 2010; Rowe et al., 2000; Wager and Smith, 2003).  It remains unclear whether different executive processes are anatomically segregated within the PFC (the operation-segregation model; D'Esposito et al., 1999; Owen et al., 1999), or whether, alternatively, the

lateral cortex is characterized by domain-specificity in which there are separate systems for different informational domains (e.g., object, spatial) (e.g., Goldman-Rakic, 1995; Levy and Goldman-Rakic, 1999; 2000).  According to the domain-specificity model, the DLPFC is more important for spatial working memory, whereas the region just ventral to it (inferior convexity) mediates working memory for objects (e.g., McCarthy et al., 1994; Wilson et al., 1993).

Whereas the lateral convexity has been implicated in processes that support working memory function, the ventromedial PFC/orbitofrontal cortex (VMPFC/OFC) has been implicated in processes important for reversal learning and decision-making.  Decision-making involves weighing information about value to select the most appropriate response option (Greening et al., 2011) and, like working memory, involves multiple component processes (Fellows, 2007; Weller et al., 2009) that include response inhibition, affective shifting, value assessment and, depending on the decision context, reversal learning (Fellows and Farah, 2003; 2005; 2007).  To the extent that decision-making requires the on-line maintenance of task relevant information, activation in DLPFC (or in ventrolateral PFC) can be observed during some types of decision-making tasks (Ernst et al., 2002), but ventromedial/orbitofrontal regions are also recruited and are thought to subserve other processes.  A classic task for assessing decision-making in humans is the IGT.  The Iowa Gambling Task (IGT; Bechara et al., 1994) is a widely used task in both clinical and laboratory settings and simulates real-life decision-making (Lawrence et al., 2009).  Based on imaging and patient studies, decision-making as measured by the IGT recruits several regions of the cortex, but activity in the VMPFC/OFC (defined as the ventral region of the medial PFC and the medial orbitofrontal cortex; Fellows, 2007) and the DLPFC are most reliably predictive of advantageous performance (e.g., Bechara et al., 1994; 1998; Christakou et al., 2009; Lawrence et al., 2009).  Work is ongoing to further understand the functional role of the different brain areas, but to date, it appears that the VMPFC/OFC is particularly important in reversal learning and value assessment (Fellows and Farah, 2003; 2005; 2007) while the DLPFC likely plays a role in the working memory processes required to sustain IGT performance (Bechara et al., 1998).

Consistent with its hypothesized importance in reversal learning, patients with lesions of the VMPFC/OFC are impaired on simple reversal tasks (Fellows and Farah, 2003; 2005) as well as probabilistic reversal learning tasks (e.g., Berlin et al., 2004; Hornak et al., 2004).

Neuroimaging studies in healthy subjects have revealed activation in the VMPFC/OFC, the ventrolateral PFC, DLPFC, and dorsomedial PFC during reversal learning (e.g., Budhani et al., 2007; Cools et al., 2002; Greening et al., 2011; Hampshire et al., 2012; O'Doherty et al., 2003). The ventrolateral PFC may help guide responding by shifting representations of motor responses or object features (Mitchell et al., 2008) or by modulating relationships between stimuli and response when the current response is no longer optimal or a pre-potent response must be inhibited (Mitchell, 2011). The dorsolateral and dorsomedial PFC may be involved with resolving decision conflict through attention (Mitchell, 2011). However, the key region that may be most critical for the actual reversal of a response is the VMPFC/OFC, ostensibly through its role in detecting contingency change through prediction error signaling (Budhani et al., 2007; Hampshire et al., 2012; Mitchell, 2011; O`Doherty et al., 2003). This brain region shows the clearest link with reversal learning based on lesion data (Greening et al., 2011). Both human and non-human primates with lesions of the VMPFC/OFC are impaired on a variety of reversal learning tasks (e.g., Berlin et al., 2004; Dias et al., 1996; Fellows and Farah, 2003; 2005; Hornak et al., 2004; Rygula et al., 2010; Tsuchida et al., 2010). The VMPFC/OFC may keep track of the relative value of stimuli, be involved in re-evaluating contingencies, and flexibly guide behaviour when expectancies are violated by connecting a trial with a specific outcome (e.g., Fellows and Farah, 2007; Hampshire et al., 2012; Plassmann et al., 2010; Tsuchida et al., 2010).

*2.2.2 Sex Steroids and the PFC*

Over the past few decades, animal studies have identified two broad classes of steroid action in the CNS (see Arnold, 2009; Breedlove and Hampson, 2002). *Organizational effects* are permanent effects on brain morphology, which are induced by exposure to androgens or their metabolites during critical periods in prenatal or perinatal development. In contrast, *activational effects* are reversible effects, often changes in neurochemistry, that are induced by the levels of hormones temporarily present in the adult bloodstream. Both classes of effects have implications at the functional level, and either type of effect acting alone, or both in combination, can lead to functional sex differences.

Growing evidence suggests that the PFC, in particular, is susceptible to modulation by sex steroids. Steroids exert direct effects in regions of the brain that contain the requisite

receptors. Therefore it is significant that the estrogen receptor subtypes ERα and ERβ are found in the cerebral cortex, including the PFC, of the rat (Shughrue et al., 1997;1998), rhesus monkey (Pau et al., 1998; Wang et al., 2004; 2010) and tentatively, in the DLPFC of humans (Perlman et al., 2005), although the distribution of these receptors in humans is not yet well-mapped. These observations are supported by post-mortem studies that reveal high accumulations of estrogen in the adult human PFC (Bixo et al., 1995), and the presence of estrogen-metabolizing enzymes in frontal cortex (Platia et al., 1984).

Whether the PFC is also a potential target for androgens in the human brain remains to be seen, but androgen receptor-immunoreactivity has been identified in dorsolateral and orbitofrontal PFC in adult rhesus monkeys (Finley and Kritzer, 1999). Testosterone may increase spine synapse density in the PFC, as gonadally intact male vervet monkeys had 70% higher spine density in the PFC than castrated males. In female monkeys, treatment with either estradiol (Hao et al., 2007; Tang et al., 2004) or testosterone (Hajszan et al., 2008) increases spine density in the PFC following ovariectomy. In favor of a functional role in the PFC, androgens and estradiol ($E_2$, the dominant form of estrogen in females of reproductive age) modulate activity in several neurotransmitter systems within the PFC (Aubele and Kritzer, 2011; Bethea et al., 2002; Handa et al., 1997; Inagaki et al., 2010; Kritzer and Kohama, 1998; 1999; Sumner and Fink, 1995; Tinkler et al., 2004) including the dopaminergic and serotonergic systems, which are believed to play a key role in working memory, reversal learning, and decision-making (e.g., Calaminus and Hauber, 2008; Cools and D'Esposito, 2011; Ha et al., 2009; Krugel et al., 2009; Mehta et al., 2001; Rogers, 2011; Watanabe et al., 1997).

Because anatomical sex differences are typically due to actions of androgens during pre- or perinatal development and often serve as a marker for brain areas that retain responsiveness to steroids in adulthood, evidence indicating anatomical differences between males and females in the PFC supports the idea that sex steroids are active in this region. Anatomical sex differences in the human PFC have been reported by a number of studies. Relative to total brain volume, women have larger gray matter volume in DLPFC compared to men (Goldstein et al., 2001; Lunders et al., 2009; Schlaepfer et al., 1995). Conversely, there is evidence that men have larger cortical volume in certain regions of VMPFC/OFC, notably Brodmann's areas (BA) 11 and 12 (Goldstein et al., 2001; 2002; but see Welborn et al.,

2009), though data are mixed (Gur et al., 2002; Raine et al., 2011; Wood et al., 2008) and may vary with age of subjects; one study reported a larger, regionally-specific decrease in volume of the medial OFC in males over the age of 50 compared to females (Cowell et al., 2007). In rhesus monkeys, the VMPFC/OFC develops at a faster rate in male than female infants (Goldman et al., 1974), a developmental difference that has been empirically related to testosterone exposure (Clark and Goldman-Rakic, 1989). Anatomical differences between the sexes must be interpreted with caution, however, as sex differences in the packing density of neurons do exist in some cortical areas (Witelson et al., 1995), complicating the interpretation of gross volumetric differences.

Over the past 10 years, a few behavioural reports have begun to suggest that certain cognitive functions dependent on the PFC may differ between the sexes. A female advantage in time to completion and accuracy on a spatial working memory task that heavily emphasizes executive processes like monitoring and updating (Duff and Hampson, 2001; Lejbak et al., 2009) has been reported, but no sex difference has been found on span tasks (Duff and Hampson, 2001; Farrell Pagulayan et al., 2006; Robert and Savioe, 2006) which do not recruit the PFC, but instead involve posterior regions of cortex (e.g., D'Esposito and Postle, 1999; Wager and Smith, 2003). Although it is not yet clear under what conditions a female advantage is seen, additional support for a sex difference in working memory comes from two studies, one in children (Vuontela et al., 2003) and one in adults (Speck et al., 2000), which found females performed more accurately than males on the *n*-back task. These *n*-back studies have yet to be confirmed. Sex differences in brain activation have also been reported during the *n*-back task (Li et al., 2010; Speck et al., 2000), but are not supported by all *n*-back studies (Schmidt et al., 2009).

In contrast, several studies using the IGT, a measure of decision making that invokes the VMPFC/OFC, have shown a sex difference in the opposite direction. Males tend to choose more cards from the advantageous decks than females leading to a sex difference in performance that is evident in the later stages of the task (e.g., Bolla et al., 2004; Overman et al., 2006; 2011; Reavis and Overman, 2001; Weller et al., 2009). Sex differences in activation of the OFC during IGT performance have also been reported (Bolla et al., 2004; Rogalsky et al., 2012), although confirmation of these differences is needed. The effects of lateralized lesions of the VMPFC/OFC on IGT performance also may differ between males

and females (Tranel et al., 2005). It is not clear whether sex differences observed in the imaging and patient studies reflect differences in brain organization or only the use of different cognitive strategies to solve the task.

Only two studies have examined behavioural sex differences in reversal learning which, like the IGT, strongly recruits the VMPFC/OFC. Overman and colleagues (1996) found a male advantage on an object reversal task in young children (15 to 30 months of age) similar to what has been found in infant monkeys (Clark and Goldman-Rakic, 1989), but adult men and women did not differ on the same task. A later study using a more complex task found no evidence of a sex difference in probabilistic reversal learning in either children or adults (Overman, 2004).

In support of the idea that the PFC is sexually differentiated a few studies have begun to suggest that cognitive functions dependent on the PFC are influenced by levels of circulating sex steroids. While it does not demonstrate the presence of a sex difference directly, responsivity to sex steroids would imply a resultant sex difference. Reavis and Overman (2001) observed that young men with lower blood testosterone performed better on the IGT than did men with higher testosterone levels. The same relationship was seen by van Honk and colleagues (2004) in women who were given an exogenous injection of testosterone. Reversal learning too may be influenced by androgens, although the one study that currently exists suggests an organizational not activational effect: the sex difference observed in object reversal learning in infant monkeys was eliminated by treating females with testosterone propionate during the perinatal period (Clark and Goldman-Rakic, 1989). With respect to estrogens, improved performance on measures of verbal and spatial working memory has been observed in postmenopausal women receiving estrogen treatment (Duff and Hampson, 2000; Krug et al., 2006) and in young women with healthy menstrual cycles, in whom circulating estradiol levels were negatively correlated with errors on a spatial working memory task (Hampson and Morley, 2013). Conversely, young women treated with a drug that inhibited gonadotropin releasing hormone production, causing ovarian function to be suppressed, showed poorer performance on the *n*-back task compared to pre-treatment and compared with controls (Grigorova et al., 2006). Thus, emerging evidence supports the idea that circulating sex steroids may influence cognitive functions governed by the PFC.

*2.2.3 Present Study*

Although the data available are still limited, a growing body of physiological, anatomical, imaging, and hormonal evidence supports the hypothesis that the PFC is a sexually differentiated cortical region. The objective of the current study was to further explore the idea that the PFC is sexually differentiated by comparing the performance of the two sexes on cognitive tasks known to preferentially recruit different regions of the PFC. It was hypothesized that women would outperform men on working memory tasks that emphasize lateral PFC-dependent executive processes like monitoring and updating. This hypothesis was based on reports that higher levels of circulating estrogens favorably impact working memory performance in women. On the other hand, based on findings by Overman showing a male advantage on the IGT (Overman et al., 2006; Reavis and Overman, 2001) it was hypothesized that men would outperform women on the IGT and potentially other tasks that heavily depend on the VMPFC/OFC, such as reversal learning (Budhani et al., 2007; Hornak et al., 2004; O'Doherty et al., 2003). Empirical support for these hypotheses would indicate that there is regional specificity within the PFC, and that the PFC is not homogeneous with respect to sex differences at the functional level.

**2.3  METHOD**

*2.3.1  Participants*

Healthy young adults ages 17-35 were recruited from the University of Western Ontario and received monetary compensation or course credits for their participation. Because both head injury and major depression can adversely affect working memory and because use of hormonal medications could potentially impact sex differences generated by endogenous sex steroids, participants were only included if they reported no history of a head injury or other neurological disorder, if they had no previously diagnosed mental health condition or evidence of active depression on the Profile of Mood States (McNair et al., 1971), and if they did not use hormonal medication including oral contraceptives. As several of our tasks involved fairly complex verbal instructions and adequate comprehension was necessary to ensure the validity of the resulting test scores, participants whose second language was English were included only if they met an established criterion on a basic English vocabulary task given during the test session (i.e., a score no lower than one standard deviation below

the typical mean on the Verbal Meaning Test (Thurstone and Thurstone, 1963). Twenty-three participants could not meet the language criterion and were not included in statistical analyses. The total number of participants in the final sample was 93 (45 males, 48 females). The male ($M = 19.69$, range = 17-28 years) and female ($M = 19.54$, range = 17-32 years) groups were matched on age. All participants gave written informed consent. The study received ethical approval from the Non-Medical Research Ethics Board at the University of Western Ontario (see Appendix A).

*2.3.2 Materials*

*2.3.2.1 Working memory.*

To investigate whether there is a sex difference in working memory performance, we chose well-established working memory tasks whose anatomical basis has been supported by both imaging and patient research (Self-Ordered Pointing and the *n*-back task; e.g., Braver et al., 1997; Cohen et al., 1997; Petrides and Milner, 1982).

     *2.3.2.1.1 Self-Ordered Pointing (SOP; adapted from Petrides and Milner, 1982).* SOP is a well-validated measure of working memory (e.g., Bryan and Luszcz, 2001; Petrides and Milner, 1982; Ross et al., 2007), which is impaired in neurological patients who have frontal lobe lesions (Petrides and Milner, 1982) and increases activation in the dorsolateral PFC of healthy volunteers in imaging studies (Curtis et al., 2000; Petrides et al., 1993).

The version used for the current study was non-computerized and modified from the original by adding an additional set size of 14 to ensure the task was sufficiently difficult for a young, healthy population, in order to avoid floor effects. All set sizes, excluding the practice set, made use of stimuli that were easily visually differentiated, but abstract (e.g., abstract art, quilt patterns) to discourage the use of verbal strategies. Following instructions, the participant was given a practice set of 4 items to ensure the task was understood. They then proceeded to the test, which involved set sizes of 6, 8, 10, 12, and 14 items (three trials at each set size).

Each set consisted of a stack of cards with images arranged in a two-column format (Figure 2.1). Within each set the same images were shown on each card, but in a different spatial

**Page 1**

Image 1 | Image 2
Image 3 | Image 4
Image 5 | Image 6

**Page 2**

Image 6 | Image 5
Image 4 | Image 1
Image 2 | Image 3

**Page 3**

Image 3 | Image 6
Image 2 | Image 5
Image 1 | Image 4

**Page 4**

Image 5 | Image 3
Image 2 | Image 1
Image 6 | Image 4

**Page 5**

Image 2 | Image 1
Image 6 | Image 3
Image 4 | Image 5

**Page 6**

Image 5 | Image 6
Image 1 | Image 3
Image 4 | Image 2
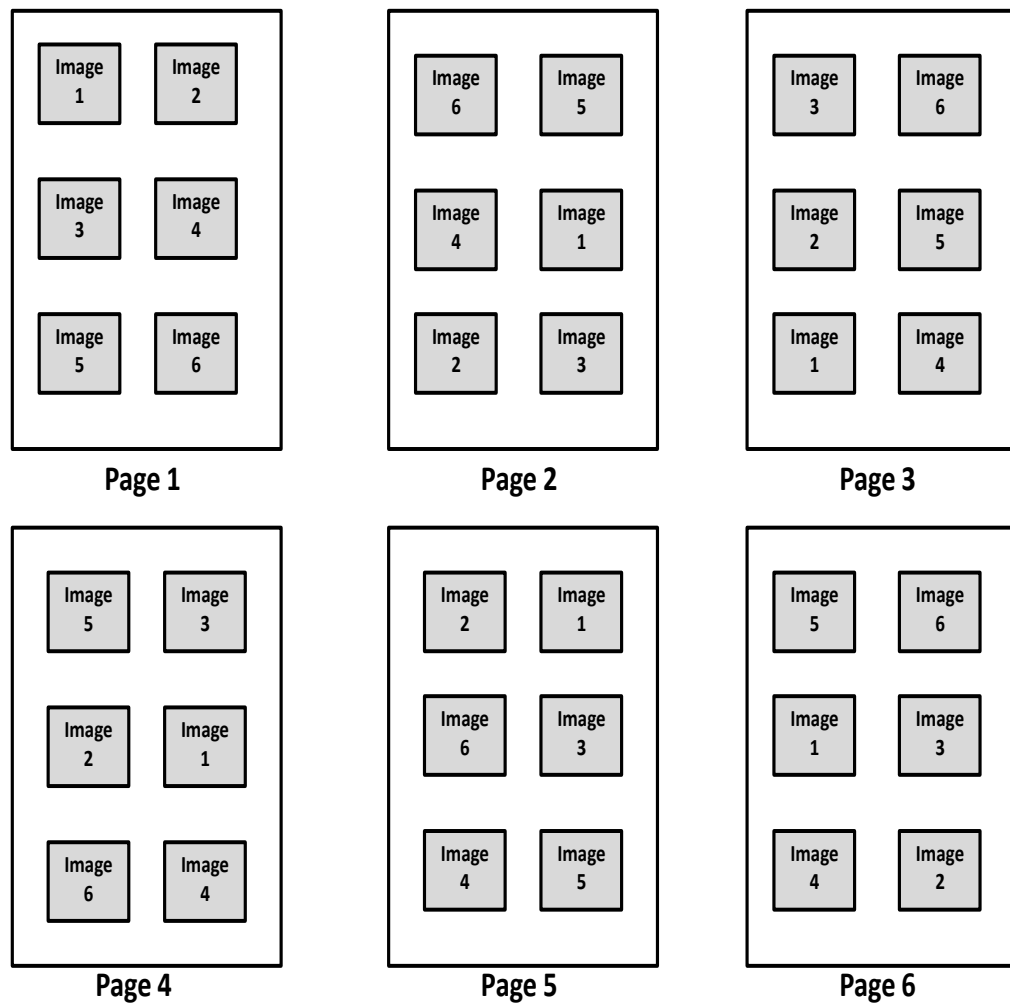
**FIGURE 2.1.** An example of a six item trial from Self-Ordered Pointing. The same set of images appeared on each of the six pages (cards), but the spatial location of each image varied randomly from card to card. One page (card) was shown at a time. Participants pointed to one image on each card, so that by the end of a trial, each image had been pointed to once and only once. To achieve this goal, participants had to keep a mental record of the images they pointed to (not the spatial locations) and continually update this record within working memory.

arrangement. At the beginning of each new set size, the participant was given 20-60 s (depending on the size of the set) to become acquainted with the stimuli to be used. The participant was then to go through the stack, pointing to one item on each card, so that by the end of a trial, each item had been pointed to once, and only once. To perform accurately, participants thus had to maintain and update a record of their responses in working memory as the task progressed.

A working memory error was committed when a participant pointed to the same item more than once within a trial. For each set size, the total number of working memory errors committed (summed across the three trials) and time to completion (in seconds) was recorded.

*2.3.2.1.2 The N-Back Task (Cohen et al., 1997; Gevins and Cutillo, 1993).* The *n*-back task requires a participant to monitor a series of letters presented one at a time on a computer screen and to press a button whenever the current letter matches the letter presented *n* trials back (Figure 2.2). Working memory is required in order to monitor and continually update an ongoing mental record of the stimuli presented (e.g., Bledowski et al., 2010; Owen et al., 2005).

The stimuli consisted of 15 white letters (both upper and lower case and non-phonetically similar) shown in 150 point font on a black background, at an exposure time of 1000 ms and an inter-trial interval of 700 ms. Stimuli were presented using E-Prime 2.0 software. There were 100 stimuli in each condition. Participants completed three conditions: 0-Back, 2-Back, and 3-Back. Thirty-three of the letters were targets in each condition. There was a pre-specified target in the 0-back condition (the letter *x*). The 0-back condition which required no manipulation of information served as a control for attention and other performance-related factors, whereas the 2- and 3-back conditions made strong demands on the executive processes of working memory. Participants responded on each trial, by pressing one of two buttons on a response pad to register matches and non-matches.

As in previous work (Kane et al., 2007; Karatekin et al., 2009; Tsuchida and Fellows, 2008), signal detection theory was used to generate measures of sensitivity ($d_L'$) and bias ($c_L$) for each condition. The number of hits, correct rejections, misses, and false alarms were calculated for each participant. Sensitivity and bias measures were then calculated using the
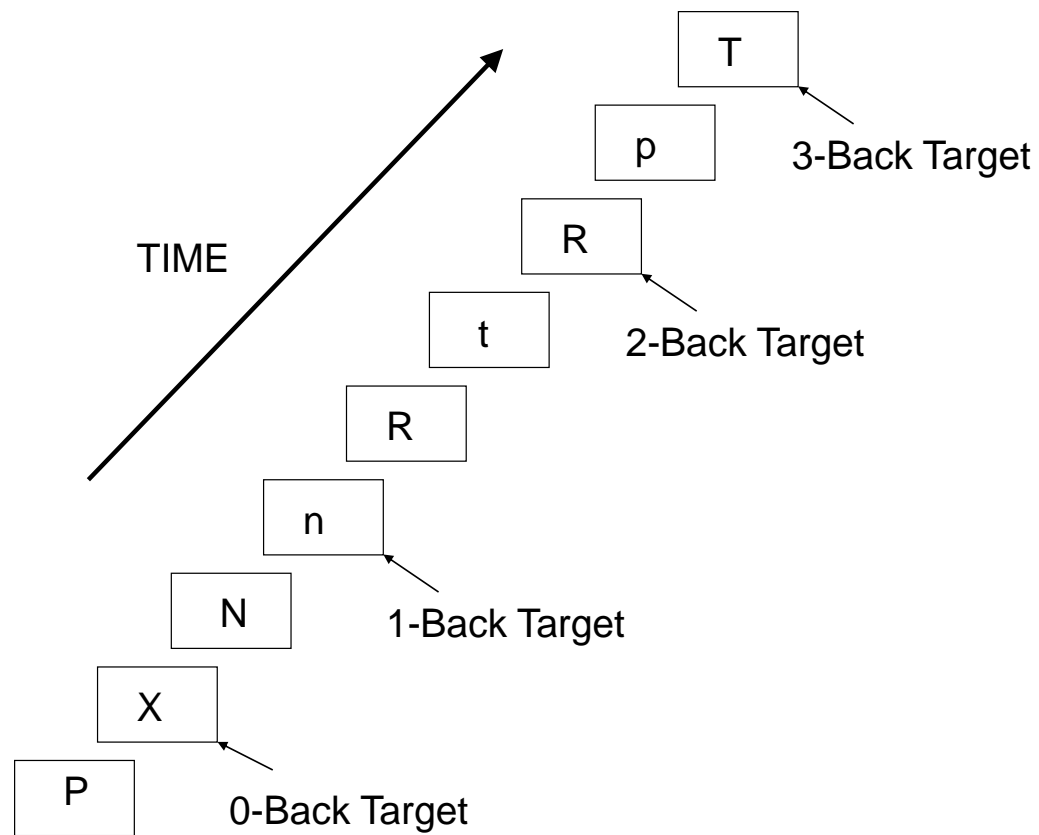
**FIGURE 2.2.** In the *n*-back task, a series of letters was presented one at a time and the participant had to monitor the series for targets. Targets were letters that matched a letter presented *n*-trials back. The 0-back target was the letter "x". Adapted from Cohen et al. (1997).

formulae from Kane and colleagues (2007), with .01 adjustments made for hit rates and false alarm rates equal to 0 or 1. Logistic distributions were used rather than normal distributions as the results obtained are the same, but calculations are simplified with logistic distributions (Snodgrass and Corwin, 1988). Sensitivity provided a measure of the participant's ability to distinguish targets from non-targets. The maximum score for $d_L'$ was 12.33 which represented error free performance, whereas a score of 0 represented chance performance. Bias ($c_L$) provided a measure of the participant's tendency to respond that a target was present. Lower scores for $c_L$ represent a more liberal strategy (responding that the target was present) and higher scores represent a more conservative strategy (responding that the target was absent). This measure of bias was chosen over other commonly used measures like β as $c_L$ is independent of changes in $d_L'$ (Snodgrass and Corwin, 1988).

The *n*-back task reliably increases activation in the DLPFC in healthy volunteers, as judged from imaging studies (e.g., Braver et al., 1997; Cohen et al., 1997; Owen et al., 1998; 2005).

### 2.3.2.2 Decision-making and reversal learning.

*2.3.2.2.1 Iowa Gambling Task (Bechara et al., 1994).* The IGT is a computer-administered task used to assess the ability to utilize feedback to guide decision-making. It involves choosing "cards" one at a time from four virtual decks of cards shown on the computer screen. The version of the IGT used in the current study was from the Psychology Experiment Building Language Battery (Mueller, 2009) and is identical the task originally developed by Bechara et al. (1994) except that the top card moves to the bottom of the deck on each draw. Choosing a card is associated with a win and/or a loss, paid in virtual money which is tallied on the computer screen. Participants are instructed to try to maximize their total winnings over the 100 card choices that comprise the task.

Participants learn the payoffs associated with each deck through experience, and are not explicitly told the payoffs. In the present study, choosing a card from one deck paid $100, but led to losing money over time (-$250/10 trials) due to many medium sized ($150-350) losses (reward to punishment ratio is 10:5). Choosing a card from a second deck also paid $100, but led to losing money over time ($250/10 trials) due to an infrequent, large ($1250) loss (reward to punishment ratio is 10:1). These two decks were considered the "bad" decks because they led to losses. On the other hand, the other two decks were considered "good"

decks because they led to a net gain over time (+ $250/10 trials) even though they both paid only $50 per card selection. The two good decks differed from each other in their punishment magnitude and frequency, as summarized in Table 2.1. Participants usually begin the IGT by selecting from the "bad" decks because the immediate reward payout is higher but with experience, healthy subjects gradually reverse this initial tendency and select from the "good" decks, which have a larger payoff over the long run (Bechara et al., 1994). Four versions of the task were programmed so as to counterbalance the physical location of the decks on the screen.

As in previous reports (Bechara et al., 2000), the 100 trials of the IGT were broken down into 5 blocks (20 trials/block) for purposes of statistical analysis. The number of cards selected from each deck was recorded on each block. The number of 'good' cards selected during the task as a whole and on each block was computed by totaling the cards selected from the good decks. Participants do not develop a complete understanding of the deck differences until approximately the 80$^{th}$ trial (Bechara et al., 1997) and previous studies have found a sex difference that emerges during the later blocks after this learning has occurred (Reavis and Overman, 2001). Thus, a sex difference was not expected until the late stages of the task.

As a supplementary method of scoring, we applied the Expectancy Valence Learning Model (Busemeyer and Stout, 2002), which has been used in some previous studies. This model yields 3 measures that afford a more refined way of interpreting any sex difference observed on the IGT. The *attention to losses* parameter (*w*) can range from 0 to 1. Values < 0.5 represent greater attention to losses than to gains on the part of a participant and values > 0.5 represent greater attention to gains than losses (Gullo and Stieger, 2011). The *recency* parameter (*a*) ranges from 0 to 1 and reflects the degree to which recent vs past information is attended to (Yechiam et al., 2005). Higher values indicate more attention to recent information (Gullo and Stieger, 2011). The *choice consistency* parameter (*c*) assesses the consistency with which a participant applies learned expectancies when making choices (Yechiam et al., 2005). Values of *c* range from -5 to +5 with positive scores indicating increasing consistency over the course of the task (reliance on expectancies from past outcomes) and negative scores indicating decreasing choice consistency over the task (perhaps due to non-attendance, boredom, or fatigue) (Gullo and Stieger, 2011). An index of model fit was also calculated using the $G^2$ statistic which is the log-likelihood difference of

**TABLE 2.1**

The Decks of the Iowa Gambling Task (IGT) Used in the Present Study

| Deck | Win/Loss Ratio | Net Payoff Per 10 trials | Reward Magnitude | Loss Magnitude |
|------|----------------|--------------------------|------------------|----------------|
| 1 | 10:5 | -$250 | +$100 | -$150 to -$350 |
| 2 | 10:1 | -$250 | +$100 | -$1250 |
| 3 | 10:5 | +$250 | +$50 | -$25 to -$75 |
| 4 | 10:1 | +$250 | +$50 | -$250 |

fit between the Expectancy Valence Model and a baseline model that assumes choices are independently and identically distributed across trials (Busemeyer and Stout, 2002). A positive value of $G^2$ indicates the Expectancy Valence Model outperforms the baseline model. All parameters were calculated in MATLAB (MathWorks Inc., 2007) using formulae and methods described in Busemeyer and Stout (2002).

Performance on the IGT robustly increases activation in the VMPFC of healthy volunteers in imaging studies (e.g., Christakou et al., 2009; Lawrence et al., 2009) and is impaired in neurological patients with lesions to the VMPFC (e.g., Bechara et al., 1994;1998; Fellows and Farah, 2005).

   *2.3.2.2.2 Probabilistic reversal learning (PRL).* We used a reversal learning task modeled after Budhani et al. (2007), created using E-Prime 2.0 (Figure 2.3). The task consisted of two conditions (each ~ 6 minutes in length, each employing 3 different pairs of objects). On each trial, the participant viewed a pair of common, neutrally-valenced objects on a computer screen (fruit or musical instruments, Snodgrass and Vanderwart, 1980) and selected one of the two objects by pressing a button. Depending on which object was selected, the participant won or lost 100 points. Each trial was 2 s in length (object was shown for 1100 ms and feedback was shown for 900 ms). Participants were not told which item in each pair was correct and had to learn this through trial and error. Participants were told that the correct object could change over the course of the task, but were not told when or if a reversal would take place. The feedback given was probabilistic. In the first condition, the reinforcement contingency was 90-10 (on 90% of trials correct feedback was given and on 10% incorrect feedback was given) and the reinforcement contingency was 80-20 for the second condition. After each selection, feedback was provided (a screen that said *You win 100 points* or *You lose 100 points*) and the participant's current points total was shown.

After 20 trials of each pair of stimuli, two of the pairs underwent reversal (i.e., the other object in the pair became the correct, rewarded selection). The third pair remained unchanged. A measure of accuracy was calculated for each contingency condition, with a separate accuracy score for the acquisition and reversal stages of the task. For the two reversing pairs, *acquisition accuracy* was the number correct in the 10 trials immediately
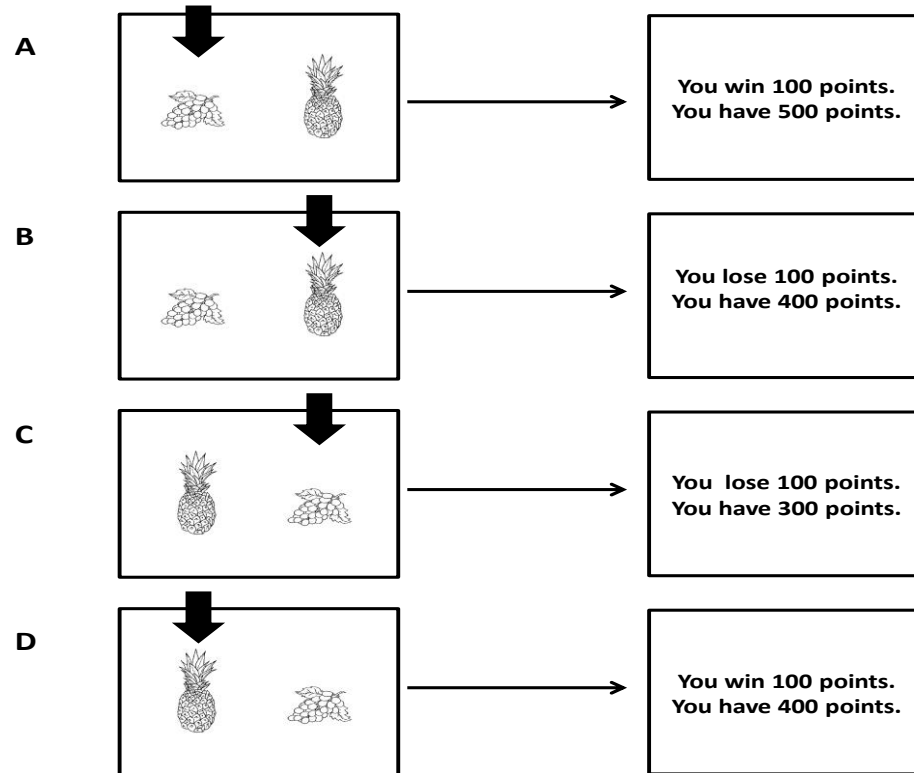
**FIGURE 2.3.** The Probabilistic Reversal Learning (PRL) Task. The vertical arrows represent the choices made by a hypothetical participant. In this example, grapes are the correct choice. Trial A represents a trial where a correct response was rewarded. Trial B represents a trial where an incorrect choice was punished. Due to the probabilistic nature of the feedback, incorrect feedback was given on 10% or 20% of trials. Trial C represents a trial where a correct choice was inappropriately punished. Trial D represents a trial where an incorrect choice was rewarded.

before reversal, and *reversal accuracy* was the number correct in the 10 trials immediately after the reversal for each pair, and represented the number of correct selections regardless of the feedback given[1].

Probabilistic reversal learning has been shown in imaging and lesion studies to recruit the VMPFC/OFC (e.g., Fellows and Farah, 2003; 2005; Hornak et al., 2004; O'Doherty et al., 2003).

*2.3.2.3  Control tasks.*

*2.3.2.3.1  Span Tasks.* Because a longer immediate span could conceivably confer an advantage on the SOP, independent of its executive demands, the digits forward task (Wechsler, 2008) and a nonverbal analog task ('image span') were administered to measure the capacity of immediate span.  Digits forward was given using standard procedures.  For image span, the examiner used a page from the 12-item set of the SOP, and tapped the images in progressively longer sequences in order to establish each participant's image span. The score on each task was the maximum number of digits recalled (or images tapped) in correct order.   Span tasks do not require the PFC but instead recruit posterior perisylvian cortex (e.g., D'Esposito and Postle, 1999; Wager and Smith, 2003).  Because executive processes like active maintenance are not required, a sex difference was not anticipated.

*2.3.2.3.2  Verbal Meaning Test (Thurstone and Thurstone, 1963).*  In order to confirm that the male and female groups were matched in overall ability, a standardized vocabulary test was administered.  Vocabulary tasks are predictive of general intelligence (Vernon, 1971; Wechsler, 2008; Ziegler and Doehrman, 1979).  The score was the number correct.

*2.3.2.3.3  California Weather Task (CWT; Knowlton et al., 1994).*  As a final control task, the CWT was used to assess the possibility that any sex difference found on the IGT

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[1]In ~3% of cases, a participant fixedly chose the same object from one pair throughout the acquisition and reversal phases of a particular contingency condition.  Such a pattern could artifactually generate a satisfactory-appearing score after reversal (e.g., all 10 trials correct after reversal), even though no reversal had in fact occurred.  To remedy this problem, we used a correction whereby their reversal score was calculated based on the actual (though incorrect) object selected during acquisition.  For example, a score of 9 (out of 10) correct after reversal that was based merely on repeatedly selecting the same incorrect object as during the acquisition phase, would be inverted to create a reversal accuracy score of 1.

and/or PRL might arise from understanding probabilities, an element that is intrinsic to both of these tasks.  The CWT requires decision-making based on probabilistic cues.  On each trial, participants were shown combinations of one, two or three cards (out of a total pool of 4 cards) on a computer screen and had to decide if the set of cards best predicted "sun" or "rain".  Participants were instructed to learn to predict the weather, by guessing whether each set of cards was associated with sun or rain.  Each card in fact predicted sun or rain with fixed probabilities (see Figure 2.4), which had to be learned implicitly over the course of the task.  The combination of cards displayed thus determined which weather outcome was correct on each trial.  Each card and each outcome (sun or rain) occurred equally often over the 70 trials.  Visual feedback (*correct* or *incorrect*) and auditory feedback (a high tone if correct or a low tone if incorrect) were given for 2 s after each response.  A response was correct if the participant selected the outcome that was in fact most associated with the set of cards displayed.  The dependent variable was the percentage of correct responses made over the whole task.  The version of the CWT created for the current study differed from the original by Knowlton and colleagues (1994) in that it required only 70 trials (versus 200 in the original) and by default used slightly higher cue probabilities (77% and 63% in the current study versus 76% and 58% in the original).

Performance of the CWT increases activation in the striatum (Poldrack et al., 2001) and is impaired in patients with Parkinson's Disease (Knowlton et al., 1996).  A previous study in healthy subjects by Reavis and Overman (2001) revealed no sex difference.  In the present study, the CWT was always given last as it is a demanding task that can influence performance on subsequent tasks (Reavis and Overman, 2001).

*2.3.3  Statistical Analyses*

All analyses were done using IBM SPSS 19.0 statistical software.  Mixed design ANOVAs were used to investigate the sex difference on all the experimental tasks.  The within-subjects factors included set size (6, 8, 10, 12, 14; Self-Ordered Pointing), condition (0, 2, 3; *n*-back), block (1-5; IGT), or reinforcement contingency (90-10, 80-20; Probabilistic Reversal Learning) and the between-subjects factor was sex (male, female).  The dependent variables were number of errors and time to completion (Self-Ordered Pointing), bias and sensitivity (*n*-back), number of cards selected (Good Decks and Decks 1-4) and Expectancy Valence

| | | | | |
|---|---|---|---|---|
| **A** | | | | |

| | | | | |
|---|---|---|---|---|
| **Rain** | **77%** | **63%** | **37%** | **23%** |
| **Sun** | **23%** | **37%** | **63%** | **77%** |
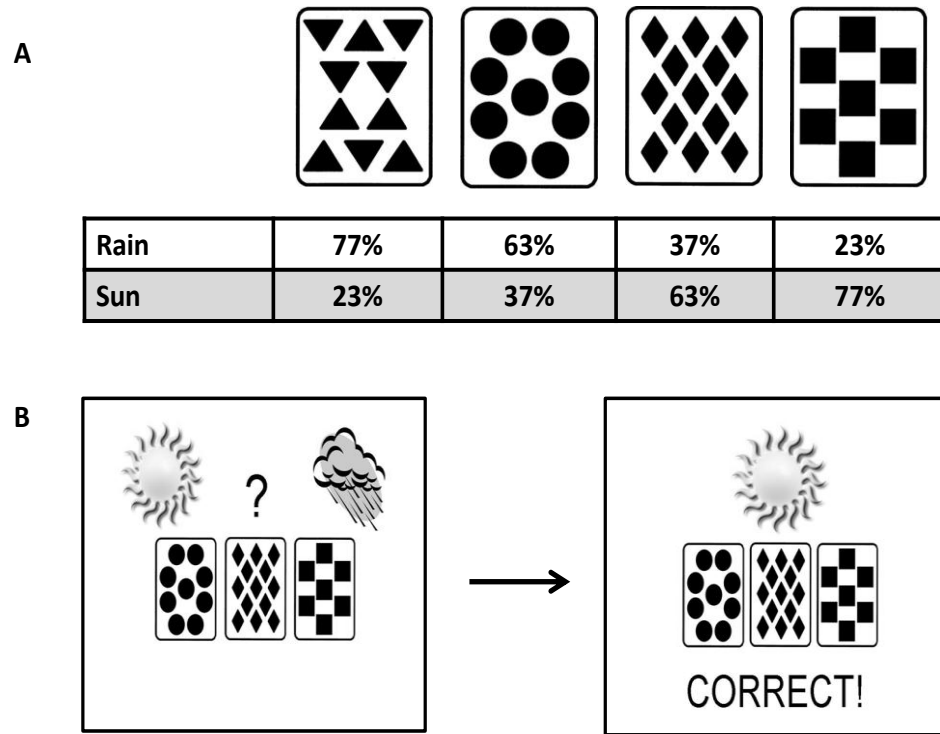
**FIGURE 2.4.** The California Weather Task. The top panel (A) depicts the 4 cues used and their associations with rain and sun in the present study. The bottom panel (B) shows one trial on the task where a participant first sees the choice screen (shown at left), then upon making a selection, the feedback screen is displayed (shown at right).

model parameters ($w$, $a$, $c$, $G^2$; IGT), or response accuracy for Acquisition and Reversal (Probabilistic Reversal Learning).  The Greenhouse-Geisser epsilon was used to correct for any sphericity violations in the repeated measures variables and interactions (Kirk, 1995). Independent-samples t-tests were used to determine whether a sex difference existed on the control tasks.  An alpha level of .05 was used for all statistical tests.

## 2.4  RESULTS

### 2.4.1  Decision-Making and Reversal Learning

*2.4.1.1  Iowa Gambling Task.*  The number of cards selected from the good decks showed a significant sex difference (Sex: $F(1, 90) = 4.16$, $p = .044$), particularly during the later blocks of the IGT, replicating the initial report by Reavis and Overman (2001) (see Figure 2.5).  Males selected more good cards than females overall.  There was also a significant main effect of block (Block: $F(3, 306) = 5.79$, $p < .001$), whereby the number of good card selections increased with increasing exposure to the task.  Because Reavis and Overman (2001) reported the sex difference only became evident during the later blocks, we performed *t*-tests to confirm whether the same pattern applied to the present dataset.  A male advantage was confirmed on Block 3 ($t(90) = 2.48$, $p = .015$) and Block 4 ($t(90) = 2.05$, $p = .043$) but not on the earlier blocks.  To discover whether the male advantage was due to a sex difference in the decks preferred by females and males, the individual decks were examined separately.  As seen in Figure 2.5, females showed a significant preference for Deck 2 (one of the 'bad' decks) over all other decks (Deck: $F(3, 141) = 28.49$, $p < .001$; all $p$'s $< .006$), whereas males selected more cards from Deck 4 (one of the 'good' decks), compared to females (Sex: $F(1, 90) = 8.56$, $p = .004$).  No other sex differences or sex-related interactions were significant.

After applying the Expectancy Valence Model to the data, it was found that the overall fit of the model differed significantly between the sexes.  The Expectancy Valence Model fit the female IGT data better ($M = 1.73$, $SD = 4.63$) than the male data ($M = -1.07$, $SD = 5.34$) (Sex: $F(1, 90) = 7.23$, $p = .009$).  There were no significant sex differences in any of the three model parameters (Recency: Sex: $F(1, 90) = 0.10$, $p = .748$; Attention to Losses: Sex: $F(1, 90) = 2.42$, $p = .123$; Choice Consistency: Sex: $F(1, 90) = 0.21$, $p = .645$) (Table 2.2).  Nor
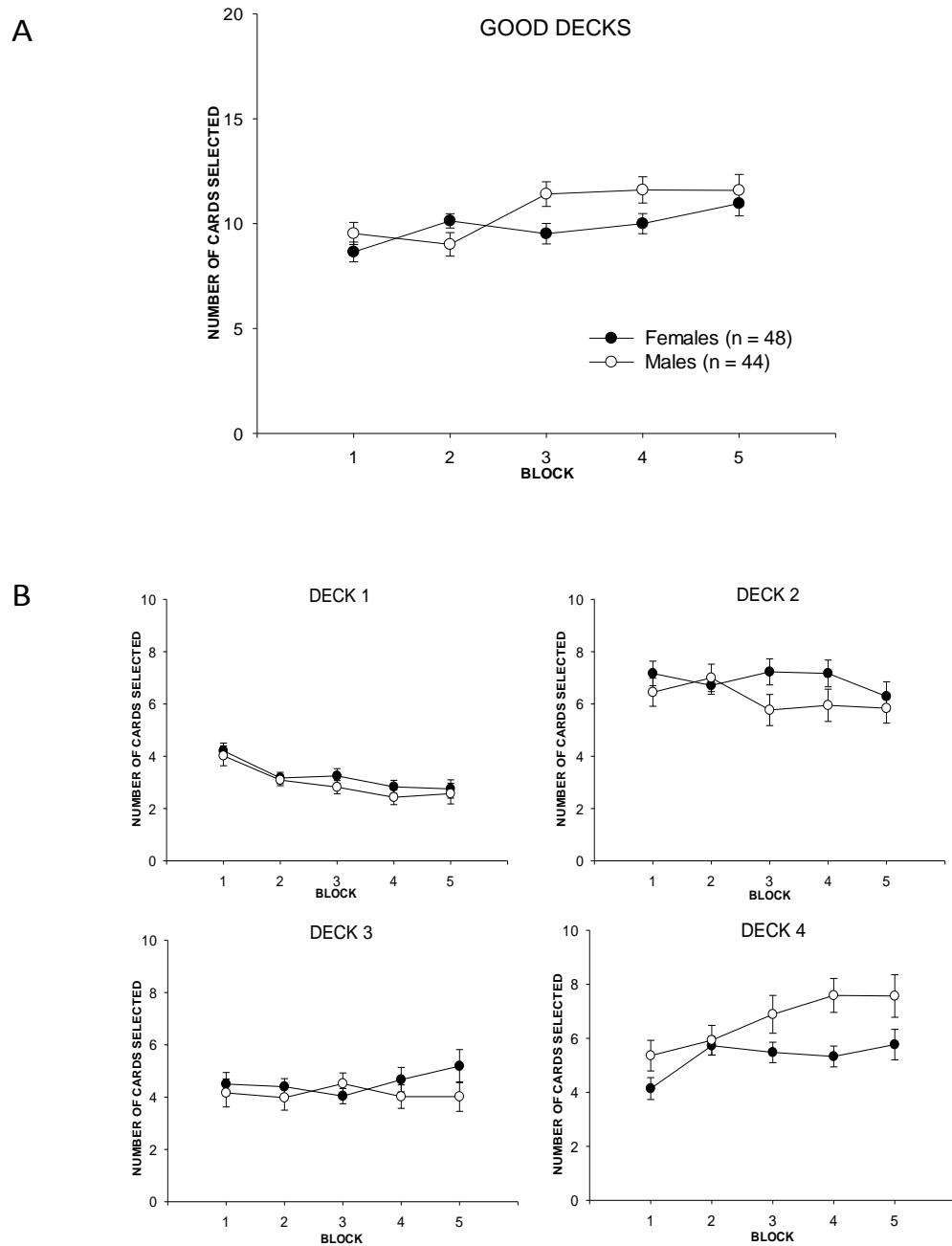
**FIGURE 2.5.** Mean number of good cards selected (Panel A) and mean number of cards selected from each deck on the IGT as a function of sex and block (Panel B). Error bars represent SEM. Males selected significantly more cards from the good decks than did females, especially during the later blocks. Females selected significantly more cards from Deck 2 than all other decks. Males selected significantly more cards from Deck 4 than females. There was no sex difference in card selections from Deck 1 or Deck 3.

**TABLE 2.2**

Mean (*SD*) Scores of Males (*n* = 44) and Females (*n* = 48) on the Expectancy Valence Model Parameters from the IGT

| Parameter | Block 1 | Block 2 | Block 3 | Block 4 | Block 5 |
|---|---|---|---|---|---|
| Recency | | | | | |
| Males | 0.66 (0.40) | 0.49 (0.42) | 0.46 (.40) | 0.58 (0.39) | 0.56 (0.41) |
| Females | 0.64 (0.38) | 0.46 (0.39) | 0.52 (0.42) | 0.57 (0.41) | 0.65 (0.38) |
| Attention to Losses | | | | | |
| Males | 0.46 (0.40) | 0.49 (0.42) | 0.48 (0.41) | 0.47 (0.41) | 0.38 (0.44) |
| Females | 0.45 (0.38) | 0.67 (0.37) | 0.53 (0.41) | 0.58 (0.41) | 0.46 (0.43) |
| Choice Consistency | | | | | |
| Males | 0.04 (3.66) | -1.29 (3.85) | -0.41 (3.95) | -1.12 (3.68) | -1.05(3.55) |
| Females | 0.38 (3.76) | -1.16 (3.97) | -0.97 (3.96) | -0.41 (4.05) | -0.85(3.44) |

*Note.* Attention to losses values less than 0.5 represent more attention to losses than to gains and values greater than 0.5 represent more attention to gains than to losses. Higher values on recency indicate more attention to recent information and lower scores represent more attention to past information. Positive scores on the choice consistency measure indicate increasing consistency over time (reliance on expectancies based on past outcomes) and negative scores indicate choice consistency decreasing over time.

were there any significant interactions between sex and blocks of the IGT (Recency: Sex x
Block: $F(4, 336) = 0.61$, $p = .648$; Attention to Losses: Sex x Block: $F(4, 351) = 0.84$, $p = .500$; Choice Consistency: Sex x Block: $F(4, 341) = 0.34$, $p = .841$).

*2.4.1.2  Probabilistic reversal learning.*  There was no evidence of a sex difference in
accuracy during Acquisition (Sex: $F(1, 89) = 0.65$, $p = .424$) (see Figure 2.6).  Accuracy of
acquisition was higher in the 90-10 than the 80-20 condition (Reinforcement Contingency:
$F(1, 89) = 29.70$, $p < .001$).  There was no significant interaction between sex and condition
(Sex x Reinforcement Contingency: $F(1, 89) = 1.44$, $p = .233$).

After Reversal, a significant sex difference was observed (Sex: $F(1, 89) = 4.88$, $p = .030$).
Males were more accurate than females following a reversal as shown in Figure 2.6. This
effect was seen in both the 90-10 condition and in the 80-20 condition (which was always
administered second).  There was no significant interaction between sex and condition (Sex x
Reinforcement Contingency: $F(1, 89) = 0.15$, $p = .704$).

### 2.4.2  Working Memory

*2.4.2.1  Self-Ordered Pointing.*  Contrary to our hypothesis, there was no significant
difference between males and females in the number of working memory errors made during
Self-Ordered Pointing (Sex: $F(1, 89) = 0.04$, $p = .850$) (see Figure 2.7).  There was a
significant main effect of set size (Set size: $F(3, 289) = 77.47$, $p < .001$), whereby a greater
numbers of errors were made at longer set lengths.  There was no significant interaction
between set size and sex (Set size x Sex: $F(3, 289) = 0.32$, $p = .829$).  Similarly, no
significant difference between males and females was found on time to completion (Sex: $F(1, 88) = 0.04$, $p = .835$; data not shown).

*2.4.2.2  N-back.*  As shown in Figure 2.8, on the *n*-back task there was no significant
sex difference in sensitivity to targets (Sex: $F(1, 84) = 1.58$, $p = .212$) or in response bias
(Sex: $F(1, 84) = 0.24$, $p = .627$; data not shown).  There was a significant main effect of *n*-back condition (0-, 2-, or 3-back) for sensitivity (Condition: $F(2, 143) = 207.68$, $p < .001$)
and bias (Condition: $F(2, 143) = 12.68$, $p < .001$), indicating reduced sensitivity to targets in
the 2-back and 3-back compared to the 0-back condition, but no interaction between sex and
*n*-back condition.  Thus there was no evidence of a sex difference, either in sensitivity
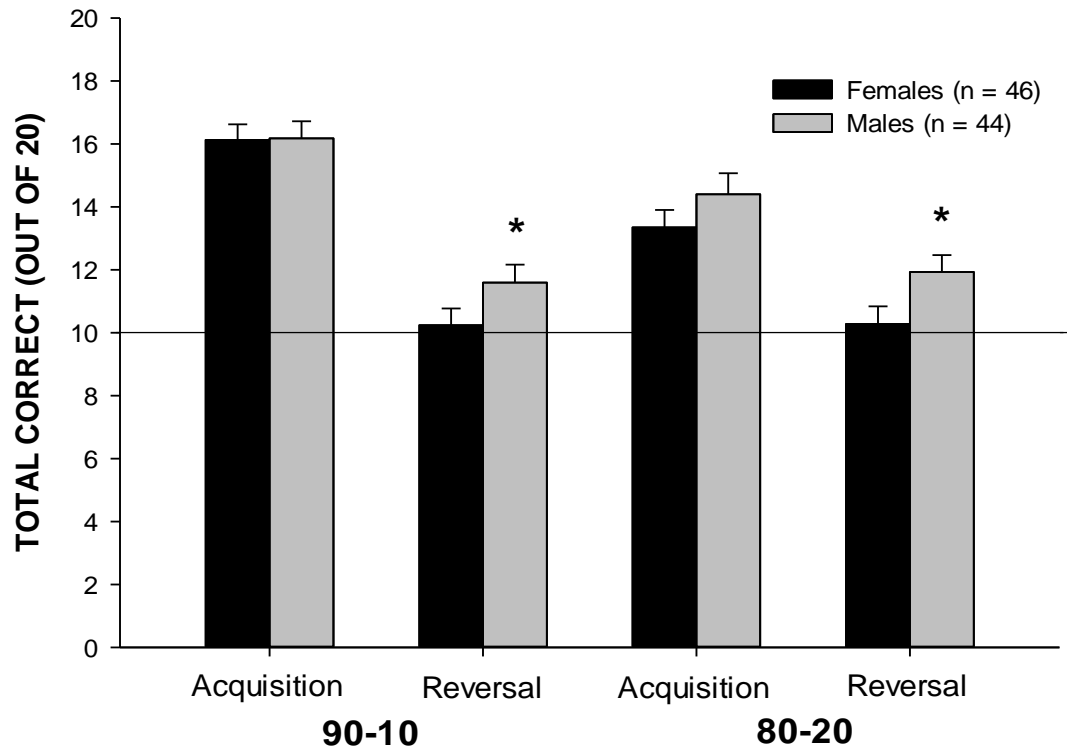
**FIGURE 2.6.** Mean accuracy during acquisition and reversal on the Probabilistic Reversal Learning task as a function of sex and reinforcement contingency. Error bars represent SEM. Males were more accurate during Reversal than females. This pattern was seen in both the 90-10 and 80-20 conditions. There was no sex difference during the Acquisition stage of the task.
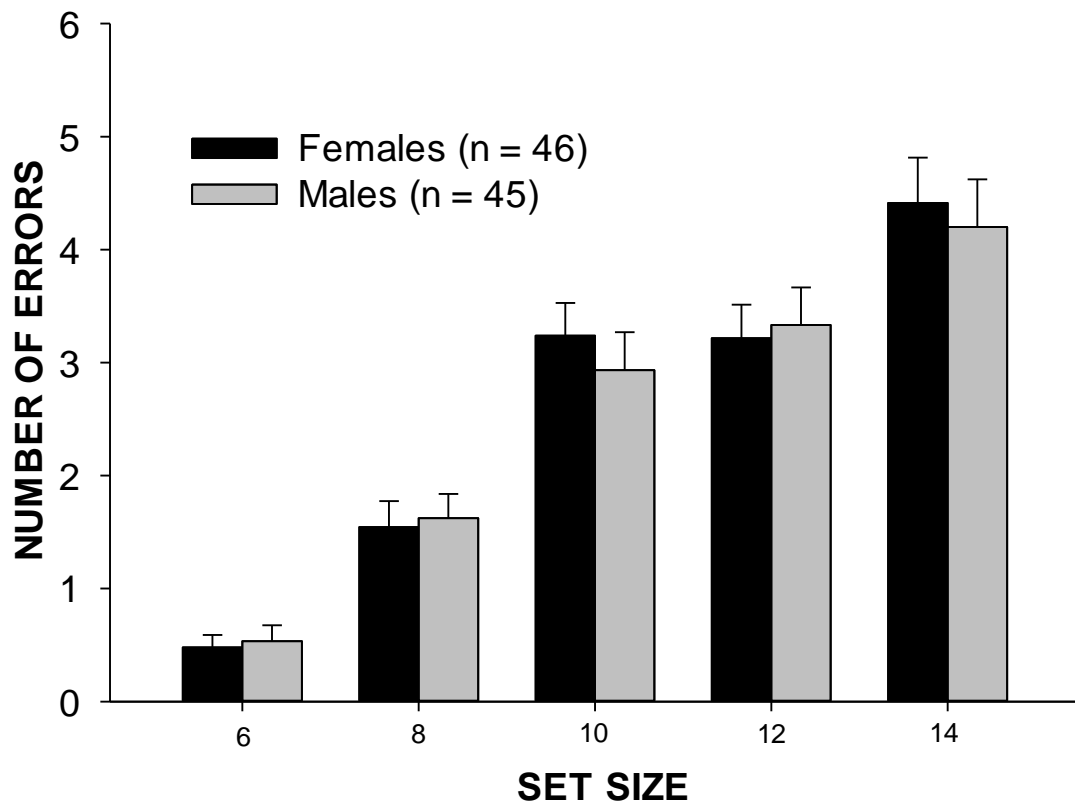
**FIGURE 2.7.** The mean number of working memory errors committed on Self-Ordered Pointing as a function of sex and set size. Error bars represent SEM. There was no significant difference between males and females in the number of working memory errors committed.
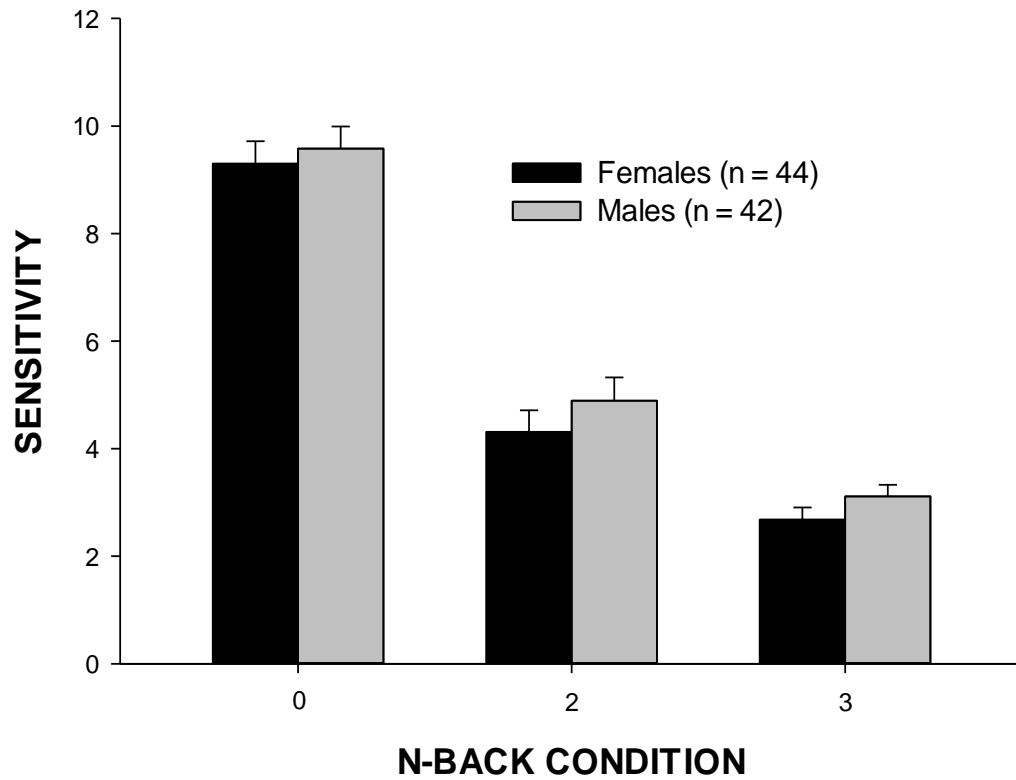
**FIGURE 2.8.** Mean sensitivity across the three conditions of the *n*-back task as a function of sex. Error bars represent SEM. Higher scores represent better ability to distinguish between targets and non-targets. There was no significant difference between males and females during any condition of the *n*-back task.

(Condition x Sex: $F(2, 143) = 0.10$, $p = .872$) or in bias (Condition x Sex: $F(2, 144) = 0.01$, $p = .976$) during any condition of the *n*-back task, nor during the task as a whole.

### 2.4.3 Control Tasks

2.4.3.1 *Span tasks.* There was no sex difference in image span ($t(90) = -1.58$, $p = .118$; Table 2.3), but quite unexpectedly, males had longer digit spans than females on Digits Forward ($t(91) = -2.21$, $p = .030$) in the present sample. As a result, it was not clear if the absence of a female advantage on the working memory tasks could be a result of obscuration by the group difference in the capacity of the immediate span. Therefore the Self-Ordered Pointing and *n*-back analyses were re-run using digit span as a covariate in an analysis of covariance (ANCOVA). Digit span proved not to be a significant covariate in the ANCOVA on Self-Ordered Pointing errors ($F(1, 88) = 1.14$, $p = .289$), but was a significant covariate in the ANCOVA on *n*-back sensitivity ($F(1, 83) = 11.29$, $p = .001$). The main effect of sex (Sex: $F(1, 83) = 0.24$, $p = .627$), however, and the interaction between *n*-back condition and sex (Sex x *n*-back condition: $F(2, 141) = 0.02$, $p = .972$) remained non-significant.

2.4.3.2 *Verbal Meaning Test.* The male and female groups were well-matched on the Verbal Meaning Test ($t(91) = -0.18$, $p = .860$) (Table 2.3). Thus group differences in performance seen on the other tasks were unlikely to be due to a group difference in general intellectual ability.

2.4.3.3 *California Weather Task.* There was no significant difference between the males and females in accuracy on the California Weather Task ($t(91) = 0.29$, $p = .775$) (see Table 2.3).

## 2.5  DISCUSSION

Sex differences on cognitive tasks dependent on the PFC have not been systematically investigated to date. The current study explored the idea that functions of the PFC are sexually differentiated by comparing men's and women's performance on tasks known to recruit discrete regions of frontal cortex. We hypothesized that females would show an advantage on working memory tasks, while males would show an advantage on decision-making and reversal learning tasks that preferentially drive the VMPFC/OFC. Only one of these hypotheses was supported.

**TABLE 2.3**

Mean (SD) Scores of Males and Females on the Control Tasks

| Test | Males ($n = 45$) | Females ($n = 48$) | $p$ value |
|---|---|---|---|
| Image Span | 5.53 (0.84) | 5.26 (0.85) | .118 |
| Digits Forward | 7.38 (0.91) | 6.85 (1.32) | .030* |
| Verbal Meaning Test | 30.49 (9.70) | 30.13 (10.18) | .860 |
| California Weather Task (% correct) | 67.51 (11.03) | 68.15 (10.51) | .775 |

*Note.* $p < .05$.

Contrary to prediction, we failed to find a female advantage on working memory tasks that place heavy demands on executive components of the working memory system. Males and females performed equally well on Self-Ordered Pointing and the *n*-back task. Despite attempts to completely match the groups demographically, the males still had a higher span for digits than did females. We interpret the difference in immediate span as sampling variation only, as a sex difference in digit span is not typically seen, nor found in the Wechsler standardization sample. The group difference in span may have played a role in the non-significant findings for the two working memory tasks, but using digit span as a covariate did not change the findings for either Self-Ordered Pointing or the *n*-back task.

Sex differences in working memory have been reported in a small number of past studies (e.g., Duff and Hampson, 2001; Lejbak et al., 2009; Speck et al., 2000), but not by others (Nagel et al., 2007; Schmidt et al., 2009). Some of these studies made use of well-characterized working memory tasks (*n*-back task: Nagel et al., 2007; Schmidt et al., 2009; Speck et al., 2000; Vuontela et al., 2003; digit ordering: Duff and Hampson, 2001), whereas others (Duff and Hampson, 2001; Lejbak et al., 2009) used a spatial working memory task adapted from Passingham (1985), which is severely impaired in monkeys following lesions of the DLPFC, but for which human data from imaging or patient studies do not currently exist. All tasks used in past studies and the current study emphasize executive processes of the working memory system (i.e., monitoring, updating, active maintenance), but it is possible that the exact type of control processes required is a relevant consideration for seeing a sex difference. It is possible that not all of these processes are sexually differentiated, or not equally so. Different tasks evoke slightly different executive control processes depending on task requirements or place unequal demands on these processes relative to other tasks. It may be significant that the tasks that showed a female advantage in the studies by Duff and Hampson (2001) or Lejbak and colleagues (2009) emphasized manipulation and active maintenance within working memory whereas the *n*-back task emphasizes monitoring, processes that may exhibit some anatomical segregation within the PFC. Due to the behavioural nature of the present study, and the fact that we did not systematically vary the precise working memory requirements, it is not possible to reach any conclusion about which executive processes are important for eliciting sex differences in working memory. Future studies should attempt to address this issue.

Domain-specificity has been proposed to characterize the lateral PFC, but is less likely to explain the absence of a sex difference on our working memory tasks. It has been argued that the DLPFC assumes greater importance for spatial working memory, while ventrolateral regions might be more important under conditions where stimuli to be remembered are non-spatial. In previous studies, a female advantage has been found with both spatial and verbal types of stimuli. Multi-experiment reports by two separate research groups found a reliable female advantage on a task requiring memory for spatial locations (Duff and Hampson, 2001; Lejbak et al., 2009), but a female advantage also has been found on letter and digit versions of the *n*-back task (Speck et al., 2000) and on a spoken digit randomization task (Duff and Hampson, 2001). A later study found a male not female advantage on spatial and common object versions of the *n*-back, but no sex difference on a letter version (Lejbak et al., 2011). In the current study the stimuli were either explicitly verbal (letters) or could potentially be verbally encoded, even though we chose abstract visual stimuli (abstract art) on the SOP to discourage the use of verbal strategies as much as possible. Other studies, too, found no difference between the sexes on letter versions of the *n*-back (Li et al., 2010; Nagel et al., 2007; Schmidt et al., 2009) and this is in line with the findings of the current study.

The sensory modality used to present information may be important. Visual and auditory information appear to elicit different patterns of brain activation in imaging studies of letter versions of the *n*-back task. Specifically, auditory presentation has been shown to activate the dorsolateral PFC to a greater extent than visual presentation (Crottaz-Herbette et al., 2004; Rodriguez-Jimenez et al., 2009) suggesting that auditory versions of the *n*-back might be more useful in future studies when examining possible differences in the dorsolateral PFC-dependent components of the working memory system. Future studies should attempt to elucidate whether the sensory modality used to present information is important for eliciting a sex difference.

Although we excluded women using oral contraceptives because of their marked effects on estrogen levels, we did not control phase of the menstrual cycle in testing our female group. Given increasing evidence that estrogens play a role in the functioning of the working memory system (e.g., Duff and Hampson, 2000; Grigorova et al., 2006; Hampson and Morley, 2013; Krug et al., 2006), allowing the menstrual cycle to vary randomly may lead to variability in the female working memory data and potentially attenuate the size of any

observed sex difference.  Previous studies (Duff and Hampson, 2001; Lejbak et al., 2009; Speck et al., 2000) did not control the phase of the menstrual cycle in female participants, indicating it is still possible to find a sex difference under these circumstances.  Nonetheless, a stronger test of the hypothesized sex difference would be a study where estradiol levels were explicitly controlled.

Findings from both the IGT and Probabilistic Reversal Learning support the hypothesis that a male advantage exists on tasks that strongly recruit the VMPFC/OFC.  As the task progressed, men selected more cards from the 'good' decks on the IGT and this was driven by a male preference for 'good' Deck 4 compared to women.  On the PRL, there was no difference between men and women during Acquisition, but men outperformed women during the Reversal stage of both reinforcement conditions (90-10 and 80-20).  There was no sex difference on the California Weather Task which suggests that the male advantage was not related to making use of probabilities during task performance.

A commonly used reinforcement learning model, the Expectancy Valence Model, was applied to the IGT data.  We found no difference between the sexes on any of the Expectancy Valence Model parameters (recency, attention to losses, and choice consistency).  This result is in agreement with a recent study by de Visser and colleagues (2010) that also failed to find sex differences on any of the model parameters.  It seems probable that other important factors that predict performance are not accounted for by the current model.  Indeed, one criticism of the Expectancy Valence Model is that the attention to losses parameter in particular does not account for variance, probability, and expected value components of risk, so the model cannot fully explain how IGT performance is associated with adaptive decision-making under conditions of risky gains and losses (Weller et al., 2009).  Recent work suggests other models (e.g., a heuristic-based win-stay/lose-shift model) may fit data from the IGT better than the more commonly used Expectancy Valence Model (Worthy et al., 2013).

Several previous studies have reported a sex difference on the IGT (e.g., Bolla et al., 2004; Overman, 2004; Overman et al., 2006; Reavis and Overman, 2001).  The current study confirms these findings of a male advantage.  Given that the IGT and reversal learning share several task elements, such as using value-based feedback to guide decisions or reversing a

response that is no longer optimal, it is reasonable to expect there may also be a sex difference on reversal learning tasks. Overman and colleagues (1996) found a male advantage on a simple object reversal task in young children (15 to 30 months of age). The current study is the first to show a sex difference in reversal learning in adults.

Previous studies reporting a sex difference on the IGT have ruled out sex differences in mathematical ability (Overman et al., 2006) as a functional basis for the sex difference. It remains unclear which processing component(s) lead to the observed male advantage. One candidate component involved in both the IGT and PRL is the reversal element. On the IGT, participants usually begin the task by preferring the 'bad' decks because the reward payout is higher but gradually shift to selecting from the lower payout, 'good' decks as the task proceeds because they yield a better payoff over the task as a whole (Bechara et al., 1994). Thus, participants must learn to reverse their initial preference for the 'bad' decks in order to perform optimally. In a similar fashion, participants must learn to reverse their preference for the initially rewarded stimulus on the PRL after a reversal takes place and the initial response is no longer rewarded. It is possible that there is a sex difference in the attention given to, or impact of, reversal cues. However, the IGT and PRL also share other common task elements such as the need for inhibitory control or learning based on reward and punishment, and it is alternatively possible that the sex difference derives from these sources.

Some studies provide evidence against inhibitory control as a possible explanation of the sex difference. For example, studies using inhibitory tasks like the Stroop colour-word task or the Stop-Signal Task have failed to find a sex difference in behavioural performance (e.g., Cross et al., 2011; Li et al., 2006; 2009; MacLeod, 1991). On the other hand, previous studies finding a sex difference on the IGT might suggest that the rewarding and punishing elements of the task are important determinants of the sex difference. Females tend to select more cards from Deck 2 than males (e.g., Goudriaan et al., 2007; Overman, 2004) and in the present work, females preferred Deck 2 over all other decks. Deck 2 offers a high payout ($100) per card selection, and high frequency of reward, with a large punishing loss of $1250 only once in every 10 trials. It has been suggested that reward frequency may be a more salient consideration for females than males during the IGT, whereas decision-making in males is mainly guided by real long-term payoff (Overman, 2004). Recent studies support the possibility of two separate strategies used during IGT performance by normal participants

('dual process hypothesis'; Chiu et al., 2008; Stocco et al., 2009). In principle, this logic suggests that females ought to favour Decks 2 and 4 due to their low ratio of punishments relative to rewards (both decks have 1 punishment per 10 trials), however empirically the female preference is driven largely by Deck 2 (Goudriaan et al., 2007; Overman, 2004; Overman et al., 2011; present study), suggesting reward magnitude and not just frequency is important. Males chose more cards than females from decks with high net payoff (Deck 3, Overman et al., 2011; Deck 4, present study), even though these decks have low reward magnitude, supporting the idea that decision-making was guided by long-term payoff not immediate reward incentives. Thus, one tenable potential explanation for the sex difference in decision-making observed on the IGT is differential reliance on reward/punishment information.

Can a difference in reward salience account for the sex difference observed on the PRL? During the PRL task, participants win points for correct selections and lose points for incorrect selections (in addition to winning or losing points based on incorrect feedback as a result of the probabilistic nature of the task). When a reversal takes place, individuals who have learned the correct object selection are now punished (lose points) if they continue to select the originally rewarded object. If there is a sex difference in reward saliency, it could conceivably reveal itself as a sex difference at reversal as greater willingness on the part of females to stick with a pattern of learned behavior that was previously frequently rewarded, and only intermittently punished. A recent study by Robinson and colleagues (2010) found improved performance in females on an observational reversal learning task after dopamine depletion, a manipulation that appeared to shift sensitivity of performance from reward to punishment processing.

The current study provides preliminary support for the hypothesis that functions related to the VMPFC/OFC may be sexually differentiated in humans. Androgen receptors have been found in orbitofrontal regions in adult rhesus monkeys (Finley and Kritzer, 1999) and androgens may modulate dopaminergic and serotonergic systems within the PFC (Handa et al., 1997), systems that play key roles in decision-making and reversal learning (e.g., Calaminus and Hauber, 2008; Ha et al., 2009; Rogers, 2011). A fruitful direction for future research will be to unveil which latent components of the IGT and probabilistic reversal learning tasks are important determinants of the observed sex difference in behaviour.

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**CHAPTER 3**

**DOES RISK-TAKING MEDIATE THE RELATIONSHIP BETWEEN TESTOSTERONE AND DECISION-MAKING ON THE IOWA GAMBLING TASK?**

Kelly L. Evans and Elizabeth Hampson

## 3.1  ABSTRACT

We hypothesized that men with high testosterone (T) would perform more poorly than men with low T on the Iowa Gambling Task (IGT), a task widely used in the laboratory and clinic to assess decision-making, and that an effect of T on risk-taking propensity would mediate the effect.  Sixty-one healthy adult males completed the IGT.  Current T was measured in saliva and T levels during early development were estimated using the 2D:4D digit ratio.  Men with high T levels chose fewer cards from the advantageous decks on the IGT.  Financial risk-taking, measured by the Jackson Personality Inventory, was negatively correlated with the number of good card selections.  Mediation analysis showed that risk-taking was a significant mediator of the association between IGT and 2D:4D ratio (but not current T levels).  An organizational effect of androgens during early development may affect adult IGT performance indirectly through an influence on willingness to take risks.

## 3.2  INTRODUCTION

A recent trend in the study of risk-taking is to examine the role of testosterone in self-reported willingness to take risks, overt risky behaviors, and risky financial decision-making. For example, in university students, testosterone levels have been found to correlate positively with risk-taking during a laboratory investment game with real monetary payoffs (Apicella et al., 2008) and both low and high levels of testosterone were associated with less risk aversion on a task involving certain outcomes and risky gambles (Stanton et al., 2011a). Apicella et al. (2008) have proposed an evolutionary explanation for the link between testosterone and risk propensity suggesting that increased risk-taking by males (specifically in the financial domain) leads to the gain of resources and in turn, to increased mating opportunities.

In addition to circulating hormones, the effect of prenatal exposure has begun to be examined, utilizing the 2D:4D ratio (the ratio of the second to fourth digit lengths) as a proxy measure of testosterone.  A smaller 2D:4D ratio is said to reflect higher androgen levels during prenatal development, due to androgen's actions on digit growth (Manning et al., 1998). Though it is a crude indicator (Hampson & Sankar, 2012), recent evidence in mice does suggest that higher prenatal androgen levels cause elongation of the fourth digit relative to the second digit resulting in a smaller 2D:4D ratio (Zheng & Cohn, 2011) and in humans large alterations in testosterone availability during the prenatal period do affect the ratio (Brown et al., 2002).  With respect to financial decision-making, past studies found no association between 2D:4D ratio and risky financial decision-making (Apicella et al., 2008; Sapienza et al., 2009), but recent work by Stenstrom et al. (2011) found that self-reported financial risk-taking was negatively correlated with digit ratios in males, and two studies found that smaller ratios were correlated with riskier financial choices during laboratory decision-making tasks (Brañas-Garza & Rustichini, 2011; Garbarino et al., 2011).  In general, whether testosterone does reliably influence financial decision-making, and the functional mechanisms responsible, are poorly understood.

The Iowa Gambling Task (IGT, Bechara et al., 1994) is widely used in both laboratory and clinical settings and predicts real-world financial decision-making (Shivapour et al., 2012), but to date, few studies have examined whether testosterone levels influence IGT

performance. The IGT is a complex task that involves learning payoffs associated with different decks of cards over time. Two decks are advantageous because over time they lead to a net gain (despite yielding smaller immediate rewards), whereas two other decks are disadvantageous because they lead to a net loss (even though both yield larger immediate rewards). In young men, serum testosterone was inversely correlated with the number of good cards selected on the IGT in a seminal study by Reavis and Overman (2001; see also Stanton et al., 2011b). In contrast, Goudriaan et al. (2010) failed to find any association between testosterone levels and IGT performance. Thus, although there is preliminary evidence to suggest that testosterone might play a role in IGT performance, present findings do not uniformly suggest an association is present. No study has examined performance on the IGT vis-a-vis the 2D:4D digit ratio.

It has been speculated that any link between current testosterone and IGT performance could reflect a link between risk-taking and testosterone (Stanton et al., 2011b) as risk-taking does play a role in the IGT (Upton et al., 2011). However, the IGT is not a pure measure of risk-taking and in addition to risk-taking, involves inhibitory control and learning from valenced, probabilistic feedback. Thus, testosterone need not be associated with IGT performance via risk propensity, given that other processes are involved. To date, no study has examined whether risk-taking mediates the relationship between current testosterone levels and IGT performance. Such an association would broaden the empirical evidence that testosterone levels are relevant to risky financial decision-making and would supplement our current understanding of the clinical use of the IGT.

The primary objective of the current study was to investigate whether current levels of testosterone and/or prenatal levels (as reflected in the 2D:4D digit ratio) predict decision-making in males, as measured by the IGT, and to determine if the observed relationships are mediated by risk-taking propensity. Physiologically, adult testosterone influences neural activity in brain regions where its receptors are expressed. However, testosterone can also exert lasting effects on brain organization during defined periods in prenatal development, when the testes become temporarily active (Breedlove & Hampson, 2002). Currently, it is unknown which time frame is the source of any effect of testosterone on the IGT or whether the influence of developmental versus current testosterone involves different functional mechanisms. Based on findings of past research (Reavis & Overman, 2001; Stanton et al.,

2011b), it was hypothesized that men with lower levels of circulating testosterone would perform better on the IGT than men with higher levels.

## 3.3 METHOD

### 3.3.1 Participants and procedure

Sixty-seven male undergraduates ages 18-22 years ($M$=18.85, $SD$=0.98) with no history of central nervous system pathology were recruited. Two participants were excluded who either exhibited prior knowledge of the task or showed an aberrant pattern of responses (seen in only 0.6% of males who have completed the IGT in our lab, $N$=179). Four participants met criteria for problem gambling on the South Oaks Gambling Screen and were excluded because problem gamblers are an identifiably distinct group known to show altered IGT performance (Kertzman et al., 2011). The ethnic composition of the sample was White (84%), Asian (15%), Black ($<2$%). Some studies report ethnic differences in the 2D:4D ratio (Manning et al., 2007), but the whole dataset was used in the present analyses because our results, with one exception, were unchanged if limited to the White group only. To control for circadian and seasonal variation in testosterone production (Dabbs, 1990a,b), all testing took place between 1200h-1800h and during February, March, or April. The study received ethical approval from the Non-Medical Research Ethics Board at the University of Western Ontario (see Appendix B).

### 3.3.2 Materials

### 3.3.2.1 Iowa Gambling Task (IGT).

The version of the IGT used here was from the Psychology Experiment Building Language Battery (Mueller, 2009), which is identical to the original task by Bechara et al. (1994) except that the top card moves to the bottom of the deck on each draw. Four decks that differ in the magnitude of penalties and rewards and in loss frequency (see Table 3.1) are presented on a computer screen. Participants are not aware of the endpoint (100 trials) or the payoff structure of the task. To start, each participant is given a $2000 virtual loan and is instructed to try to win as much money as possible by choosing cards from the different decks. To ensure the physical ordering of the decks did not influence performance, the decks were presented on the screen in one of four arrangements, counterbalanced across participants. As

**TABLE 3.1**

The Decks of the Iowa Gambling Task

| Deck | Win/Loss Ratio | Net Payoff /10 trials | Reward Magnitude | Loss Magnitude |
|------|----------------|-----------------------|------------------|----------------|
| 1 | 10:5 | -$250 | +$100 | -$150 to -$350 |
| 2 | 10:1 | -$250 | +$100 | -$1250 |
| 3 | 10:5 | +$250 | +$50 | -$25 to -$75 |
| 4 | 10:1 | +$250 | +$50 | -$250 |

in previous reports (e.g., Bechara et al., 2000), the 100 trials of the IGT were broken down into 5 blocks (20 trials/block) for scoring and analysis. Only Block 1 and 5 of the IGT were examined statistically because most participants do not develop a full understanding of the deck differences until approximately the $80^{th}$ trial (Bechara et al., 1997) and consequently the final trials best represent individual differences in decision-making under risk (Brand et al., 2007). The primary dependent variable, following Bechara et al. (1994), was number of cards selected from the 'good' decks (i.e., Deck 3+4) that yield a positive net payoff.

### 3.3.2.2 California Weather Task (CWT).

The CWT was chosen as a control task. It shares some elements with the IGT (e.g., the probabilistic element; implicit learning), but does not have a monetary reward/punishment component. A correlation with testosterone was not predicted. The CWT is a probabilistic classification learning task in which participants are asked to decide if a set of cards shown on the computer screen predicts "sun" or "rain"(see Fig. 3.1 and Knowlton et al., 1994 for details). The version of the CWT created for the current study differed from Knowlton's original in that it involved fewer trials (70 versus 200) and by default used slightly higher cue probabilities (77% and 63% here versus 76% and 58% in the original). The dependent variable was the percentage of correct predictions.

### 3.3.2.3 Jackson Personality Inventory Revised (JPI-R).

The Risk-Taking Scale from the Jackson Personality Inventory-Revised (JPI-R; Jackson, 1994) was used to assess individual differences in risk-taking propensity. Participants selected *True* or *False* for each of 20 statements (e.g., "The thought of investing in stocks excites me."). Only the 11 items measuring propensity for financial risk were included when computing the score as financial risk-taking may be a form of male-male competition activated by testosterone that leads to resource maximization (Apicella et al., 2008).

### 3.3.2.4 Digit ratios

Digital images of both hands were obtained with fingers spread apart and palms facing down. Landmarks used to measure the lengths of the second and fourth digits were the most basal crease where the finger meets the palm and the most distal point at the finger tip. The distance between the landmarks was measured using digital callipers with a resolution of
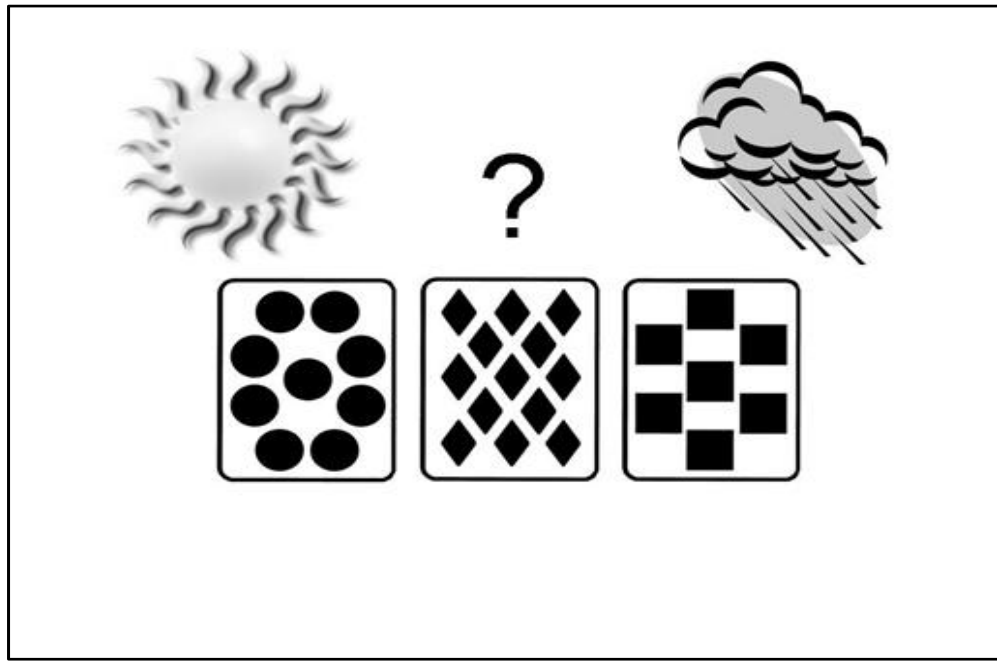
**Fig. 3.1.** On the California Weather Task, each card (4 total) predicted sun or rain with a fixed probability (77%, 63%, 37%, or 23%) which the participant had to learn implicitly over the course of the task. The correct weather outcome on each trial was determined by the combination of cards shown.

0.005 mm (Digital Measurement Metrology, Inc., Model ABS). Digit lengths were independently measured by a second rater (inter-rater reliability: IC$r$=.92 for the left ratio and IC$r$=.98 for the right). For two participants, digit ratios could not be computed due to indistinct creases. In the analyses below, the left and right digit ratios from the primary rater were averaged to control Type I error as the hands were well correlated, $r(59)$=.72, $p<.001$ and the results were virtually identical for the two hands separately.

### 3.3.3  Hormonal quantification

Saliva was collected at the beginning and end of the test session. The mean of the first and second saliva samples was used as the best estimate of individual differences in testosterone concentration, $r(61)$=.90, $p<.001$. Participants refrained from eating, drinking (except plain water), smoking, chewing gum, or toothbrushing for 1 h before arrival. Saliva was collected into polystyrene culture tubes and frozen at -20˚C until assay. Assays were performed in duplicate, using a $^{125}$I Coat-A-Count kit for testosterone (Siemens, Deerfield, IL) modified for saliva. The sensitivity of the assay was 5 pg/mL and the intra-assay coefficient of variation was 7%.

### 3.3.4  Statistical analyses

Descriptive analyses were done using IBM SPSS 19.0. Pearson correlation coefficients were used to assess bivariate relationships. Time of day was controlled in the analyses involving current testosterone through the use of partial correlations.

To estimate indirect effects, a mediation analysis was performed using the bootstrapping method (Preacher & Hayes, 2004). This involved the nonparametric re-sampling of the dataset to make repeated estimates (5000 times as recommended by Preacher and Hayes, 2008). This approach is more powerful than the three-step regression method of Baron and Kenny (1986) and the Sobel test (Sobel, 1982) because it allows a way to test the statistical significance of the indirect effect (*ab*) and makes no assumptions about the shape of the *ab* distribution (Preacher & Hayes, 2004). Kappa squared ($\kappa^2$), which denotes the ratio of *ab* to the maximum indirect effect possible given the constraints of the design and the data, was used as a measure of effect size (Preacher & Kelley, 2011). The same benchmarks used for qualitatively describing the effect size of squared correlation coefficients can be applied to $\kappa^2$

(i.e., .01, .09, and .25 are considered small, medium, and large respectively). $\kappa^2$ was calculated using the MBESS R package (Kelley & Lai, 2012).

## 3.4  RESULTS

### 3.4.1  Descriptives and correlations

Means and bivariate correlations for each variable are shown in Table 3.2.  Circulating testosterone levels were within the expected range for young adult males ($M$=99.63 pg/mL, $SD$=31.25; Dabbs, 1990a).  The mean digit ratio was 0.95 ($SD$=.03), consistent with average ratios found in previous investigations (e.g., Garbarino et al., 2011).  As expected, on Block 1 participants chose more cards from the 'bad' decks, which yield large immediate rewards but long-term losses, whereas by Block 5, they learned to choose more cards from the good decks (Fig. 3.2).  Repeated-measures ANOVA confirmed a significant switch in net score (number of good minus bad cards) from a negative score on Block 1 to a positive score by Block 5, $F(3, 207)$=8.29, $p$<.001, (Block 1 vs. 5:  $p$<.01 by Tukey HSD test).

There was no significant relationship between salivary testosterone and the number of good cards selected on Block 1, $r(58)$= -.02, $p$=.879, but as hypothesized, by Block 5, higher testosterone levels were associated with fewer selections from good decks, $r(58)$= -.38, $p$=.003 (see Fig. 3.3 for the raw correlation).  Higher JPI-R risk-taking also predicted fewer selections from good decks, $r(59)$= -.30, $p$=.019.  Risk-taking was inversely correlated with 2D:4D ratio, $r(57)$= -.31, $p$=.017, indicating that smaller, more masculinized, ratios were associated with greater risk-taking.  The correlation between 2D:4D and good card selections fell short of significance but was in the expected positive direction.  Risk-taking showed a non-significant correlation with current testosterone levels, $r(58)$=.17, $p$=.187.

Performance on the California Weather Task was not significantly related to circulating testosterone, $r(58)$=.08, $p$=.522 or to digit ratio, $r(57)$=.21, $p$=.118 (for White subgroup only, $r(47)$=.29, $p$=.043), but was significantly correlated with risk-taking, $r(59)$= -.26, $p$=.041.

### 3.4.2  Mediation analyses

Results of the mediation analysis are summarized in Fig. 3.4.  There was a significant direct effect between current testosterone and the number of good cards selected on Block 5 before

**TABLE 3.2**

Means, Standard Deviations, and Correlations

| Variable | 1. | 2. | 3. | 4. | 5. | 6. |
|---|---|---|---|---|---|---|
| 1. Testosterone | - | | | | | |
| 2. 2D:4D | .02 | - | | | | |
| 3. JPI Financial Risk-Taking | .17 | -.31* | - | | | |
| 4. IGT Good Card Selections Block 1 | -.02 | -.20 | .14 | - | | |
| 5. IGT Good Card Selections Block 5 | -.38** | .16 | -.30* | -.11 | - | |
| 6. CWT | .08 | .21 | -.26* | -.16 | -.08 | - |
| *M* | 99.63 | 0.95 | 5.00 | 8.54 | 10.87 | 63.19 |
| *SD* | 31.25 | 0.03 | 2.29 | 2.94 | 3.89 | 11.66 |

*Note.* $N=61$ except for the 2D:4D ratio where $N=59$.

* $p < .05$.

** $p < .01$.
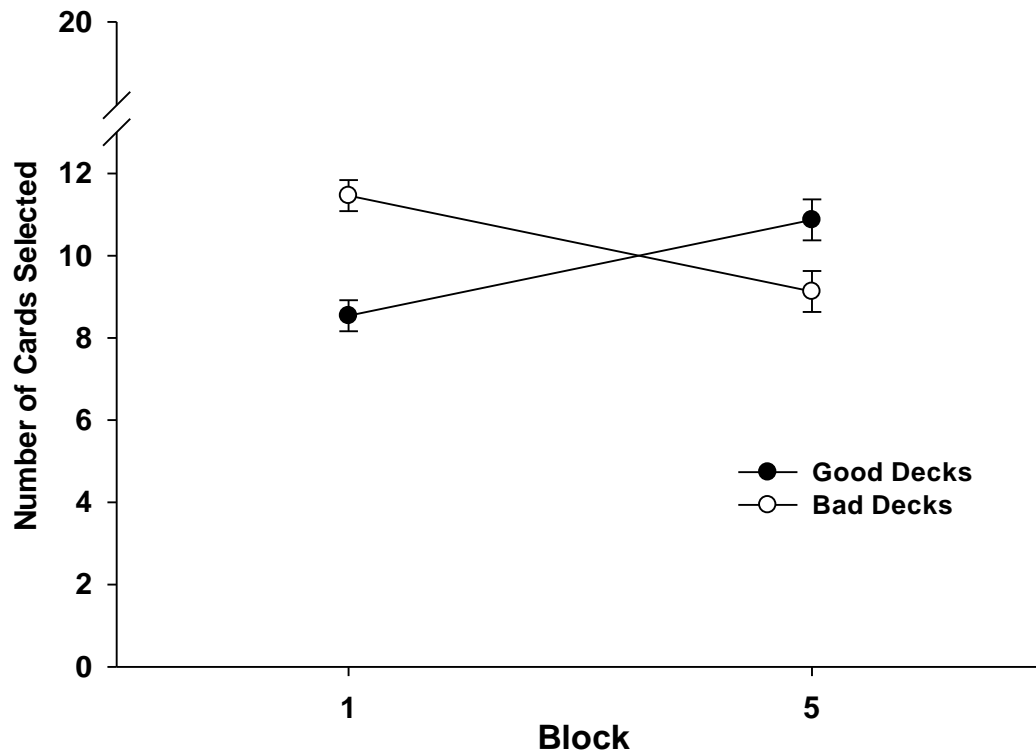
**FIGURE 3.2.** The mean number of good and bad cards selected on Blocks 1 and 5 of the IGT (±SEM). By Block 5 more cards were selected from the good decks indicating that the deck contingencies were learned as the task progressed.
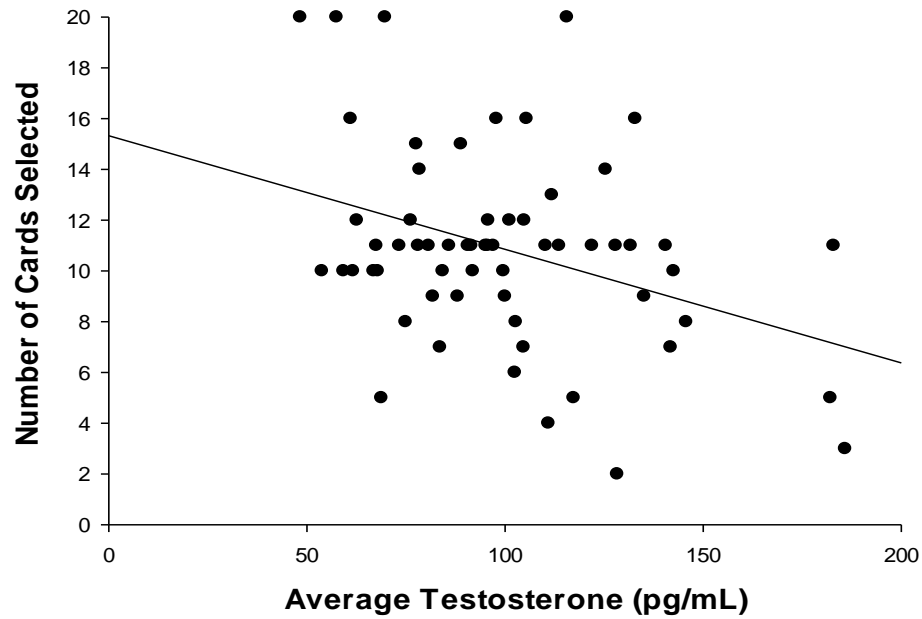
**FIGURE 3.3.** The raw correlation between testosterone and number of good cards selected during Block 5 of the IGT, ($r(59)= -.36$, $p=.043$). A quadratic model was also examined, but the linear model was the only significant fit to the data. The results remained unchanged if the four IGT scores at ceiling were removed.
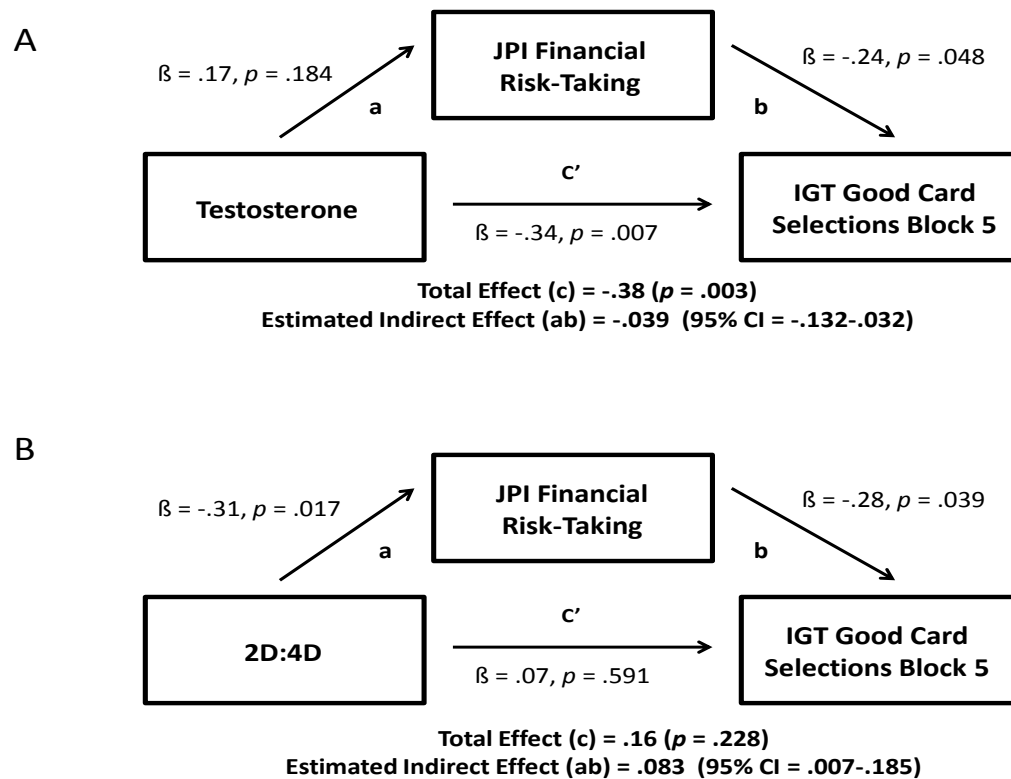
**FIGURE 3.4.** Mediation analyses for the effect of testosterone (panel A) and digit ratio (panel B) on the number of good cards selected on Block 5 of the IGT, directly (*c'*) and indirectly through risk-taking (*ab*).

controlling for risk-taking ($\beta$= -0.38, $p$=.003). However, there was no evidence that risk-taking was a significant mediator of the relationship (estimated indirect effect: $ab$= -.039, 95% CI= -.132-.032, $\kappa^2$=.044). On the other hand, the direct effect between digit ratio and good cards selected on Block 5 was not significant prior to controlling for risk-taking ($\beta$=0.16, $p$=.228). An indirect effect of a mediator on the relationship between two variables can still occur when there is no significant direct effect prior to controlling for the mediator (Preacher & Hayes, 2004) and indeed, there was a significant indirect effect of risk-taking on the relationship between digit ratios and good card selections on Block 5 (estimated indirect effect: $ab$=.083, 95% CI=.007-.185, $\kappa^2$=.075) (Fig. 3.4). Zero was not included in the confidence interval. A mediation analysis was also run to examine if risk-taking mediated the relationship between digit ratio and CWT performance. Here again, there was no significant direct effect of digit ratio on the CWT score prior to controlling for risk-taking ($\beta$=0.21, $p$=.118). In this case, however, the confidence interval did include zero (estimated indirect effect: $ab$=.068, 95% CI = -.013-.200, $\kappa^2$=.058).

## 3.5 DISCUSSION

The current study provides further evidence that financial decision-making is related to circulating levels of T in males, and is the first to suggest that IGT performance also may be influenced indirectly, via developmental exposure to androgens. Consistent with two previous reports (Reavis & Overman, 2001; Stanton et al., 2011b), lower circulating testosterone was associated with better performance on the IGT. This relationship was evident by Block 5, the last block of trials, where most participants have developed a full understanding of the deck differences (Bechara et al., 1997) and where decisions are made under conditions of known risk (Brand et al., 2007). By itself, risk-taking was inversely correlated with the number of good cards selected, in agreement with past studies showing that risky performance on the Balloon Analogue Risk task or on a gambling task with explicit rules predicted fewer good card selections during the late stages of the IGT (Brand et al., 2007; Upton et al., 2011). In contrast, 2D:4D ratio (a putative marker of prenatal androgen exposure) was not significantly related to IGT performance ($r$=.16). This is at odds with two reports that smaller ratios were correlated with riskier choices on lottery and investment tasks, some having a real-world payout, though available data are limited (e.g., Garbarino et al., 2011; but $cf$., Apicella et al., 2008).

In the present study, we investigated whether any relationship between IGT performance and either circulating testosterone or digit ratios was mediated by an effect of androgens on risk-taking propensity.  For *current* testosterone, several aspects of the present findings are inconsistent with the view that risk-taking is the mediating variable.  JPI-R risk-taking was not significantly correlated with circulating testosterone levels.  In addition, the results from the mediation analysis failed to support the idea that risk-taking was a mediator of the relationship between current testosterone and IGT performance, even though that relationship was moderate in size.  This suggests there are associations between circulating testosterone and IGT decision-making that are independent of risk-taking.

On the other hand, the 2D:4D ratio was a significant predictor of risk-taking.  Consistent with these data, one previous study has reported that digit ratios and self-reported financial risk-taking are negatively correlated in males (Stenstrom et al., 2011).  In turn, risk-taking predicted IGT performance and there was also a significant indirect effect of risk-taking on the relationship between 2D:4D and IGT performance.  Risk-taking also correlated with CWT performance, but the indirect effect of risk-taking on the association between digit ratios and the CWT was not significant in the current sample.

It seems possible that androgen exposure during development influences risk propensity which then influences quality of decision-making in adulthood under conditions that involve risk.  However, caution should be exercised when interpreting findings related to digit ratios as the ratio is not a particularly refined gauge of the degree of androgen exposure (Hampson & Sankar, 2012) and is influenced in addition by other factors.  On the other hand, large alterations in testosterone availability during the prenatal or newborn period do affect the ratio (Brown et al., 2002) and other ways of measuring prenatal androgen exposure are not always practical (e.g., measuring hormones from amniocentesis).  Therefore, although the current study provides preliminary data, future work should examine the relationship between prenatal androgen levels and risk-taking using a direct technique like amniocentesis to allow stronger conclusions to be drawn.

Variance in IGT performance associated with *prenatal* testosterone may be related to risk, but the variance associated with *current* testosterone is likely related to some other element of the task.  An alternative mechanism not examined here is sensitivity to reward and/or

punishment. Some speculate that higher levels of testosterone make an individual more sensitive to reward and/or less sensitive to punishment which leads to poor performance on the IGT (van Honk et al., 2004). In rodents, testosterone has been linked to reward and has reinforcing properties which may arise due to an increase in mesolimbic dopaminergic reactivity (Yildirim & Derksen, 2012). Testosterone levels were found to correlate with activation in the striatum in response to a reward during a gambling task in adolescents (Op de Macks et al., 2011). In adult males, salivary testosterone levels were related to delayed discounting of gains, but not losses, in an inverted U-shaped fashion (Takahashi et al., 2006). One possibility, therefore, is that sensitivity to reward and/or punishment, not propensity to take risks, mediates the relationship between circulating testosterone levels and IGT performance.

The orbitofrontal cortex is important for IGT performance (e.g., Bechara et al., 1994). Androgen receptors are present in orbitofrontal regions in adult and fetal rhesus monkeys (Finley & Kritzer, 1999; Handa et al., 1988) and the gray matter volume of this region is related to testosterone levels during fetal development (Lombardo et al., 2012). Androgens modulate the dopaminergic and serotonergic systems within the PFC (Handa et al., 1997) that are thought to be involved in reward/punishment processing (Cools et al., 2011). Given that androgen receptors are present in relevant regions, by which testosterone binds to exert its physiological effects, it seems plausible that testosterone in adulthood and/or during fetal development might affect brain areas and neurotransmitter systems important for IGT performance.

In conclusion, the current data suggest testosterone is a significant predictor of decision-making on the IGT, although current and developmental levels may influence performance through different functional mechanisms. The significant correlation revealed between 2D:4D and risk-taking propensity and the significant indirect effect of risk-taking on the relationship between digit ratio and performance opens the possibility that an organizational effect of androgens could influence the IGT via an effect on willingness to take risks. Future work should verify these findings in a larger sample that includes females, in addition to males.

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**CHAPTER 4**

**SEX DIFFERENCES ON TASKS ASSESSING REWARD PROCESSING AND INTERFERENCE INHIBITION**

Kelly L. Evans and Elizabeth Hampson

## 4.1  ABSTRACT

Increasing evidence suggests that the prefrontal cortex (PFC) is influenced by sex steroids and that some cognitive functions dependent on the PFC may be sexually differentiated in humans.  Past work has identified a male advantage on complex reinforcement learning tasks, but it is unclear what latent task components are important for eliciting the sex difference.  The objective of the current study was to investigate whether there are sex differences on measures of reversal learning, response inhibition, and valenced feedback processing, elements that are shared by previously used reinforcement learning tasks.  Healthy young adults (75 males, 75 females) matched in general intelligence completed the Probabilistic Selection Task (PST), a probabilistic reversal learning task involving either positive or negative feedback, a Simon task, and the Stop-Signal task.  On the reversal learning task, females assigned to the positive condition made fewer errors than males during the reversal phase, and made fewer errors than females assigned to the negative condition.  On the PST, there was a trend for females to be more accurate than males in learning from positive (but not negative) feedback.  On the Simon task, males were faster than females, especially in the face of incongruent stimuli.  There was no sex difference in Stop-Signal reaction time.  The current findings provide preliminary support for the existence of sex differences in the processing of valenced feedback and in interference inhibition.

**Key words:**  sex difference, reversal learning, reward processing, inhibitory control, prefrontal cortex

## 4.2  INTRODUCTION

Current evidence suggests that the prefrontal cortex (PFC) may be a sexually differentiated brain area in humans and may be responsive to the actions of sex steroids.  Sex steroids can have two types of effects in the brain, which are exerted at different points in the lifespan. Permanent effects on neural structure in responsive regions of the central nervous system take place during critical periods in prenatal or perinatal development and are referred to as o*rganizational effects.*  On the other hand, *activational effects* are the result of hormones currently in the adult bloodstream and are reversible (usually effects on neurochemistry). Sex differences can be the product of organizational effects, activational effects, or a combination of the two classes of effects (Breedlove & Hampson, 2002).  Given that sex steroids influence brain regions that contain the requisite receptors, it is important that androgen receptor-immunoreactivity has been found in the orbitofrontal PFC of adult rhesus monkeys (Clark et al., 1988; Finley & Kritzer, 1999).  Recent evidence also suggests that androgens may increase spine synapse density in the PFC of adult vervet monkeys (Hajszan et al., 2008) and may modulate the neurotransmitter systems of the PFC including dopamine and serotonin (Aubele & Kritzer, 2011; Handa et al., 1997).

With respect to cognitive functions dependent on the PFC, decision-making and reversal learning have been linked to the ventromedial PFC/orbitofrontal cortex by a large number of studies (VMPFC/OFC; e.g., Bechara et al., 1994; Budhani et al., 2007; Christakou et al., 2009a; Fellows & Farah, 2003).  Given the increasing evidence that the PFC may be responsive to sex steroids, it is important that sex differences have been observed on decision-making tasks such as the Iowa Gambling Task (IGT) and reversal learning tasks. Numerous studies to date have found that adult males perform better than adult females on the IGT (e.g., Bolla et al., 2004; Evans & Hampson, submitted; Reavis & Overman, 2001; Weller et al., 2009).  Similarly, a male advantage has been found on a simple object reversal task in young children (15 to 30 mo of age) (Overman et al., 1996) and on a complex probabilistic reversal learning task in adults (Evans & Hampson, submitted; but see Overman, 2004).  However, one issue that has yet to be resolved is that the IGT and reversal learning are both complex tasks that involve multiple component processes and it is not clear which functional task element leads to a male advantage.  Prominent task elements include learning based on probabilistic feedback, the presence of reversal elements in the tasks,

inhibitory control, and learning based on reward and/or punishment. A sex difference in one or more of these processes could give rise to the male advantage observed in past studies utilizing the IGT and reversal learning tasks. The objective of the current study was to examine shared task elements with an eye toward identifying which element underlies the previously observed sex difference.

Both the IGT and some reversal learning tasks require the understanding of probabilities. Use of probabilistic information is required on the IGT as the participant must evaluate the frequency of wins relative to losses from each deck as the task progresses to determine which decks are "good" and "bad". In probabilistic reversal learning, participants use probabilistic feedback to guide their choice of the correct object during acquisition and reversal. Despite the sex differences seen on these two tasks, current literature does not support the existence of a male advantage on other tasks that require the understanding or use of probabilities. For example, no sex difference has been found on the California Weather Task (Evans & Hampson, submitted; Reavis & Overman, 2001) which requires learning probabilistic associations between stimuli and outcomes. As well, a recent meta-analysis of 242 studies of mathematics performance published since 1990 found no evidence of a sex difference in a range of mathematical abilities, including items concerning probabilities (Lindberg et al., 2010). Thus it seems unlikely that probabilities will prove to be the basis for the male advantage seen in reversal learning or the IGT.

On the other hand, inhibitory control is an important component of performance on the IGT and reversal learning which, in principle, could be the source of the male advantage. On the IGT, participants are initially drawn to the "bad" decks in which the reward payout is higher, but to optimize performance they must learn to inhibit this attraction as these decks lead to larger monetary losses over time. Participants must also inhibit the tendency to shift their choice from the "good" decks to the "bad" decks upon encountering a loss in a "good" deck. During reversal learning, participants learn to inhibit their responses to the stimuli that were rewarded during acquisition after a reversal takes place. The empirical evidence is mixed regarding whether sex differences exist in response inhibition. One reason for the discrepancies may be the fact that response inhibition can itself be broken down into simpler components. For example, inhibition has been hypothesized to include subtypes such as action cancellation, interference inhibition, and action withholding (Sebastian et al., 2013).

Sex differences might or might not exist on any of the hypothetical components of response inhibition. With respect to action cancellation tasks like the Stop-Signal paradigm, several reports have failed to find a sex difference in Stop-Signal reaction time (Cross et al., 2011; Li et al., 2006; 2009; Williams et al., 1999). In terms of action withholding tasks like the go/no-go paradigm, females have been found to be better at inhibiting a response than males in some studies (Hansen, 2011; Hooper et al., 2004), but not others (Cross et al., 2011; Garavan et al., 2006; Liu et al., 2012). For tasks that involve interference inhibition, no sex differences have been found on the Stroop paradigm (Cross et al., 2011; MacLeod, 1991; Veroude et al., 2013), but a male advantage may exist on tasks that involve inhibiting responses to obvious stimuli in favor of less obvious stimuli (Halari & Kumari, 2005; Halari et al., 2005) and on other types of interference inhibition tasks (Clayson et al., 2011; Stoet, 2010).

A male advantage on the IGT and reversal learning could also potentially be linked to the "pure" reversal element of the tasks. Both the IGT and reversal learning require participants to reverse their initial preferences (for certain decks or stimuli) in order to perform optimally. As stated above, a male advantage has been found on a basic object reversal task in young children (15 to 30 months) but not in adults, though the reversal task used was overly simplistic for an adult population (Overman et al., 1996). A later study by Overman (2004) examined reversal learning in adults using a more complex probabilistic reversal task. The task involved one pair of stimuli (one object that was rewarded and one object that was punished) with the following probabilistic reinforcement contingencies: 100-0, 93-7, 86-14 or 80-20. After an initial learning criterion was met, the stimuli reversed (three such reversals took place) and the participant had to reach the learning criterion under the reversal conditions. Overman (2004) did not find any sex difference on the complex reversal learning task, but there was evidence that participants may have found the task too challenging or too long (it took a minimum of 90 mins to complete). In addition, the sample of males and females completing the most difficult stage of the task (80-20 contingency) was very unbalanced (8 males and 24 females). For these reasons, it may not have been possible to truly evaluate any existing sex difference in reversal learning. In a recent study from our lab (Evans & Hampson, submitted), we used a complex probabilistic reversal learning task that involved 90-10 and 80-20 reinforcement contingencies, but it had the advantage of taking a

shorter time (approximately 12 mins) and was less difficult as the objects only reversed once. The male and female samples in our study were larger than in the Overman (2004) study (e.g., Evans & Hampson, submitted: $n = 44$ for males and $n = 46$ for females). Results from our study indicated that on average, males performed more accurately during the reversal phase (but not during acquisition) compared to females.

Yet another potential explanation for the male advantage observed on the IGT and on reversal learning is a sex difference in processing positive and/or negative feedback. Both the IGT and reversal learning involve receiving rewards and punishments. Previous work finding a sex difference in performance on the IGT has suggested that the reward and punishment element of the task is important as females tend to select more cards than males from the deck with large, frequent rewards and a low frequency of punishments (e.g., Overman, 2004). Thus, it could be the case that males and females differ in their use of, or sensitivity to, reward and punishment information. The findings from our recent study (Evans & Hampson, submitted) support this idea as our reversal task elicited reward and punishment (points are given or taken away depending on the response). Initially, both reward and punishment must be used to determine the correct selections during acquisition, but the punishment element becomes more important upon reversal as participants must use the punishments elicited by incorrect choices to switch their responses to the other object in the pair.

Support for the idea that processing reward and/or punishment information may be a key component underlying the observed sex difference on the IGT and reversal learning comes from a study by Weller and colleagues (2009). In addition to finding the expected male advantage on the IGT, these researchers found that while there was no sex difference in risky choices related to potential gains, women took more risks when it came to potential losses compared to men on a simpler decision-making task. These authors speculated that sex differences may be related to components of decision-making only when avoidance of losses is necessary (Weller et al., 2009). Another recent study by Robinson and colleagues (2010) found a sex difference in punishment-related reversal learning after a procedure to reduce global dopamine synthesis, whereby females displayed improved reversal learning based on punishment after dopamine depletion. However, reward-related reversal learning was unaffected. A further study found that women activated the medial PFC at the time of

reward delivery more strongly than men during a slot machine task that varied reward probability, magnitude, and expected value (Dreher et al., 2007). Thus, some limited evidence suggests there may be sex differences related to learning from reward and punishment. If this is true, it potentially could be the functional component leading to the observed male advantage on the IGT and reversal learning.

The objective of the current study was to determine which task components are the key source of the male advantage. Possible latent processes include response inhibition, "pure" reversal, and/or processing reward- and/or punishment-related feedback. Two inhibitory control tasks were included in the present work to determine whether there is a sex difference in two components of response inhibition. The Stop-Signal task assessed action cancellation and the Arrows Task assessed interference inhibition. The Probabilistic Selection Task (PST; modified from Frank et al., 2004) was used to examine learning from positive and negative feedback in the absence of reversal. If the male advantage on the IGT and reversal learning tasks is related to a sex difference in processing positive and/or negative feedback, then a sex difference in performance on the PST would be expected. Probabilistic Reversal Learning was also included in the current study. The same task from our previous study showing a male advantage (Evans & Hampson, submitted) was modified so that one version made use of positive feedback only and one version made use of negative feedback only. All other task elements remained the same. It was hypothesized that changing the feedback element of the task would eliminate the male advantage if the sex difference is related to processing positive or negative feedback. On the other hand, if the male advantage is related to the "pure" reversal element, it would be expected that males would outperform females on both versions of the reversal task regardless of the type of feedback given.

## 4.3 METHOD

### 4.3.1 Participants

Healthy young participants were recruited from the University of Western Ontario and received monetary compensation or course credits for participating. Only participants with no history of neurological (e.g., sports-related head injury) or mental health conditions, and not on psychoactive medications were included. Females were required to be naturally cycling and not currently using oral contraceptives, which suppress the production of ovarian

hormones. Nine participants showed evidence of active depression on the Profile of Mood States (McNair et al., 1971) administered during the test session, and had to be excluded. Because several of the tasks in our study involved complex instructions and adequate comprehension was necessary to ensure the validity of the resulting test scores, any participant with English as a second language who scored below one standard deviation from the mean on the Verbal Meaning Test (a test of vocabulary knowledge administered during the test session; Thurstone & Thurstone, 1963) based on local test norms was not included in statistical analyses ($n = 12$). There were 150 participants in the final sample (75 males, 75 females) with a mean age of 20.35 for males (range = 18-30 years) and a mean age for females of 20.59 (range = 17-31 years). Participants provided written informed consent before taking part in the study. The study received ethical approval from the Research Ethics Board for Non-Medical Research Involving Human Subjects at the University of Western Ontario (Appendix C).

*4.3.2 Experimental Tasks*

    *4.3.2.1 Probabilistic selection task (modified from Frank et al., 2004).* The PST consisted of a training and a test phase. During the training phase, participants viewed three pairs of objects one at a time and had to learn which object in each pair was 'correct' (Figure 4.1). The objects were abstract line drawings chosen from the Self-Ordered Pointing task of Petrides and Milner (1982). The participant selected one of the objects from each pair by pressing one of two buttons on a response box and feedback was provided ("*Correct!*" printed in blue or "*Incorrect!*" printed in red). The feedback was probabilistic and the reinforcement contingencies differed for each pair. The first pair (Pair AB) was 85-15 (object A was 'correct' on 85% of trials, object B was 'correct' on 15% of trials), the second pair (Pair CD) was 75-25, and the third pair (Pair EF) was 65-35. The pairs were presented in blocks of 60 trials (20 trials of each pair). The participants continued in the training phase until they reached a designated learning criterion or until 480 trials were completed. The learning criterion was choosing A over B in 70% of trials within a block as has been used in some past research (Rustemeier et al., 2012). Previous studies have used slightly more strict criteria for learning (e.g., choosing A over B in 70% of trials *and* C over D in 65% of trials; Wheeler & Fellows, 2008). However, learning to prefer A over B is the key to successful
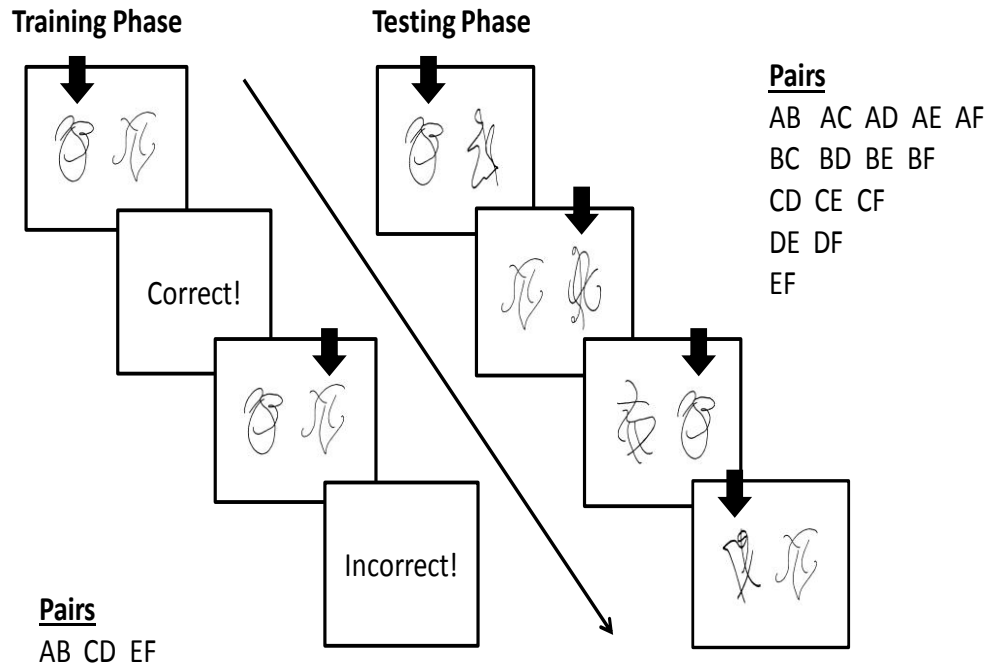
**FIGURE 4.1**. Probabilistic Selection Task. The vertical arrows represent hypothetical choices made by a participant. During training, participants had to learn which object in each of three pairs (AB, CD, EF) was correct. The reinforcement contingencies were 85-15 (AB), 75-25 (CD), and 65-35 (EF). After reaching the learning criterion or completing 480 trials, the test phase began. During the test phase, all possible pairings of the six objects were presented. Participants had to select the object they thought was correct in each pair shown, based on their experience from the training phase, without receiving feedback. Learning based on *positive feedback* was measured by the number of times object A was selected in all pairings other than AB. Learning based on *negative feedback* was measured by the number of times object B was avoided in all pairings other than AB.

performance during the test phase (Rustemeier et al., 2012) and the more lenient criterion used in the current study allowed the maximum number of participants to be included in the final analysis. During the testing phase, the objects were recombined to form all possible combinations (including the original 3 pairings) and the participants performed the same task, this time without receiving feedback. Each pair was presented 3 times (90 trials in total). The number of trials in which the object reinforced the most during training (i.e., object A reinforced 85% of the time) was chosen from the novel pairs (AC, AD, AE, AF) represented a measure of learning from positive feedback. The number of trials in which object B, the object reinforced the least (15% of the time), was avoided in the novel pairs (BC, BD, BE, BF) represented a measure of learning from negative feedback. Twelve matched versions of the PST were created to ensure that all objects had a chance to be object A and object B (e.g., object A = item 1 and object B = item 2 in one version) and that every object was the reinforced object in the AB pair (e.g., object A = item 2 and object B = item 1 in another version). Stimuli were presented using E-Prime 2.0.

   *4.3.2.2 Probabilistic reversal learning.* The reversal learning task used in the current study was modeled after Budhani et al. (2007) and was presented using E-Prime 2.0. The task involved two conditions (each ~ 6 minutes). In each condition, one of three possible pairs of common, neutrally valenced objects (fruit or musical instruments from Snodgrass & Vanderwart, 1980) was displayed on a computer screen on each trial. The participant selected one of the objects from each pair by pressing a button and feedback was provided. There were two versions of the task. In the *positive feedback only* version, choosing one object led to winning 100 points, choosing the other object led to winning only 10 points (Figure 4.2, Panel A). In the *negative feedback only* version, choosing one object led to losing 100 points, the other object led to losing only 10 points (Figure 4.2, Panel B). If no selection was made in the allotted time, the participant either won 10 points or lost 100 points (depending on the version). Each trial was 2 s in length (pairs were displayed for 1100 ms and feedback for 900 ms). The participants were not aware of which object in each pair was correct and had to learn this through trial and error based on the feedback received. Participants were told that the correct object could change over the course of the task, but were not aware of when or if a reversal would take place. The reinforcement contingency for the first condition was 90-10 (on 90% of trials the participant was given correct feedback by
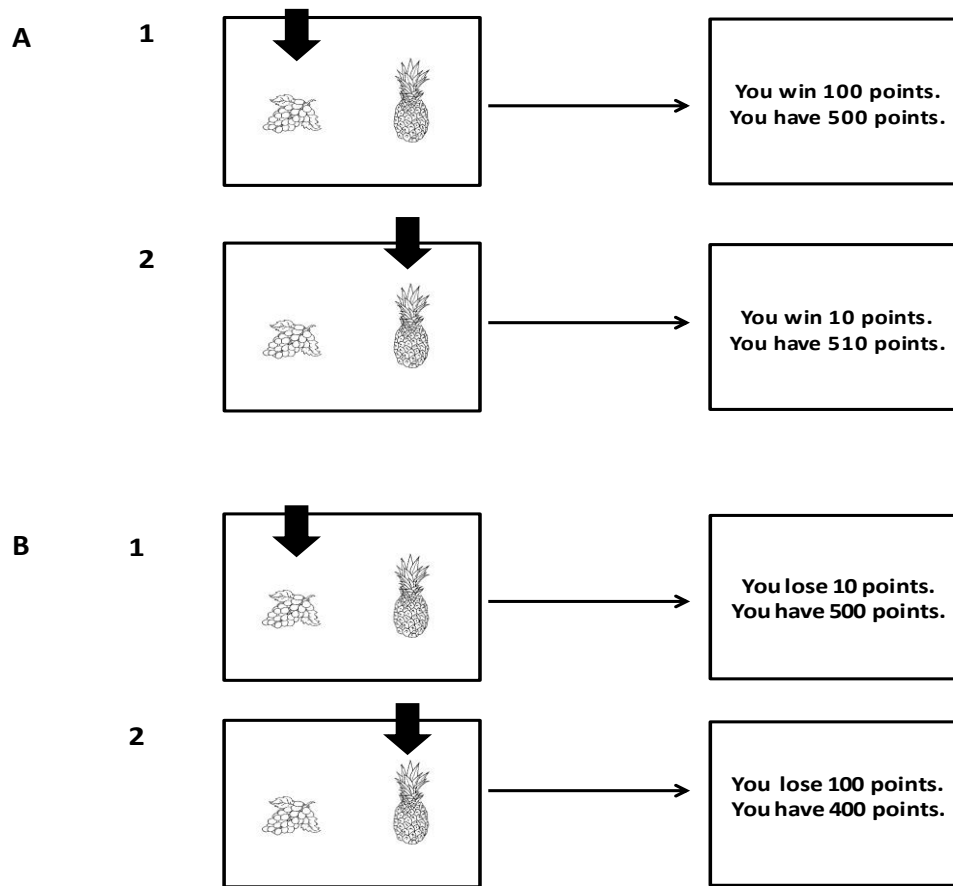
**FIGURE 4.2.** Positive version (Panel A) and Negative version (Panel B) of Probabilistic Reversal Learning. The vertical arrows represent hypothetical choices made by a participant. In Panel A, Trial 1 represents a trial where a correct response was maximally rewarded. Trial 2 represents a trial where an incorrect response was minimally rewarded. In Panel B, Trial 1 represents a trial where a correct response was minimally punished. Trial 2 represents a trial where an incorrect response was maximally punished. Due to the probabilistic nature of the task, there were also correct trials that received the minimum reward (or maximum punishment) and incorrect trials that received the maximum reward (or minimum punishment).

the computer and on 10% of trials the participant was given incorrect feedback) and was 80-20 for the second condition.  A screen with feedback (*You win 100 points/You win 10 points* (positive version) or *You lose 10 points/You lose 100 points* (negative version) and the participant's current points total was shown after each selection.  In the positive feedback only version, participants started with zero points and in the negative feedback only version, they started with 5000 points.

After 20 trials of each pair of stimuli, two of the pairs underwent reversal (i.e., the other object in the pair became the rewarded selection) and one pair remained unchanged.  Because it was hypothesized that there may be a sex difference in learning from valenced feedback, a new measure of acquisition was created for purposes of the current study, which emphasized the early stages of learning when reliance on feedback is maximized.  Specifically, to assess *acquisition accuracy*, the first ten trials of each of the three pairs in each condition were used to calculate an accuracy score.  *Reversal accuracy* was calculated using the ten trials immediately after the reversal for the two reversing pairs[1].  In each case, the accuracy score represented the number of correct selections regardless of feedback.  Two versions of the Probabilistic Reversal Learning task were created to counterbalance the objects that were considered correct during acquisition.

 *4.3.2.3  Arrows task (Davidson et al., 2006).*  The Arrows task was used to assess interference inhibition.  On each trial, a single arrow was presented on the left or right side of the computer screen.  The participant was told to press the left or right button on a response box located in front of the screen, depending on where the arrow was pointing. On congruent trials, the arrow pointed straight down toward the left or right button (arrow and button press on the same side).  On incongruent trials, the arrow appeared on the left or right of the screen but pointed diagonally toward the contralateral button (right or left button, respectively, i.e., arrow and button press on opposite sides).  The time required to respond (*Speed*, calculated as the median reaction time in milliseconds based on trials in which a correct button press

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[1]In ~3% of cases, a participant repeatedly chose the same object from one pair during both acquisition and reversal within a particular contingency condition.  This pattern often resulted in a poor acquisition score and a good reversal score (e.g., all 10 trials correct after reversal) when no reversal had in fact occurred.  To address this issue, we used a correction whereby a participant's reversal score was calculated based on the <u>actual</u> (though incorrect) object selected during acquisition.  For example, a score of 9 (out of 10) correct after reversal that was based merely on continuing to select the same incorrect acquisition object, would be inverted to create a reversal accuracy score of 1.

was made) and the number of correct responses made (*Accuracy*, the percentage of correct responses) were computed separately for congruent and incongruent trials. Any response time less than 200 ms was considered to be too fast to be made in response to an arrow and thus was considered to be anticipatory (Davidson et al., 2006). Anticipatory responses were not included when calculating Accuracy or Speed.

The Arrows task is based on the classic Simon task paradigm where a specific stimulus like a picture is tied to a response on a particular side. Responses are more accurate and faster if the stimulus and side of the response are congruent than when they are incongruent (The Simon Effect; e.g., Simon & Rudell, 1967; Simon & Berbaum, 1990). The Arrows task was used to provide a measure of interference inhibition as it involved a conflict between responses that were involuntarily co-activated due to incompatible stimulus dimensions (Sebastian et al., 2013). Participants had to inhibit their prepotent tendency to respond on the same side as the arrow on incongruent trials and instead press the button on the side opposite to the arrow. The memory load was reduced compared to a Simon task with pictures as the arrow always pointed directly to the correct response.

*4.3.2.4 Stop-Signal Task (Cambridge Neuropsychological Test Automated Battery; CANTABeclipse, Cambridge Cognition Ltd, UK).* On each trial, an arrow was presented inside a fixation circle on the computer screen, pointing horizontally to the left or right. The participant was asked to monitor the direction of the arrow and to press the corresponding button on the response box, using the index finger of the left or right hand, as quickly as possible unless they heard a beep. During a trial with a beep (which occurred on 25% of trials), the participant refrained from responding to the best of their ability.

Because the behaviour of interest in the task is actually the lack of overt behaviour (i.e., inhibiting a response), stop-signal reaction time (SSRT) must be estimated based on a theoretical model. The model commonly used is the "horse-race" model which assumes that there are two processes (the "stop" and "go" processes) that race against one another and the final behavioural outcome depends on which of the two processes wins the race (Logan & Cowan, 1984) (Figure 4.3). Only the 'go' reaction time, the time to a correct button press in response to a 'go' signal (the onset of the arrow), can be computed directly. To compute the SSRT, an individual's stop-signal delay (SSD; the time elapsed before the stop-signal (beep)
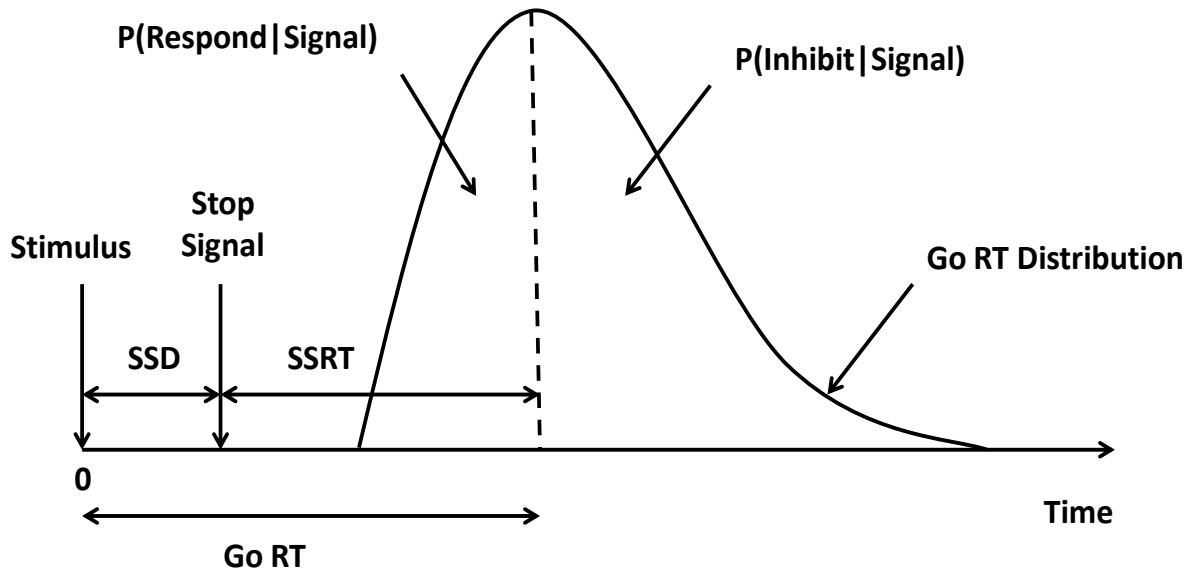
**FIGURE 4.3.** The Stop-Signal Task. The theoretical model used to compute the stop-signal reaction time (SSRT) is called the "horse-race" model. The model assumes that under conditions where a stop signal is given the "stop" and "go" processes race against each other and the process that wins the race will dictate which behaviour will be exhibited. The graph depicts the hypothetical distribution of an individual's go reaction times (median go reaction time (RT) falls at the dotted line). In trials where a stop-signal is given, the time from the 'go' stimulus presentation to the stop-signal presentation is called the stop-signal delay (SSD). A tracking procedure built into the CANTAB software monitors outcomes and adjusts each individual's SSD so that the probability of inhibition (P(Inhibit|Signal)) and the probability of responding (P(Respond|Signal)) are equal (i.e., both approximately 50%). This ensures that the SSRT is not biased as the estimate is based on the densest part of the curve (i.e., at 50%), not the tails of the distribution (Band et al., 2003; Leotti & Wager, 2010). To calculate the SSRT, the SSD is subtracted from the median go reaction time.

is presented) is subtracted from their median go reaction time observed over a series of trials. Using a tracking procedure built into the software, the delay interposed before the stop-signal occurs (the SSD) is adjusted for each individual such that the timing of the auditory signal will result in successful response inhibition on 50% of trials. The tracking procedure ensures that the stop-signal is generated based on each participant's actual performance so that the signal will come later after a successful inhibition trial (making performance on the next stop trial more difficult) and earlier after an unsuccessful inhibition trial (making inhibition on the next stop trial easier) and ensures task difficulty is controlled across participants (Congdon et al., 2012). The Stop-Signal Task was used as a measure of inhibitory control and assesses the ability to cancel an already ongoing motor response (Sebastian et al., 2013). Median go reaction time was calculated for the whole task and measures of the proportion of successful stops, SSD, and SSRT (in milliseconds) were generated for the last half of the task.

### 4.3.3  Control Tasks

*4.3.3.1  Verbal Meaning Test (Thurstone & Thurstone, 1963).* This paper and pencil test assessing vocabulary knowledge has 60 items and the participant was allowed 4 minutes to complete as many items as possible. For each item, the participant must choose the word from a list of five alternatives that best matches the meaning of a target word. The score was the number of correct items. This task was included to assure the groups were matched in overall ability, as vocabulary tasks have been shown to be predictive of general intelligence (Vernon, 1971; Wechler, 1981; Ziegler & Doehrman, 1979).

*4.3.3.2  Positive and Negative Affect Schedule (PANAS; Watson et al., 1988).* The PANAS has 20 items that describe different emotions. There are 10 positive adjectives (e.g., interested, excited) and 10 negative adjectives (e.g., distressed, upset). Participants were asked to rate each adjective on a scale that ranged from 1 (*very slightly or not at all*) to 5 (*extremely*), according to how much they felt that way on the day of testing. Total scores were calculated for positive affect and negative affect separately. The PANAS was given at the beginning of the test session to determine whether mood played a role in the sex difference on any of the experimental tasks.

*4.3.4 Procedure*

The order of the Probabilistic Reversal Learning task and the Probabilistic Selection Task was counterbalanced across participants to control any potential carryover effects. Two versions of the Probabilistic Reversal Learning task were used: a negative feedback only version and a positive feedback only version. Four groups were tested consisting of males and females who were randomly assigned to each condition. Of the 75 males, 36 were in the Positive condition and 39 were in the Negative condition. Of the 75 females, 39 were in the Positive condition and 36 were in the Negative condition. The object in each pair considered the 'correct' choice during acquisition on the Probabilistic Reversal Learning and the object that comprised object A on the Probabilistic Selection Task also was counterbalanced.

*4.3.5 Statistical Analyses*

All analyses were done using IBM SPSS 19.0 statistical software. Univariate ANOVAs were used to determine whether a sex difference existed on each experimental task. MANOVA was not utilized because its use in the omnibus context is considered questionable (Huberty & Morris, 1989). The Greenhouse-Geisser epsilon was used to correct for any sphericity violations in the repeated measures variables and interactions (Kirk, 1995). An alpha level of .05 was used for all statistical tests involving sex differences, in view of the exploratory nature of the present work and for improved statistical power in light of a subset of participants who failed to meet the learning criterion on the Probabilistic Selection Task (see below).

## 4.4 RESULTS

*4.4.1 Experimental Tasks*

 *4.4.1.1 Probabilistic selection task.* There was one outlier on the Choose A accuracy measure who scored greater than three standard deviations below the mean. This data point was removed from all PST analyses. The number of participants reaching the learning criterion in the training phase was 119 (80% of all participants), consistent with prior studies that used the same criterion used here (e.g. 75%; Rustemeier et al., 2012). Therefore, this subset of participants was used to analyze the test phase of the Probabilistic Selection Task and all other tasks in the current study for consistency. There was no significant difference

between the number of males (57 of 75) and females (62 of 74) reaching criterion, $\chi^2(1) = 1.41$, $p = .236$ nor was there any difference between males ($M = 184.89$, $SD = 136.17$) and females ($M = 221.92$, $SD = 143.35$) in the number of trials needed to reach criterion, $F(1, 117) = 2.08$, $p = .152$.

To test the hypothesis of a sex difference in learning from positive or negative feedback, the number of trials in which participants successfully chose A or successfully avoided B during the test phase were entered, respectively, into an ANOVA with sex (male, female) and test order (PRL first, PST first) as between-subjects factors. Test order was included to test for carryover effects. There were no significant main effects or interactions involving test order (e.g., order did not significantly interact with sex on the Choose A measure ($F(1, 115) = 0.46$, $p = .498$) or the Avoid B measure ($F(1, 115) = 0.14$, $p = .707$). Therefore, test order was excluded as a factor to simplify the analysis. As shown in Figure 4.4, females in the present sample tended to be more accurate in choosing A (learning from positive feedback) compared to males, $F(1, 117) = 3.77$, $p = .055$. There was no significant difference between males and females in successfully avoiding B (learning from negative feedback), $F(1, 117) = 0.09$, $p = .762$.

    *4.4.1.2 Probabilistic reversal learning.* There was one outlier on the Reversal measure that was three standard deviations below the mean. This data point was removed from all PRL analyses. A mixed design ANOVA was performed with the between-subjects factors of sex, test order, and feedback condition (positive, negative) and reinforcement contingency (90-10, 80-20) as a within-subjects factor. The dependent variables were accuracy during acquisition and accuracy after the reversal. In contrast to the PST, test order was found to interact significantly with sex, feedback, and reinforcement contingency during the Reversal phase, $F(1, 111) = 4.65$, $p = .033$, and to interact with reinforcement contingency ($F(1, 111) = 5.91$, $p = .017$) during Acquisition. Thus, to avoid higher-order interactions and assess learning from valenced feedback in the purest form, only participants who had completed the reversal learning task first were assessed, and only on the 90-10 contingency as it was always given before the 80-20 condition. This allowed us to assess performance in the absence of carryover effects from the PST, or carryover effects from previously experienced reversals.
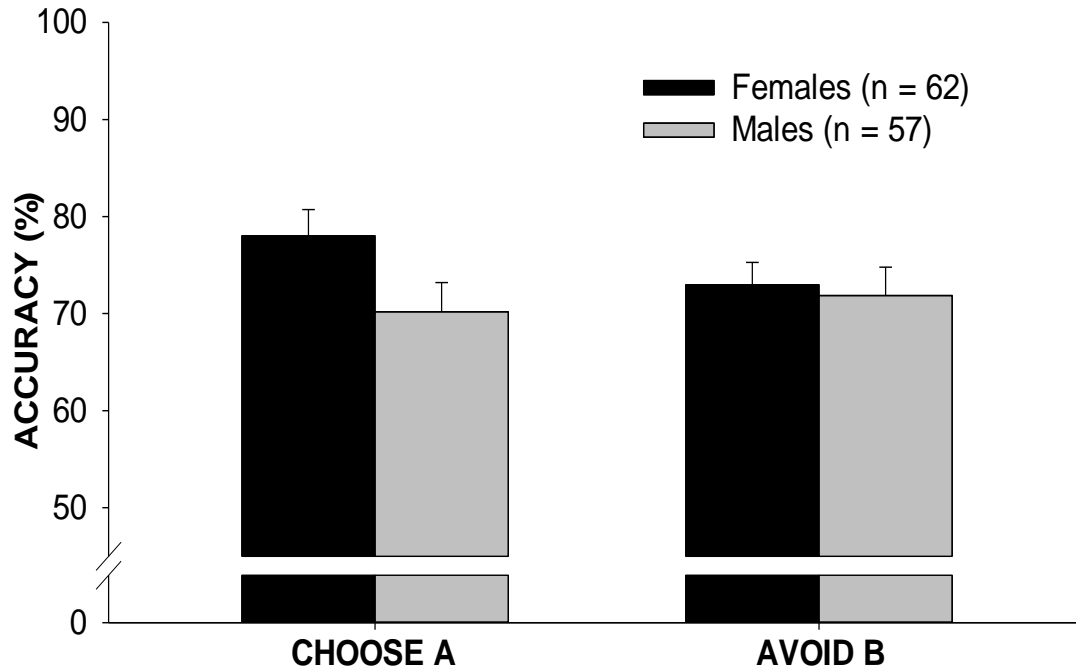
**FIGURE 4.4.** Mean accuracy during the testing phase on the Probabilistic Selection Task as a function of sex. Error bars represent SEM. There was no significant sex difference in learning from negative feedback (avoiding B), but the difference in mean accuracy between males and females in learning from positive feedback (choosing A) approached significance ($p = .055$).

As seen in Figure 4.5 (Panel A), in the 90-10 condition, there was no overall main effect of sex (Sex: $F(1, 53) = 0.94$, $p = .337$) or main effect of feedback condition (Feedback: $F(1, 53) = 2.21$, $p = .143$) on accuracy during early acquisition.  Females in the positive condition tended to perform better than females in the negative condition, but the interaction between sex and type of feedback did not reach statistical significance (Sex x Feedback, $F(1, 53) = 3.14$, $p = .082$).  It had been hypothesized that a male advantage would be seen following reversal, regardless of the type of feedback received, if the advantage stemmed from the pure reversal element of the task.  After Reversal (Figure 4.5, Panel B), however, there was no significant main effect of sex (Sex: $F(1, 53) = 2.22$, $p = .142$).  Instead, the interaction between sex and feedback condition was significant (Sex x Feedback: $F(1, 53) = 9.74$, $p = .003$).  During the reversal phase, females assigned to the positive feedback condition showed higher accuracy than males assigned to the same condition ($q(53) = 4.40$, $p < .01$ by Tukey-Kramer test) and scored higher than the females assigned to the negative feedback condition ($q(53) = 4.22$, $p < .01$).  Although the means were reversed, there was no significant sex difference in the negative feedback condition ($q(53) = 1.72$, $ns$) and only the male group performed above chance (see Figure 4.5, Panel B).

*4.4.1.3  Arrows task.*  The Arrows data were analyzed using a mixed design ANOVA with trial type (congruent, incongruent) as a within-subjects factor and sex as a between-subjects factor.  Separate ANOVAs were run with accuracy and speed as the dependent variables.  For accuracy (data not shown), there was a significant main effect of trial type ($F(1, 116) = 41.42$, $p < .001$) such that accuracy was higher on congruent than incongruent trials, as expected.  This confirms the classic Simon Effect.  There was no main effect of sex ($F(1, 116) = 0.12$, $p = .733$) and no significant interaction between sex and trial type, $F(1, 116) = 2.53$, $p = .115$.

The RT data are shown in Figure 4.6.  A significant Simon Effect was confirmed, whereby there was a main effect of trial type ($F(1, 116) = 116.87$, $p < .001$).  Reaction times were shorter on congruent trials than incongruent trials.  The main effect of sex was significant ($F(1, 116) = 23.00$, $p < .001$); males made faster responses than females.  Importantly, the interaction between sex and trial type was also significant, $F(1, 116) = 8.44$, $p = .004$, indicating that the magnitude of the male advantage was larger for the incongruent trials, in which the inhibition of a prepotent response was required.
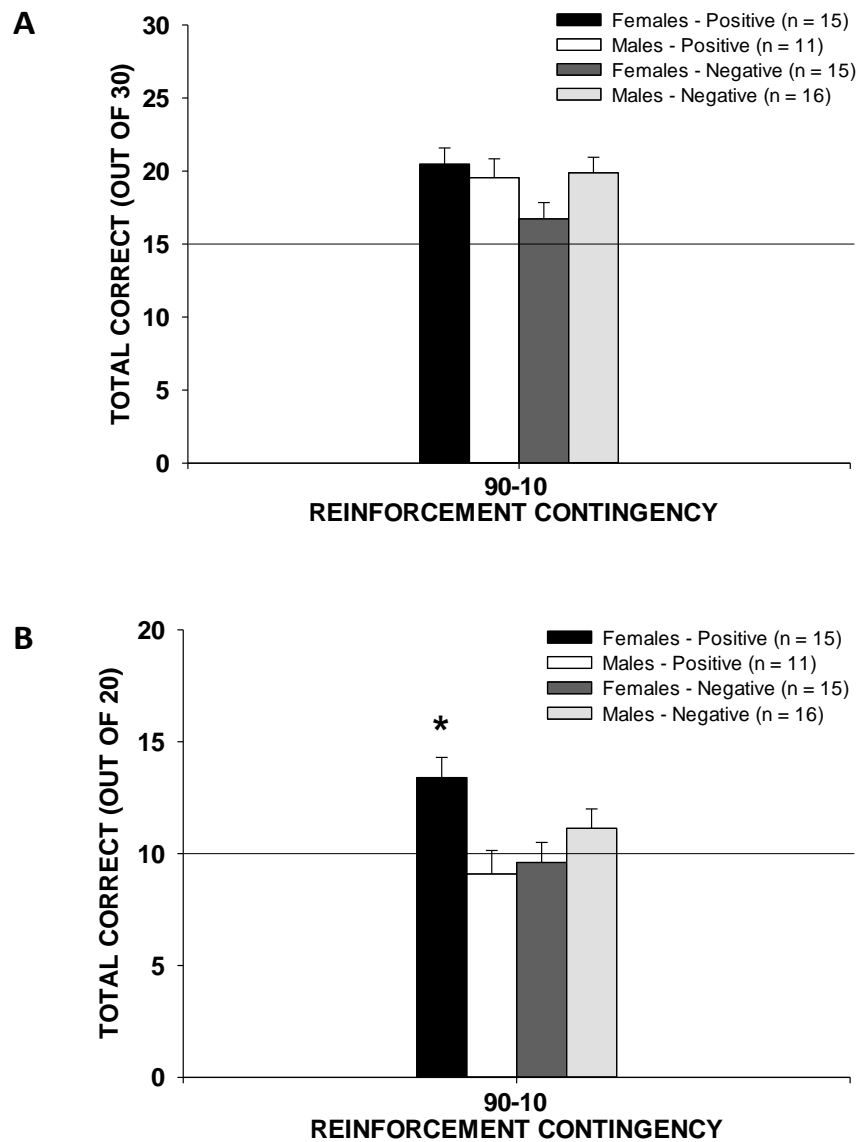
**FIGURE 4.5.** Mean accuracy during acquisition (Panel A) and during the reversal phase (Panel B) of the Probabilistic Reversal Learning task as a function of sex and type of feedback received. Error bars represent SEM. During acquisition, the interaction between sex and type of feedback approached significance ($p = .082$). After reversal, there was a significant interaction ($p = .003$), such that females assigned to the positive feedback condition performed better than males, but in the negative feedback condition, the sex difference was not significant.
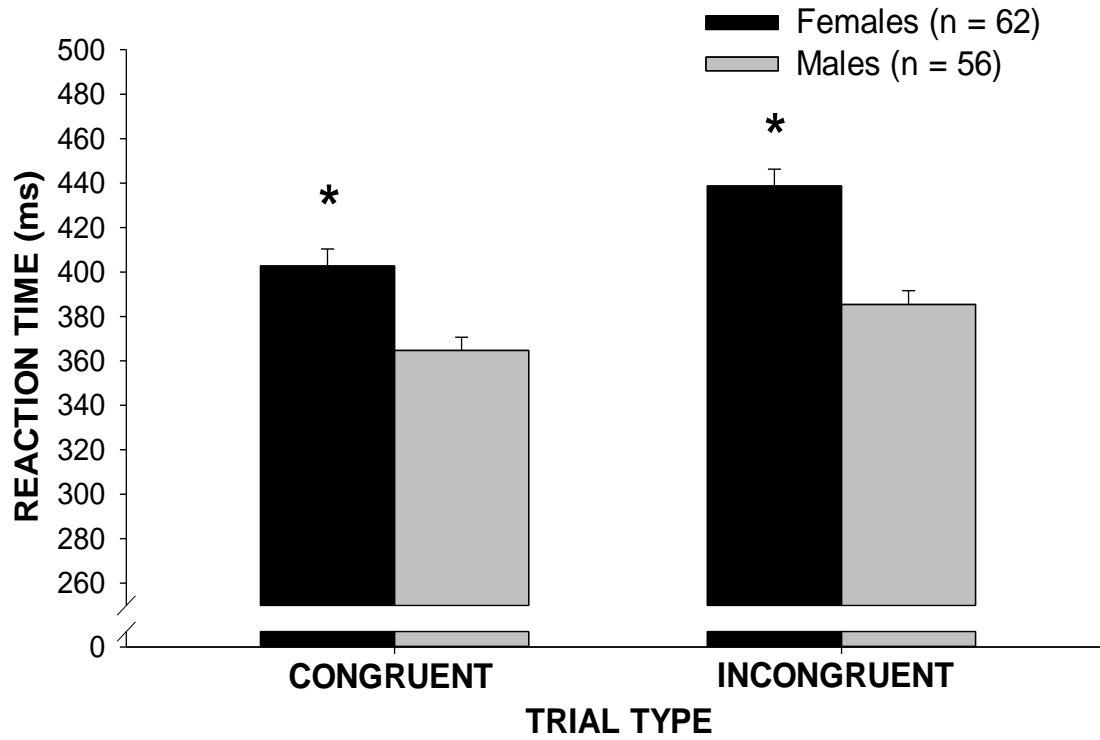
**FIGURE 4.6.** Mean reaction time on the Arrows task as a function of sex. Error bars represent SEM. Males were faster than females in both conditions, but the sex difference was significantly larger for incongruent than for congruent trials.

*4.4.1.4 Stop-Signal Task.* The Stop-Signal Task was analyzed using one-way ANOVAs with sex as a between-subjects factor. The SSRT, which represents the RT to successfully inhibit a pre-programmed motor response, was the dependent variable of interest for testing the hypothesis of a male advantage. However, to help interpret the data, the median reaction time on go trials, the proportion of successful stops, and SSD, also were analyzed. Because this meant 4 ANOVAs for the Stop-Signal Task, $p = .01$ was adopted as the criterion for significance. Across the whole task, there was a significant difference between males and females in median go reaction time ($F(1, 109) = 7.99$, $p = .006$) such that males were faster than females (see Table 1). On average, males also had shorter stop-signal delays ($F(1, 109) = 7.16$, $p = .009$). There were no significant differences between males and females on the proportion of successful stops ($F(1, 109) = 0.13$, $p = .715$) or, most importantly, on SSRT ($F(1, 109) = 0.34$, $p = .560$) (Table 4.1).

*4.4.2 Control Tasks*

*4.4.2.1 Verbal Meaning Test.* As expected, an ANOVA with sex and feedback group as factors showed no significant sex difference on the Verbal Meaning Test and no significant differences as a function of feedback condition assignment (Sex: $F(1, 116) = 0.16$, $p = .691$; Feedback: $F(1, 116) = 1.31$, $p = .255$; Sex x Feedback: $F(1, 116) = 0.07$, $p = .791$). In the positive group, males ($M = 30.74$, $SD = 10.77$, $n = 27$) achieved similar mean scores to females ($M = 29.58$, $SD = 10.41$, $n = 33$). The mean scores of males ($M = 28.27$, $SD = 9.58$, $n = 30$) and females ($M = 28.03$, $SD = 7.23$, $n = 30$) in the negative group were also similar.

*4.4.2.2 PANAS.* Analysis of the mood scores unexpectedly revealed a significant main effect of sex on the PANAS Positive Affect score (Sex: $F(1, 116) = 4.71$, $p = .032$). Females had lower average scores on the Positive Affect scale than did males (see Table 4.2). No other effects were significant, either for Positive Affect or Negative Affect. Positive Affect was not a significant covariate when entered into any of the above reported analyses (data not shown) suggesting that the sex difference in Positive Affect did not play a role in the present findings.

**TABLE 4.1**

*Performance Measures on the Stop-Signal Task for Males and Females*

| Measure | Males (*n* = 48) | Females (*n* = 63) |
|---|---|---|
| Median Go Reaction Time | 353.10 (70.05) | 403.38 (106.92) * |
| Proportion of Successful Stops | 0.498 (0.07) | 0.503 (0.07) |
| Stop-Signal Delay (SSD) | 177.90 (91.49) | 232.71 (117.24) * |
| Stop-Signal Reaction Time (SSRT) | 175.21 (42.25) | 170.59 (40.41) |

*Note.* * $p < .01$.

**TABLE 4.2**

*Mean (SD) Scores of Males and Females on the Positive and Negative Affect Schedule*

|  | Males (n = 57) | Females (n = 62) |
|---|---|---|
| Positive Affect | 30.09 (6.08) | 27.33 (7.32) * |
| Negative Affect | 14.11 (4.43) | 14.50 (4.55) |

*Note.* * *p* < .05.

**4.5  DISCUSSION**

A male advantage has been reported on reinforcement learning tasks such as the IGT and reversal learning (e.g., Evans & Hampson, submitted; Overman et al., 1996; Reavis & Overman, 2001; Weller et al., 2009).  These tasks are functionally complex and involve many component processes that could be the source of the male advantage.  A critical determinant of performance on both the IGT and reversal learning is the ability to flexibly alter behaviour based on valenced feedback.  The presence of reversal elements in the tasks, the need for inhibitory control, and the processing of reward- and/or punishment-related cues, are all functional components that could be significant.  The objective of the current study was to begin to identify the task component(s) that are important for eliciting the sex difference on reinforcement learning tasks.

Previous research has found a male advantage in young children (Overman et al., 1996) and in adults (Evans & Hampson, submitted) on certain reversal learning tasks.  We hypothesized that if the male advantage were due to the "pure" reversal element, then males would outperform females on both versions of the Probabilistic Reversal Learning task used in the present study, regardless of the type of feedback received, because both versions required the reversal of a learned response.  A male advantage in reversal *per se* was not supported by our data.  In fact, in the positive feedback condition there was a significant *female* advantage during the reversal phase.  This suggests the male advantage observed on the IGT and reversal learning tasks in previous studies is not attributable to a sex difference in the ability to alter a previously learned stimulus-feedback association when contingencies change.

An alternative hypothesis, also tested here, is the possibility that a sex difference exists in learning from positive or negative feedback.  This was tested through the use of the Probabilistic Selection Task and by revising the Probabilistic Reversal Learning task used in previous work to create separate reward-based and punishment-based learning conditions.  Some data from the current study did support the idea that there is a sex difference in processing valenced feedback, both under initial learning and in re-learning after a change in the rewarded object had occurred.  Specifically, females who were randomly assigned to the *positive* feedback condition of the PRL significantly outperformed males during the re-learning trials that followed a reversal.  Males assigned to the positive feedback condition

performed at chance. This pattern was supported by the Probabilistic Selection Task where, in the absence of any reversals, females tended to show higher accuracy than males in choosing the stimulus that was rewarded during the learning phase ($p = .055$). If anything, the sex difference was reversed among the males and females assigned to receive *negative* feedback on the PRL, both after reversal and during initial acquisition, but in the present study the sex differences seen in the negative condition were not significant.

A sex difference in the processing of valenced feedback would be consistent with several previous observations and conjectures. A sex difference on the IGT has been documented (e.g., Evans & Hampson, submitted; Goudriaan et al., 2007; Overman, 2004; Weller et al., 2009; van den Bos et al., 2012), whereby males select more cards from the advantageous decks than do females. The sex difference appears to be driven by a consistent difference in the preference shown for a deck that has frequent, large rewards and infrequent punishments (i.e., females select more cards from this particular deck even though, objectively, the deck leads to reduced winnings over the long term). This finding has led to speculation that there may be a difference between the sexes in how reward and punishment is used to guide IGT performance (Overman, 2004; Overman et al., 2006). It has been suggested that females rely more on immediate reward and punishment information, and do so for a longer period of time, whereas males more rapidly adopt a perspective that focuses on objective long-term payoffs allowing them to select the advantageous response options on the IGT (Overman et al., 2011; van den Bos et al., 2012). In further work using a different gambling task, females showed a larger response to reward, but not punishment, compared to males as indexed by an electrophysiological measure (feedback-related negativity) (Santesso et al., 2011). On the other hand, Moeller and Robinson (2010) discovered that females slowed their responses during a categorization task in response to error feedback to a larger degree than males and suggested that this is related to a sex difference in punishment sensitivity, although it should be noted that responses to positive feedback were not measured. Thus, data from previous work and tentatively, the current study, support the general hypothesis that a sex difference may exist in the processing of, or sensitivity to, valenced feedback. The present study is one of the first to systematically address this possibility at an empirical level.

A sex difference in responding to valenced feedback may not be the only task component leading to a male advantage on reinforcement learning tasks. Many such tasks require

inhibitory control processes. In the current study, a male advantage was found on the Arrows, but not on the Stop-Signal Task. These two tasks measure different aspects of response inhibition, and in that sense the present dissociation may be theoretically informative. The Arrows task assesses interference inhibition, whereas the Stop-Signal Task assesses action cancellation. It is plausible that a sex difference might exist in one form of inhibitory control, but not the other. Although dedicated studies of sex differences do not exist in the current literature, the dissociation seen in the present study is supported by the limited data available. A male advantage has been reported during a task that involved inhibiting responses to obvious stimuli (numbers shown counting forward) in favor of less obvious stimuli (numbers shown counting backward) (Halari & Kumari, 2005; Halari et al., 2005) and several studies using other interference inhibition tasks (i.e., the Flanker task) have also found that males are faster and make fewer errors than females (Clayson et al., 2011; Stoet, 2010). An fMRI study by Christakou and colleagues (2009b) found a sex difference in the pattern of brain activation elicited during a Simon task. Also in agreement with the current findings, past studies have found no sex differences on measures of inhibitory control that involve the cancellation of a prepotent action such as the Stop-Signal task (Cross et al., 2011; Li et al. 2006; 2009). Thus, it may be the case that there is a male advantage on inhibitory control tasks that involve interference, but not on inhibitory tasks that involve cancellation of an action.

If, in fact, males do have enhanced inhibitory control related to interference and females focus more on rewards during task performance then it may help to explain why males perform better than females on the IGT and on reversal learning tasks where responses must be learned and re-learned through the provision of both positive and negative feedback. With respect to reversal, previous studies that found sex differences (Evans & Hampson, submitted; Overman et al., 1996) employed tasks that allot reward and punishment as feedback to learn which stimuli are correct. However, when a reversal occurs, it is punishing information that is most relevant for learning the new task contingencies. Thus, in such studies, males may have the advantage if they are better able to inhibit responses to previously rewarded stimuli in the face of interference when contingencies suddenly change, whereas females, if they are more focused on reward, may take longer to learn the new task contingencies when they are signalled by negative feedback. In support of this idea, a female

advantage on reversal learning was observed in the current study if feedback was made positive after reversal.

Similar conclusions have recently been discussed by van den Bos and colleagues (2012; 2013) in relation to findings from the IGT. This group suggested that the sex difference in IGT performance is related to sex differences in two forebrain circuits that regulate decision-making functions. The affective loop involving the OFC, amygdala, and ventral striatum is proposed to be responsible for responding to valenced stimuli and adjusting behaviour based on changing contingencies, whereas the cognitive loop comprising the dorsolateral PFC, anterior cingulate cortex, and the dorsal striatum is responsible for suppression of undue responding to stimuli that have been deemed irrelevant or distracting (van den Bos et al., 2013). Sex differences in brain activation observed during IGT performance support this hypothesis; Bolla and colleagues found a greater activation in men than in women of the lateral OFC and dorsolateral PFC during IGT performance, whereas women activated the medial OFC to a greater extent than men (Bolla et al., 2004). Indeed, recent neuroimaging work using a reversal task suggests that the lateral OFC is involved in modulating the weights of stimulus-response mappings to override a routine response, whereas activation in the medial OFC is correlated with processing and evaluation of rewarding, positive feedback (Hampshire et al., 2012). Van den Bos and colleagues (2012) speculated that the sex difference in IGT performance is not due to a sex difference in sensitivity to reward or punishment, but in how reward and punishment is regulated by top-down cognitive control-- men maintain long-term perspective due to a stronger tendency to suppress responding to immediate events while women require more trials than men before suppressing the tendency to respond to immediate rewarding or punishing feedback.

One way for sex differences in reward or punishment-based processing and inhibitory control to be mediated is via sex differences in neurochemistry. Both serotonin and dopamine have been implicated in the processing of valenced feedback and in inhibitory control in human studies. For example, dietary tryptophan depletion (to reduce central serotonin levels) led to a reduced discrimination of gain magnitude during a gambling task (Rogers et al., 2003) and to more errors when responding to rewarded stimuli during a passive avoidance task (Finger et al., 2007). Lowering serotonin also reduced punishment-induced inhibition without affecting general motor response inhibition or sensitivity to aversive outcomes during an

affective go/no-go task (Crockett et al., 2009) and enhanced punishment prediction during an observational reversal learning task (Cools et al., 2008). Individuals with low dopamine synthesis in the striatum were found to be better at reversals based on punishment, whereas individuals with high dopamine synthesis were better at reversals based on reward (Cools et al., 2009).

A growing body of evidence supports the idea that there are sex differences in both the serotonergic and dopaminergic systems (see Cosgrove et al., 2007 for a review). Females have higher D2-like and serotonin 1A (5-HT$_{1A}$) receptor binding potential than males in the frontal cortex (Jovanovic et al., 2008; Kaasinen et al., 2001; Parsey et al., 2002) and higher dopamine availability in the striatum than males (e.g., Lavalaye et al., 2000; Mozley et al., 2001; Wong et al., 2012), whereas males have higher rates of serotonin synthesis throughout the brain including the frontal cortex (Nishizawa et al., 1997; Sakai et al., 2006). These sex differences may arise, in turn, from sex steroid actions on relevant neurotransmitter systems. Androgens and estrogens have been found to modulate serotonin and dopamine activity in the PFC in rats and monkeys (e.g., Aubele & Kritzer, 2011; Handa et al., 1997; Kritzer & Kohama, 1998; 1999; Sumner & Fink, 1995). Circulating testosterone levels have been shown to predict performance on the IGT (Evans & Hampson, in press; Reavis & Overman, 2001; Stanton et al., 2011; van Honk et al., 2004). Furthermore, estrogen appears to modulate reward processing by enhancing reactions to reward and decreasing reactions to emotionally negative stimuli (see Sakaki & Mather, 2013 for a review) and may be involved in reward-related response inhibition (Amin et al., 2006).

Preliminary experimental data from rodents and humans supports the idea that dopamine and serotonin levels are involved in the regulation of sex differences in reinforcement learning. Given the evidence that individuals with high baseline levels of dopamine may be impaired on reversal learning based on punishment compared to reward (Cools et al., 2009) and that females may have higher dopamine availability than males in various brain areas as mentioned above, Robinson and colleagues (2010) hypothesized that females would perform poorly on tasks that involve punishment processing. Males and females underwent a procedure to decrease global dopamine levels via dietary restriction of phenylalanine and tyrosine and then performance was examined on a reversal learning task that assessed reward and punishment processing separately. After dopamine depletion, females displayed

improved reversal learning based on punishment, but no change in reversal learning based on reward (Robinson et al., 2010). In rats, females lacking the serotonin reuptake transporter (leading to increased levels of serotonin) performed better on the IGT compared to female controls (Homberg et al., 2008). Conversely, decreasing serotonin levels by using a tryptophan deficient diet led to poorer IGT performance in male rats compared to controls (Koot et al., 2012). Thus, these early findings suggest a link between sex differences related to processing of reward and punishment during reinforcement learning and sex differences in dopamine and/or serotonin.

The current study provides preliminary support for the hypothesis that females are more focused on positive feedback during reinforcement learning tasks than males and that males are more flexible than females in switching between choice options in the face of interference during task performance. Future research should continue to tease apart the components that contribute to performance on complex reinforcement learning tasks in an effort to better understand the sex differences that have been demonstrated and the biological or contextual mechanisms that are responsible for those differences.

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**CHAPTER 5**

**5.1 GENERAL DISCUSSION**

There have been few concerted attempts in the literature to systematically investigate sex differences in the cognitive functions mediated by the prefrontal cortex (PFC). The purpose of the current thesis was to add to the existing knowledge base by testing the hypotheses that selected PFC-dependent cognitive functions are sexually differentiated and are modulated by sex steroids.

In Chapter 2, sex differences were investigated on classic working memory tasks that emphasize monitoring and updating and on commonly used reinforcement learning tasks that involve decision-making and reversal learning. As predicted, I found a male advantage on the Iowa Gambling Task (IGT; Bechara et al., 1994) and the reversal phase of the Probabilistic Reversal Learning task (Budhani et al., 2007). These findings provide preliminary support to the hypothesis that functions dependent on the ventromedial/orbitofrontal cortex (VMPFC/OFC) are sexually differentiated in the human brain. No sex difference was found on the California Weather Task which suggests that the male advantage was not related to the understanding or use of probabilities. However, explanations in terms of basic response reversal, inhibitory control, and learning from valenced feedback (other elements shared by the IGT and reversal learning tasks) were not ruled out based on the data collected in Chapter 2 (and were addressed in more detail in Chapter 4). In addition, the application of the Expectancy Valence Model (the most commonly used model in the human decision-making literature) to the IGT data failed to reveal any sex difference in the parameters that are included in the model (attention to losses, attention to recent information, and choice consistency). It should be noted that the Expectancy Valence Model did not fit the male data well. Recent work by other laboratories has also begun to question the applicability of the Expectancy Valence Model (Worthy et al., 2013). It is possible that a different model would more successfully capture the locus of the sex differences. Future studies should examine the possibility of applying newly described models (Cazé & van der Meer, 2013) to the IGT to gain a better understanding of why a male advantage exists (see below for further discussion).

Unexpectedly, Chapter 2 failed to find a female advantage on Self-Ordered Pointing and the *n*-back task. This is contrary to the female advantage on working memory tasks previously reported by Duff and Hampson (2001) and by Speck and colleagues (2000). However, the lack of an observed sex difference on the working memory measures used here does not rule out the possibility of a female advantage on other working memory tasks or under a different set of task parameters. Future research should examine how the different executive processes recruited (e.g., manipulation vs. monitoring), how the stimuli chosen (e.g., spatial vs. non-spatial), and how the sensory modality utilized to present stimuli (e.g., visual vs. auditory) may differentially influence the performance of males and females.

Chapter 3 investigated whether current testosterone and/or prenatal testosterone as indexed by digit ratios predicted performance on the IGT in males and whether this relationship was mediated by a willingness to take risks. Circulating testosterone was negatively correlated with advantageous card selections on the IGT supporting an activational role of androgens, by which levels of testosterone currently in the circulation may modulate prefrontal function, but there was no evidence to suggest that this relationship was mediated at a functional level by individual differences in risk-taking propensity. On the other hand, the relationship between the 2D:4D ratio and IGT performance <u>was</u> mediated by risk-taking. The 2D:4D ratio is controversial, but within the constraints of the prevalent interpretation of the meaning of individual variation in the ratio, a relationship to risk-taking supports an organizational role of androgens (i.e., that higher levels of exposure to androgens during the prenatal period may indirectly affect IGT performance through an influence on the willingness to take risks). Thus, Chapter 3 provided new evidence that financial decision-making in men is related to circulating testosterone levels and is the first to suggest that this relationship is *not* mediated by risk taking. This leaves open the possibility that the relationship between current testosterone and IGT performance is mediated by some other element of the task, such as reward/punishment processing which forms an integral part of decision-making on the IGT. A further novel finding of Chapter 3 is that IGT performance may be influenced by developmental androgen exposure via an effect on risk-taking propensity. Because the 2D:4D ratio is an indirect index, future studies should attempt to use a more direct technique such as measuring prenatal hormones *in utero* via amniocentesis then comparing with adult behaviour to allow stronger conclusions to be drawn regarding the organizational influence

of androgens on decision-making. The time span of such direct studies is exceedingly long, but could feasibly be accomplished by retrospectively analyzing preserved amniotic fluid samples among individuals who have already reached adulthood.

The tasks used in Chapter 2 of the current thesis were chosen because they are widely used to assess frontal function in research and/or clinical studies. However, these tasks are intrinsically complex in nature and do not reveal precisely which shared task element(s) is/are important for eliciting the observed male advantage. It has been suggested that the male advantage in IGT performance specifically may be related to how the task is organized and may not be due to a male advantage in decision-making per se (van den Bos et al., 2013). In an attempt to address this issue, Chapter 4 examined the performance of male and females on tasks that assessed aspects of inhibitory control, reversal learning, and learning based on reward and/or punishment to try to disentangle various explanations for the sex difference by examining simpler functional components of these complex tasks. Chapter 4 used two inhibitory control tasks (Arrows and the Stop-Signal task), the Probabilistic Selection Task, and a modified version of the Probabilistic Reversal Learning task used in Chapter 2 that was modified to provide negative or positive feedback only, in an attempt to address whether the sex difference was related to inhibitory control, "pure" reversal learning, and/or reward or punishment processing. The findings from Chapter 4 allow one possible explanation for the male advantage on the reinforcement learning tasks to be ruled out--basic response reversal does not appear to be the likely source of the male advantage. A significant finding of Chapter 4 was that although there was no significant sex difference in the negative feedback condition of the Probabilistic Reversal Learning task (PRL), there was a female advantage in the positive feedback condition. More complex explanations, therefore, are likely the key to understanding why there was a male advantage on reinforcement learning tasks in Chapter 2. On one hand, there may be a sex difference in the processing or saliency of reward given the female advantage seen in the positive feedback condition of the PRL after reversal and trends for a female advantage during acquisition in the positive condition of the PRL and on the positive feedback learning measure from the Probabilistic Selection Task. On the other hand, there may be a sex difference in interference inhibition given the male advantage observed on the Arrows task. Thus, one probable explanation for the previously observed male advantage on the IGT and reversal learning tasks is the combination of sex differences in both valenced

feedback processing and in interference-related inhibitory control. How exactly this might lead to the male advantage was elaborated and discussed in Chapter 4.

Future studies should attempt to determine more precisely the point(s) in valenced feedback processing where a sex difference occurs. It could be the case, for example, that there is a bias in the reward and punishment neural systems that results in the observed sex differences in value-based decision-making. Indeed, individual differences in dopamine synthesis capacity have been shown to predict the degree to which individuals learn from prediction errors (Cools et al., 2009; Robinson et al., 2010) and there is support for sex differences in dopamine synthesis capacity and availability (Laakso et al., 2002; Mozley et al., 2001; Wong et al., 2012). Thus, one speculative way that an altered balance in reward/punishment processing could manifest itself is through a sex difference in the prediction error system (Robinson et al., 2010). Prediction errors are defined as the difference between the amount of reward or punishment received and the amount expected. Prediction errors pertain to both reward and punishment and can be positive (the amount received is larger than expected) or negative (the amount received is less than expected) (Cazé & van der Meer, 2013). For example, "rewarding" prediction errors would occur if one received an unexpected reward or omission of punishment, whereas "punishing" prediction errors would occur if one received an unexpected punishment or omission of reward. Current evidence suggests that learning from positive and negative feedback (including the prediction errors that are associated with this learning) is based on dissociable mechanisms in the brain (Cazé & van der Meer, 2013). Different learning rates based on positive and negative feedback have been reported (Frank et al., 2007; Sharot, 2011) and can lead to biased estimates of expected reward or punishment and in turn optimal or suboptimal decisions depending on the context (Cazé & van der Meer, 2013). Differential weighting given to "punishing" over "rewarding" prediction errors can increase the estimation of the true value of the choices, increasing the probability of selecting the best option depending on the gain/loss context (Cazé & van der Meer, 2013). The same logic applies to the tasks used in the current dissertation as it would be optimal to rely more on "punishing" prediction errors when learning from feedback as these errors would be most informative to alter future behaviour. With respect to sex differences, perhaps females update their beliefs regarding the real value of choice options more than males do after "punishing" prediction errors in the context of gain (e.g., leading to enhanced performance by females on

the positive feedback version of the PRL in Chapter 4), give more weight to "rewarding" prediction errors in the context of gain and loss (e.g., leading to suboptimal performance of females on the IGT and the PRL in Chapter 3), and give an equal weighting to both types of prediction errors in the context of loss (e.g., leading to similar performance between the sexes on the negative feedback version of the PRL in Chapter 4).  Future research should focus on achieving a more refined understanding of the exact nature of the sex difference in how valenced feedback is processed.  This could be accomplished through the application of new statistical models that have separate learning rate parameters for positive and for negative prediction errors (Cazé & van der Meer, 2013).

At the physiological level, one way that PFC-dependent cognitive functions could become sexually differentiated is if sex steroids have organizational and/or activational effects on the PFC.  Current evidence is consistent with this possibility as estrogens, androgens, and their respective receptors are present in the PFC (e.g., Clark et al., 1988; Finley & Kritzer, 1999; Pau et al., 1998; Perlman et al., 2005; Wang et al., 2004).  Further work has shown that estrogens and androgens can alter the neural structure (e.g., Hajszan et al., 2007; 2008; Hao et al., 2007; Tang et al., 2004) and the neurochemistry of the PFC (e.g., Aubele & Kritzer, 2012; Inagaki et al., 2010; Kritzer & Creutz, 2008; Kritzer & Kohama, 1998; 1999; Tinkler et al., 2004).  Given that the dopaminergic and serotonergic systems, in particular, have been shown to play a crucial role in PFC-dependent cognitive functions like working memory, reinforcement learning, and inhibitory control (e.g., Calaminus & Hauber, 2008; Cools & D'Esposito, 2011; Rogers, 2011), the idea that sex steroids can alter PFC neurochemistry indicates that modulation of cognitive functions dependent on this brain region and these neurotransmitters by sex steroids is plausible.  In addition, performance on PFC-dependent cognitive tasks has been shown in several studies to correlate with levels of estrogens and androgens presently in the bloodstream at the moment when cognitive testing takes place. Estradiol levels have been found to predict performance on working memory tasks (Duff & Hampson, 2000; Grigorova et al., 2006; Hampson & Morley, 2013), whereas testosterone levels have been found to predict performance on the IGT (Chapter 3 of the current thesis; Reavis & Overman, 2001; Stanton et al., 2011; van Honk et al., 2004).  Taken together, this body of work suggests that one mechanism by which the cognitive functions of the PFC are

sexually differentiated is via modulation by sex steroids (during development and/or during adulthood) of the neural structure or the neurochemistry of the PFC.

While there is support for the PFC being a site of sex steroid action and for being crucially involved in the cognitive functions under study in the present work, it could be argued that the relevant site of steroid action is still unknown, and that sex steroid actions on subcortical targets like the amygdala could alternatively give rise to sex differences in inhibitory control or reward processing. There is evidence that performance on the IGT involves the amygdala, in addition to the VMPFC/OFC. For example, patient studies have indicated that selective amygdala lesions impair performance on the IGT (Bechara et al., 1999; Brand et al., 2007). Findings in rats using a rodent version of the IGT confirm the involvement of the amygdala in performance (Zeeb & Winstanley, 2011). It may be the case that communication between the amygdala and the VMPFC/OFC is critical to value-based decision-making as very new data show impairment on the IGT and a disruption in the assessment of reward value in rats with disconnection of the VMPFC/OFC and amygdala (Zeeb & Winstanley, 2013). Thus, it may be argued that sex differences also could arise as a result of the modulation of prefrontal and subcortical connectivity via sex steroids. Recent work in humans suggests that this could be possible given the finding that endogenous testosterone modulates connectivity between the VMPFC/OFC and the amygdala during social emotional tasks (van Wingen et al., 2010; Volman et al., 2011). Reward processing also involves the striatum (Frank et al., 2004; Frank & Claus, 2006), and prediction errors in particular may be represented in the nucleus accumbens (e.g., Cools et al., 2009; Jocham et al., 2011; Niv et al., 2012).

The behavioural nature of the data from the current thesis cannot address whether the sex differences observed are the result of the differential functioning of the PFC only, the result of differential functioning of other brain regions outside of the PFC, or are the result of an alteration in the connections between cortical and subcortical sites through the actions of sex steroids. Some evidence suggests, however, that subcortical targets may not be the primary region involved in the observed sex differences. For example, Bolla and colleagues (2004) studied brain activation during IGT performance using positron emission tomography (PET). In this study, males had greater activation in the lateral OFC and DLPFC than females, whereas females had greater activation in the medial OFC than males. The sex difference in activation observed by Bolla and colleagues (2004) is important in light of fMRI studies

suggesting that the lateral OFC is involved in altering the weights assigned to stimulus-response mappings to override a response or processing information relating to loss and the medial OFC is related to the processing of rewarding feedback (Hampshire et al., 2012; O'Doherty et al., 2003), functions that align with the behavioural sex differences observed in the current work. Thus, although such studies do not rule out the involvement of subcortical regions in the observed behavioural sex differences, they do support the idea that the PFC proper is involved.

An important unresolved question is why, theoretically, sex differences exist in valenced feedback processing and interference-related inhibitory control. One possibility is that the observed differences between males and females in these cognitive functions are epiphenomenal, serving no adaptive function. A more satisfying explanation is that variations in sex steroids and their effects on cognitive functions have been selected because they increase adaptive behaviours (Caldú & Dreher, 2009). It has been argued that hormones have evolved to shape the central nervous system in ways that optimize reproductive success like the sharpening of perceptual cues or the downregulation of behaviours that stand in the way of optimal reproduction (Hampson, 2008). Some researchers have speculated as to the evolutionary functions served by the hormonal regulation of the reward system. It is possible that changes in the reactivity of the reward system via the modulatory influence of sex steroids play a role in facilitating procreation through changes in receptivity or desire (Caldú & Dreher, 2009). There could also be an adaptive function served by a male advantage in interference-related inhibitory control that is related to the traditional male and female roles in ancient hunter-gatherer societies. It has been suggested that a male advantage in ignoring irrelevant targets might be beneficial when hunting game (i.e., focus on one prey animal and ignore the herd), whereas it might be better for females when gathering to be open to all response options (i.e., be open to all potentially edible items in an area so as not to miss any) (Stoet, 2010). Future work should take on the goal of answering the question of why sex differences might exist in reward processing and interference inhibition.

At a practical level, the demonstration of sex differences has implications for the proper design and interpretation of imaging and behavioral studies and the use of PFC-dependent measures in clinical assessment. It is clear from the data of the current thesis that the sex of participants should be stratified as a potential source of variance related to PFC-dependent

cognitive tasks. Data from the current thesis also have implications for real world financial decision-making. Indeed, past studies suggest that androgen levels may be predictive of the behaviour of male stock traders (Coates & Herbert, 2008; 2009) and taken together with the data from the current thesis, these findings suggest that biological factors including adult and perhaps prenatal levels of androgens could potentially influence the quality of financial decisions and the willingness to assume financial risk. In addition, the current work also has implications for sex differences in the prevalence of psychological disorders like depression which is more common in females. It has been proposed that affective biases that result from underlying differences in neurotransmitter systems such as dopamine have the potential to influence susceptibility to affective disorders (Robinson et al., 2010), and addiction where it has been proposed that the value of predicted reward is boosted via dopamine release in the face of uncertainty (Symmonds et al., 2013). In fact, sex differences exist in all phases of drug abuse (Lynch, 2006; Becker & Hu, 2008), and are hypothesized to result from sexual differentiation of the dopaminergic reward system via sex steroids like estradiol (Anker & Carroll, 2010). In both animals and humans, females are more vulnerable to drug abuse than males (females require a lower dose than males to begin regular self-administration, escalate drug use more quickly to addiction, and have a higher risk of relapse) as the result of being more responsive to the rewarding effects of drugs (Anker & Carroll, 2010; Becker & Hu, 2008). The findings of the current thesis, which suggest that females are more responsive to rewarding feedback in the context of decision-making, support and extend the work on drug abuse in humans and animal models.

In conclusion, the data from the current dissertation provide further support for the idea that the PFC and the cognitive functions that rely on it are sexually differentiated. Future work is needed to delineate more precisely the locus of differences in reward-related reinforcement learning and inhibitory control. As stated in the General Introduction, sex differences arise due to an interaction between genetic, hormonal, and environmental factors (Bachevalier & Haggar, 1991; McCarthy & Arnold, 2011). Therefore, the hormonal influence on cognitive functions supported by the current thesis should be viewed as one piece of an overall model.

## 5.2 REFERENCES

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**APPENDIX A: Ethics Approval Chapter 2**

**Department of Psychology** The University of Western Ontario
Room 7418 Social Sciences Centre,
London, ON, Canada N6A 5C1
Telephone: (519) 661-2067 Fax: (519) 661-3961

**Use of Human Subjects - Ethics Approval Notice**

| Review Number | 09 05 04 | Approval Date | 09 05 20 |
|---|---|---|---|
| Principal Investigator | Elizabeth Hampson/Kelly Evans | End Date | 09 12 24 |
| Protocol Title | Predicting and remembering recent events | | |
| Sponsor | n/a | | |

This is to notify you that The University of Western Ontario Department of Psychology Research Ethics Board (PREB) has granted expedited ethics approval to the above named research study on the date noted above.

The PREB is a sub-REB of The University of Western Ontario's Research Ethics Board for Non-Medical Research Involving Human Subjects (NMREB) which is organized and operates according to the Tri-Council Policy Statement and the applicable laws and regulations of Ontario. (See Office of Research Ethics web site: http://www.uwo.ca/research/ethics/)

This approval shall remain valid until end date noted above assuming timely and acceptable responses to the University's periodic requests for surveillance and monitoring information.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the PREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of research assistant, telephone number etc). Subjects must receive a copy of the information/consent documentation.

Investigators must promptly also report to the PREB:
a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to the PREB for approval.

Members of the PREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the PREB.
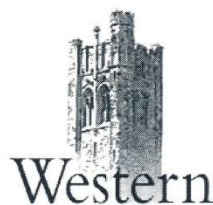
Clive Seligman Ph.D.

Chair, Psychology Expedited Research Ethics Board (PREB)

The other members of the 2008-2009 PREB are: David Dozois, Bill Fisher, Riley Hinson and Steve Lupker

CC: UWO Office of Research Ethics

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# APPENDIX B:  Ethics Approval Chapter 3

**Department of Psychology** The University of Western Ontario
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Telephone: (519) 661-2067 Fax: (519) 661-3961

## Use of Human Subjects - Ethics Approval Notice

| Review Number | 10 06 10 | Approval Date | 10 06 30 |
|---|---|---|---|
| Principal Investigator | Elizabeth Hampson/Kelly Evans | End Date | 10 08 31 |
| Protocol Title | The relationship between hormones and decision making | | |
| Sponsor | n/a | | |

This is to notify you that The University of Western Ontario Department of Psychology Research Ethics Board (PREB) has granted expedited ethics approval to the above named research study on the date noted above.

The PREB is a sub-REB of The University of Western Ontario's Research Ethics Board for Non-Medical Research Involving Human Subjects (NMREB) which is organized and operates according to the Tri-Council Policy Statement and the applicable laws and regulations of Ontario.  (See Office of Research Ethics web site: http://www.uwo.ca/research/ethics/)

This approval shall remain valid until end date noted above assuming timely and acceptable responses to the University's periodic requests for surveillance and monitoring information.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the PREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of research assistant, telephone number etc). Subjects must receive a copy of the information/consent documentation.

Investigators must promptly also report to the PREB:
a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to the PREB for approval.

Members of the PREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the PREB.

Clive Seligman Ph.D.

Chair, Psychology Expedited Research Ethics Board (PREB)

The other members of the 2009-2010 PREB are: David Dozois, Bill Fisher, Riley Hinson and Steve Lupker

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# APPENDIX C: Ethics Approval Chapter 4

**Western**

**Department of Psychology** The University of Western Ontario
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## Use of Human Subjects - Ethics Approval Notice

| Review Number | 11 02 17 | Approval Date | 11 02 25 |
|---|---|---|---|
| Principal Investigator | Elizabeth Hampson/Kelly Evans | End Date | 11 12 31 |
| Protocol Title | Making choices using pictures and symbols | | |
| Sponsor | n/a | | |

This is to notify you that The University of Western Ontario Department of Psychology Research Ethics Board (PREB) has granted expedited ethics approval to the above named research study on the date noted above.

The PREB is a sub-REB of The University of Western Ontario's Research Ethics Board for Non-Medical Research Involving Human Subjects (NMREB) which is organized and operates according to the Tri-Council Policy Statement and the applicable laws and regulations of Ontario. (See Office of Research Ethics web site: http://www.uwo.ca/research/ethics/)

This approval shall remain valid until end date noted above assuming timely and acceptable responses to the University's periodic requests for surveillance and monitoring information.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the PREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of research assistant, telephone number etc). Subjects must receive a copy of the information/consent documentation.

Investigators must promptly also report to the PREB:
a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to the PREB for approval.

Members of the PREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the PREB.

Clive Seligman Ph.D.

Chair, Psychology Expedited Research Ethics Board (PREB)

The other members of the 2010-2011 PREB are: Mike Atkinson (Introductory Psychology Coordinator), David Dozois, Vicki Esses, Riley Hinson  Albert Katz (Department Chair), and Tom O'Neill (Graduate Student Representative)

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# CURRICULUM VITAE

## Kelly L. Evans

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## <u>Degrees</u>

Doctor of Philosophy, 2014
Behavioural & Cognitive Neuroscience, University of Western Ontario
Thesis: *Sexual differentiation of the prefrontal cortex in humans: Examining behavioural sex differences and the modulatory role of androgens*
Advisor: Dr. Elizabeth Hampson

Master of Science, 2006
Behavioural & Cognitive Neuroscience, University of Western Ontario
Thesis: *Toward an animal model of the spatial navigation deficits in Alzheimer's disease: The role of somatostatin and serotonin in the acquisition of the Morris water maze*
Advisor: Dr. Donald Peter Cain

Bachelor of Science, 2004
Psychology (Honors), University of Western Ontario
Thesis: *Stress and reproductive hormones: Effects on performance of the Morris water maze*
Advisor: Dr. Donald Peter Cain

## <u>Academic Awards and Honors</u>

| | | |
|---|---|---|
| Post Graduate Scholarship – Doctoral ($42,000) | Natural Sciences & Engineering Research Council | 2008-2010 |
| Province of Ontario Graduate Scholarship ($15,000) | Ministry of Training, Colleges & Universities | 2007-2008 |
| Graduate Research Scholarship | University of Western Ontario | 2007-2008 |
| Province of Ontario Graduate Scholarship ($15,000) | Ministry of Training, Colleges & Universities | 2006-2007 |
| Post Graduate Scholarship – Masters ($17,300) | Natural Sciences & Engineering Research Council | 2005-2006 |
| Special University Scholarship | University of Western Ontario | 2004-2005 |
| University Gold Medal | University of Western Ontario | 2003-2004 |
| Scholarship of Distinction | University of Western Ontario | 2000-2001 |

## Publications

*Refereed Journal Articles:*

Dyer, K. L. & Cain, D. P. (2007). Water maze impairments after combined depletion of somatostatin and serotonin in the rat. *Behavioral Brain Research*, *181*, 85-95.

Evans, K.L. & Hampson, E. (2014). Does risk-taking mediate the relationship between testosterone and decision-making on the Iowa Gambling Task? *Personality and Individual Differences*, *61-62*, 57-62.

*Articles Submitted and In Preparation:*

Evans, K.L. & Hampson, E. Sex differences on prefrontally-dependent cognitive tasks. *Brain and Cognition*, under revision.

Evans, K.L. & Hampson, E. Sex differences on tasks assessing reward processing and interference inhibition. *Behavioural Brain Research*, under revision.

Hampson, E., Phillips, S-D., Duff-Canning, S.J., Evans, K.L., Merrill, M., Pinsonneault, J.K., Sadée, W., & Steiner, M. Working memory in pregnant women and its relation to antepartum depression. To be submitted to the *Journal of Clinical and Experimental Neuropsychology*.

*Published Abstracts:*

Evans, K.L. & Hampson, E. (2013). Is there a sex difference in reinforcement learning through positive feedback? *Abstracts of the Canadian Society for Brain, Behaviour, and Cognitive Science*. Prog. No. 238 (pp.62).

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Evans, K.L. & Hampson, E. (2011). Testosterone and decision-making: Salivary testosterone and 2D:4D digit ratios predict performance on the Iowa Gambling Task. *Society for Neuroscience Abstracts*. Washington, DC: Society for Neuroscience, Program No. 725.13.

Evans, K.L. & Hampson, E. (2010). Is there a male advantage on tasks recruiting the ventral prefrontal cortex? *Journal of the International Neuropsychological Society*, *16* (Suppl 1), 90.

Evans, K.L. & Hampson, E. (2009). Is there a female advantage in the executive components of working memory? *Abstracts of the Organization for the Study of Sex Differences*. Washington, DC: Society for Women's Health Research, 26-27.

Dyer, K.L. & Cain, D.P.  (2005).  A preliminary examination of the role of somatostatin and serotonin in acquisition of the Morris water maze: Effects on spatial navigation and implications for an animal model of Alzheimer's disease. *Society for Neuroscience Abstracts.*  Washington, DC: Society for Neuroscience, Program No. 880.3.

*Conference Presentations:*

Evans, K.L. & Hampson, E.  (2013).  *Is there a sex difference in reinforcement learning involving positive feedback?*  Presented at the 23rd annual meeting of the Canadian Society for Brain, Behaviour, and Cognitive Science, Calgary, AB, June.

Evans, K.L. & Hampson, E.  (2011).  *Testosterone and decision-making: Salivary testosteroneand 2D:4D digit ratios predict performance on the Iowa Gambling Task.*  Presented at the 41th Meeting of the Society for Neuroscience, Washington, DC, November.

Evans, K.L. & Hampson, E.  (2010).  *Is there a male advantage on tasks recruiting the ventral prefrontal cortex*?  Presented at the 38th Meeting of the International Neuropsychological Society, Acapulco, Mexico, February.

Evans, K.L. & Hampson, E.  (2009).  *Is there a female advantage in the executive components of working memory?*  Presented at the 3rd Annual Meeting of the Organization for the Study of Sex Differences, Toronto, ON, June.

Dyer, K.L. & Cain, D.P.  (2006).  *The role of somatostatin and serotonin in Morris water maze performance: Effects on spatial navigation and implications for an animal model of Alzheimer's disease.*  Presented at the 26th Annual Meeting of the Southern Ontario Neuroscience Association, Toronto, ON, May.

Dyer, K.L. & Cain, D.P.  (2005).  *A preliminary examination of the role of somatostatin and serotonin in acquisition of the Morris water maze: Effects on spatial navigation and implications for an animal model of Alzheimer's disease.*  Presented at the 35th Meeting of the Society for Neuroscience, Washington, DC, November.

Dyer, K.L. & Cain, D.P.  (2005).  *A preliminary examination of the role of somatostatin and serotonin in acquisition of the Morris water maze: Effects on spatial navigation and implications for an animal model of Alzheimer's disease.*  Presented at the 25th Annual Meeting of the Southern Ontario Neuroscience Association, Hamilton, ON, June.

## Research and Teaching Experience

*Research Assistant (January 2013 – present)*
Laboratory of Dr. Elizabeth Hampson
University of Western Ontario

*Course Instructor (September 2010 – December 2010)*
Psychology 2221a: Introduction to the Biological Basis of Behaviour
King's University College

*Lab Coordinator (September 2009 – April 2010)*
Psychology 2800E: Research Methods in Psychology
University of Western Ontario

*Lab Instructor (September 2008 – April 2009)*
Psychology 2800E: Research Methods in Psychology
University of Western Ontario

*Lab Instructor (September 2005 – April 2007)*
Psychology 281: Statistics for Psychology
University of Western Ontario

*Teaching Assistant (September 2004 – April 2005; September 2007 – April 2008)*
Psychology 020: Introduction to Psychology
University of Western Ontario

*Research Assistant (Summer 2004)*
Laboratory of Dr. Klaus-Peter Ossenkopp
University of Western Ontario

## **Membership in Learned Societies**

*Society for Neuroscience*