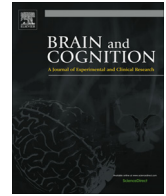




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Sex differences on prefrontally-dependent cognitive tasks



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ABSTRACT

There is preliminary evidence to suggest that the prefrontal cortex (PFC) is modulated by sex steroids in humans and other primates. The current study examined whether sex differences in performance could be discerned on two working memory tasks that emphasize monitoring and updating processes, and on two tasks that engage the ventromedial PFC/orbitofrontal cortex (VMPFC/OFC). Healthy young adults (48 females; 45 males) completed the *n*-back, Self-Ordered Pointing (SOP), Iowa Gambling Task (IGT), and a probabilistic reversal learning task. On the IGT, males selected more cards from the advantageous decks than females. 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. The sexes did not differ significantly on the *n*-back or SOP tasks. These findings provide tentative support for the hypothesis that functions carried out by the VMPFC/OFC are sexually differentiated in humans.

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1. Introduction

Over the past three decades, a significant body of work has been devoted to understanding the diverse functions of the prefrontal cortex (PFC). 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 (e.g., Aubele & Kritzer, 2011; Bixio, Backstrom, Winbald, & Anderson, 1995; Finley & Kritzer, 1999; Hajszan, MacLusky, & Leranth, 2008; Handa, Hejna, & Lorens, 1997; Hao et al., 2007; Kritzer & Kohama, 1998; Kritzer & Kohama, 1999; Pau, Pau, & Spies, 1998; Perlman et al., 2005; Platia, Fencel, Elkind-Hirsch, Canick, & Tulchinsky, 1984; Tang et al., 2004; Tinkler, Tobin, & Voytko, 2004; Wang, Hara, Janssen, Rapp, & Morrisson, 2010; Wang et al., 2004). 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 behavioral level.

1.1. Role of the PFC in working memory, decision-making and reversal learning

Working memory may 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 perisylvian regions (e.g., D’Esposito & Postle, 1999; Paulesu, Frith, & Frackowiak, 1993; Postle, Berger, & D’Esposito, 1999; Wager & Smith, 2003), but areas of the PFC including dorsolateral PFC (DLPFC) and ventrolateral PFC are required for a number of executive processes that can be performed on the contents of working memory, including active maintenance, manipulation, monitoring, and updating (e.g., Awh et al., 1996; Champod & Petrides, 2010; Chase, Clark, Sahakian, Bullmore, & Robbins, 2008; D’Esposito et al., 1999, 2006; Funahashi, Chafee, & Goldman-Rakic, 1993; Owen, McMillan, Laird, & Bullmore, 2005; Owen et al., 1999; Postle, Berger, & D’Esposito, 1999; Postle et al., 2006; Provost, Petrides, & Monchi, 2010; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Wager & 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 & Goldman-Rakic, 1999, 2000).

Whereas the lateral convexity has been implicated in processes that support working memory, the ventromedial PFC/orbitofrontal

Abbreviations: CNS, central nervous system; CWT, California Weather Task; DLPFC, dorsolateral prefrontal cortex; IGT, Iowa Gambling Task; PFC, prefrontal cortex; PRL, probabilistic reversal learning; SOP, Self-Ordered Pointing; VMPFC/OFC, ventromedial prefrontal cortex/orbitofrontal cortex; WAIS-IV, Wechsler Adult Intelligence Scale-Fourth Edition.

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cortex (VMPFC/OFC) has been implicated in tasks that require decision-making and reversal learning. A classic and widely used task for assessing decision-making in humans is the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). It requires one to learn to make choices that lead to optimal future outcomes and has been found to correlate with real-life financial decision-making (Shivapour, Nguyen, Cole, & Denburg, 2012). Based on imaging and patient studies, 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, Damasio, Tranel, & Anderson, 1998; Bechara et al., 1994; Christakou, Brammer, Giampietro, & Rubia, 2009; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 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 & 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).

With respect to reversal learning, neuroimaging studies in healthy subjects have revealed increased activation in the VMPFC/OFC, ventrolateral PFC, DLPFC, and dorsomedial PFC during task performance (e.g., Budhani, Marsh, Pine, & Blair, 2007; Cools, Clark, Owen, & Robbins, 2002; Greening, Finger, & Mitchell, 2011; Hampshire, Chaudhry, Owen, & Roberts, 2012; O'Doherty et al., 2003). However, the key region that may be most critical for the reversal of a response is the VMPFC/OFC (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) as both human and non-human primates with lesions of the VMPFC/OFC are impaired on a variety of reversal learning tasks (e.g., Berlin, Rolls, & Kischka, 2004; Dias, Robbins, & Roberts, 1996; Fellows & Farah, 2003, 2005; Hornak et al., 2004; Rygula, Walker, Clarke, Robbins, & Roberts, 2010; Tsuchida, Doll, & Fellows, 2010). The VMPFC/OFC might keep track of the relative value of stimuli, be involved in re-evaluating contingencies, and flexibly guide behavior when expectancies are violated by connecting a trial with a specific outcome (e.g., Fellows & Farah, 2007; Hampshire et al., 2012; Plassmann, O'Doherty, & Rangel, 2010; Tsuchida et al., 2010).

1.2. Sexual differentiation of PFC-dependent cognitive functions

Very little is known about sex differences in the cognitive functions of the PFC, with the exception of the consistent finding that males outperform females on the IGT. 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, Eldreth, Matochik, & Cadet, 2004; Overman, Boettcher, Watterson, & Walsh, 2011; Overman et al., 2004, 2006; Reavis & Overman, 2001; van den Bos, Homberg, & de Visser, 2013; Weller, Levin, & Bechara, 2009). Sex differences in activation of the OFC during IGT performance have also been reported (Bolla et al., 2004), with males showing increased activation in the lateral OFC compared to females and females showing greater activation in the medial OFC than males, although confirmation of these differences is needed. It is not clear whether sex differences observed in the imaging studies reflect differences in brain organization or only the use of different cognitive strategies to solve the task.

Currently, it is not known *why* a male advantage exists on the IGT. The IGT involves many component processes (e.g., reversal learning, sensitivity to reward/punishment) and it is not known which components are the basis for the observed sex difference. Only two studies have examined behavioral sex differences in reversal learning which, like the IGT, strongly recruits the VMPFC/OFC.

Overman, Bachevalier, Schuhmann, and Ryan (1996) found a male advantage on an object reversal task in young children (15–30 months of age) similar to what has been found in infant monkeys (Clark & Goldman-Rakic, 1989; Goldman, Crawford, Stokes, Galkin, & Rosvold, 1974), 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). A possible alternative explanation for the male advantage on the IGT is a difference between males and females in sensitivity to reward and/or punishment (Bolla et al., 2004; Overman & Pierce, 2013; Overman et al., 2006, 2011), but to date, this remains an open question.

It has been proposed that a male advantage might exist on VMPFC/OFC dependent tasks due to organizational effects of androgens exerted during the postnatal testosterone surge that takes place in the first four to six months of life in humans and infant monkeys (Overman, 2004). *Organizational effects* are permanent changes in brain morphology, which are induced by exposure to androgens or their metabolites during critical periods in prenatal or early postnatal development. *Activational effects* are reversible effects, often changes in neurochemistry, that are normally seen in adults and are induced by the levels of hormones temporarily present in the 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 (Breedlove & Hampson, 2002).

It is possible that reversal learning is influenced by developmental androgen exposure because the sex difference in object reversal observed in infant monkeys can be eliminated by treating females with testosterone propionate prenatally or during the first 4 months of postnatal life (Clark & Goldman-Rakic, 1989). Further support for an organizational role of androgens comes from the finding of a sex difference in object reversal in 15–30 month old children, a timepoint well after the postnatal testosterone surge that ends around 6 months of age, suggesting a permanent change (Overman et al., 1996). However, sex differences in reversal learning have not been found after 3 years of age in humans (Overman, 2004) and this raises questions about the permanence of any effects (or perhaps whether reversal learning tasks used in past studies lack the difficulty level required to elicit sex differences). In the only study to date examining sex differences in children and adults on a probabilistic reversal learning task, Overman (2004) did not find a sex difference in children (3–6 years of age) or adults, but there was evidence that the new reversal task was too difficult and may have concealed a true sex difference. Therefore, it is still not clear if the male advantage in object reversal is only a short-term difference in developmental timing as suggested by Clark and Goldman-Rakic (1989) or if it persists beyond 3 years of age and into adulthood, constituting a true organizational effect.

With respect to the IGT, only one study to date has examined organizational influences of androgens on performance (using a proxy measure of prenatal androgen exposure; i.e., the digit ratio). In this study, while digit ratio itself did not have a direct relationship to IGT performance, there was evidence of an indirect effect via risk-taking propensity (Evans & Hampson, 2014). In addition, activational influences of androgens cannot be ruled out as associations between IGT performance and currently circulating testosterone levels have been found in adult men. Men with lower circulating testosterone perform *better* on the IGT than those with higher testosterone (Evans & Hampson, 2014; Reavis & Overman, 2001; cf., Stanton, Liening, & Schultheiss, 2011). While the direction of this association may seem counterintuitive at first (given the male advantage on the IGT), it is important to keep in mind that the IGT is a complex task that involves multiple component processes, several of which may show sex differences and may be influenced by testosterone to different degrees or in different ways. Consistent with a possible effect of adult testosterone,

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