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Review

Sex differences in cognitive impairment and Alzheimer's disease

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ABSTRACT

Studies have shown differences in specific cognitive ability domains and risk of Alzheimer's disease between the men and women at later age. However it is important to know that sex differences in cognitive function during adulthood may have their basis in both organizational effects, i.e., occurring as early as during the neuronal development period, as well as in activational effects, where the influence of the sex steroids influence brain function in adulthood. Further, the rate of cognitive decline with aging is also different between the sexes. Understanding the biology of sex differences in cognitive function will not only provide insight into Alzheimer's disease prevention, but also is integral to the development of personalized, gender-specific medicine. This review draws on epidemiological, translational, clinical, and basic science studies to assess the impact of sex differences in cognitive function from young to old, and examines the effects of sex hormone treatments on Alzheimer's disease in men and women.

1. Introduction

The popular quote, "Men are from Mars and women are from Venus", has been commonly applied to many different situations including physiology, sociology and pathology; the gender differences in cognitive functioning are no exception. The differences of learning and memory between male and female brains are confirmed by both human and animal studies from early development stages throughout their life spans. In addition, many neurological diseases exhibit gender biases, such that one sex has a greater prevalence or severity of the disease than the other. Neurological diseases in the young and the elderly also demonstrate gender-specific responses to therapies. However, the question is how much, rather than whether or not, the biology of sex contributes to normal cognitive function. Accordingly, such understanding may provide better insight into the factors that contribute to the risk of cognitive impairment. Here, we will be focusing on sex hormones – especially the role of estrogens, progesterone and testosterone – on mechanisms that relate to neuronal function and associated cognitive ability in the adult and aged individual.

2. Sex differences in cognition

Gender differences in cognitive function in adulthood and ageing have been well demonstrated. For example, men perform better on spatial memory while women excel at verbal and object location (Table 1). The sex differences in cognitive function and brain structures in later life have been demonstrated by magnetic resonance imaging (MRI) in human studies. For instance, studies found that men demonstrated larger amygdala and thalamus volumes compared to women (Neufang et al., 2009; Bramen et al., 2011; Koolschijn and Crone, 2013), whereas the size of hippocampus is larger in females compared to males (Neufang et al., 2009; Giedd et al., 1996). It is also worth noticing that there are a relatively higher number of androgen receptors in the amygdala (Clark et al., 1988) and a relatively higher number of estrogen receptors in the hippocampus (Morse et al., 1986).

2.1. Sex-type cognitive behavioral tests

Differing performances between the sexes have been observed on a number of common learning tasks in both human and animal literature. There are four classes of memory tasks for which sex differences have been frequently reported: spatial, verbal, autobiographical, and emotional memory. Typically, it has been commonly believed that males show an advantage on spatial tasks, and females on verbal tasks. However, evidence now shows that the male spatial advantage does not apply to certain spatial tasks, and that the female advantage in verbal processing extends into many memory tasks which are not explicitly verbal (Andreano and Cahill, 2009). For example, spatial tests can be further divided into three components: spatial perception, spatial rotation (spatial working memory) and spatial visualization (navigation) (Linn and Petersen,

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Table 1
Human studies of spatial rotation, navigation, object location and verbal memory.

Authors	Year	Case number	Age (years)	Advantage	*P* value
Spatial rotation					
Sharps et al. (1993)	1993	60	18–36	Male	<0.001
Epting and Overman (1998)	1998	47	19–41	Male	<0.01
Moffat et al. (1998)	1998	74	20s	Male	<0.001
Levine et al. (1999)	1999	288	4–7	Male	<0.005
Silverman et al. (2000)	2000	111	20s	Male	<0.001
Peters, 2005	2005	212	20s	Male	<0.0001
Silverman et al. (2007)	2007	95,742	20s–30s	Male	<0.05
Kaufman (2007)	2007	100	16–18	Male	<0.0001
Maylor et al. (2007)	2007	198,121	20–65	Male	<0.001
Jansen and Heil (2010)	2010	150	20–70	Male	<0.01
Tzuriel and Egozi (2010)	2010	116	6–7	Male	<0.01
Puts et al. (2010)	2010	337	20s	Male	<0.0001
Lange-Kuttner and Ebersbach (2013)	2013	97	6–9	Male	<0.05
Mantyla (2013)	2013	72	19–40	Male	<0.01
Christie et al. (2013)	2013	60	20s	Male	<0.05
Jansen and Kaltner (2013)	2013	60	60–71	Male	significant
Navigation					
Astur et al. (1998)	1998	48	20s	Male	<0.05 visual water maze
Moffat et al. (1998)	1998	74	20s	Male	<0.001 Map view
Silverman et al. (2000)	2000	186	20s	Male	<0.001 in 3D test
Malinowski and Gillespie (2001)	2001	1042	Unknown	Male	<0.001
Beatty (2002)	2002	98	16–60	Male	<0.05
Driscoll et al. (2005)	2005	70	20–60+	Male	<0.005 visual water maze
Postma et al. (2004)	2004	64	20s	Male	<0.05 only in 3D test
Tippett et al. (2009)	2009	24	60–80	Male	<0.01 2D and AD tests
Chai and Jacobs (2009)	2009	84	18–25	Male	<0.001 visual water maze
Vestergren et al. (2012)	2012	1115	25–85	Male	<0.05
Persson et al. (2013)	2013	24	18–35	Male	<0.05
Object location					
Portin et al. (1995)	1995	389	62	Female	<0.001
McGivern et al. (1997)	1997	483	10–20	Female	<0.0001
Epting and Overman (1998)	1998	47	19–41	NS	NS
Postma et al. (2004)	2004	64	20s	NS	NS
Herrera-Guzman et al. (2004)	2004	90	50–80	Female	<0.05 in cube analysis
Herrera-Guzman et al. (2004)	2004	90	50–80	Male	<0.05 in incomplete letters
Silverman et al. (2007)	2007	95,742	20s–30s	Female	<0.05
Ardila et al. (2011)	2011	788	5–16	Female	<0.05
Bracco et al. (2011)	2011	83	21–60	NS	NS
McGivern et al. (2012)	2012	141	18–26	Female	<0.001 in accuracy
McGugin et al. (2012)	2012	227	20s	Female	<0.001
Verbal memory					
Trahan and Quintana (1990)	1990	140	Unknown	Female	<0.05 in recall
Mann et al. (1990)	1990	175	Teens	Female	<0.001 in fluency, recall
Youngjohn et al. (1991)	1991	1492	20–70	Female	<0.005 in recall
Savage and Gouvier (1992)	1992	134	15–76		NS in delay recall
Portin et al. (1995)	1995	389	62	Female	<0.005 in WAIS
Berenbaum et al. (1997)	1997	57	20–40	Female	<0.05 in CVLT
Kimura and Clarke (2002)	2002	81	20s	Female	<0.01 in CVLT
Yonker et al. (2003)	2003	36	35–85	Female	<0.05 in recall
Kimura and Seal (2003)	2003	53	Unknown	Female	<0.05 in recall
Neri et al. (2012)	2012	900	65+		NS in fluency
Munro et al. (2012)	2012	957	67–89	Female	<0.001 in verbal learning
Murre et al. (2013)	2013	28,116	11–80	Female	<0.001
Heinzel et al. (2013)	2013	523	51–82	Female	<0.001 in semantic fluency

CVLT = California Verbal Learning Test, WAIS = Wechsler Adult Intelligence Scale.

1985). In Table 1, we include a review of human spatial ability and verbal performance with sex-favored components.

2.1.1. Human studies

2.1.1.1. Spatial rotation memory test. There are simple (two-dimensional stimuli) and complex (three dimensional stimuli) tasks. The rotation of simple two-dimensional stimuli can lead to greater activation of the left parietal area rather than the right parietal area, while the complex three-dimensional rotations are associated with more right parietal activation than left parietal activation (Roberts and Bell, 2003). Interestingly, brain imaging studies have identified distinctly different networks activating during mental rotation tasks for men and women, such as increased activation in the parietal lobules in men, and increased activity in frontal areas in women (Hugdahl et al., 2006; Seurinck et al., 2004; Gizewski et al., 2006). The unique frontal activity in women has been interpreted as evidence of a different cognitive strategy from men to solving mental rotation problems. Studies also showed that if sex hormone variation across the menstrual cycle in women was taken into account, the different activation areas during mental rotation tasks were no longer observed (Gizewski et al., 2006; Mantyla, 2013), suggests that activity in the parietal lobule region may be sensitive to ovarian hormones in women. A study on fluctuations in salivary testosterone and performance of male-biased

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