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REVIEW

Reconceptualizing sex, brain and psychopathology: interaction, interaction, interaction

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In recent years there has been a growing recognition of the influence of sex on brain structure and function, and in relation, on the susceptibility, prevalence and response to treatment of psychiatric disorders. Most theories and descriptions of the effects of sex on the brain are dominated by an analogy to the current interpretation of the effects of sex on the reproductive system, according to which sex is a divergence system that exerts a unitary, overriding and serial effect on the form of other systems. We shortly summarize different lines of evidence that contradict aspects of this analogy. The new view that emerges from these data is of sex as a complex system whose different components interact with one another and with other systems to affect body and brain. The paradigm shift that this understanding calls for is from thinking of sex in terms of sexual dimorphism and sex differences, to thinking of sex in terms of its interactions with other factors and processes. Our review of data obtained from animal models of psychopathology clearly reveals the need for such a paradigmatic shift, because in the field of animal behaviour whether a sex difference exists and its direction depend on the interaction of many factors including, species, strain, age, specific test employed and a multitude of environmental factors. We conclude by explaining how the new conceptualization can account for sex differences in psychopathology.

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Abbreviations
EPM, elevated plus maze; FST, forced swim test; UCMS, unpredictable chronic mild stress

Introduction

In recent years there has been a growing recognition of the influence of sex on brain structure and function and consequently, on the susceptibility, prevalence and response to treatment of psychiatric disorders (e.g. Palanza, 2001; Eliot, 2011; Mathis *et al.*, 2011; Mendrek and Stip, 2011; Rasakham and Liu-Chen, 2011; Vega *et al.*, 2011; Cahill, 2006; 2012; Fernandez-Guasti *et al.*, 2012; Franconi *et al.*, 2012; Hasson and Fine, 2012; Jogia *et al.*, 2012; McCarthy *et al.*, 2012; Nolen-Hoeksema, 2012; Simpson and Kelly, 2012; ter Horst *et al.*, 2012; Valentino *et al.*, 2013). Most theories and descriptions of the effects of sex on the brain are dominated by an analogy to the current interpretation of the effects of sex on the reproductive organs (McCarthy and Arnold, 2011; Joel, 2012; 2014). Yet, recently, several lines of research have challenged every aspect of this analogy. The convergence of these lines of research calls for a complete reconceptualization of sex beyond the genitalia and for rethinking the relations between sex, brain and psychopathology.

We start by presenting, in brief, the current view of the effects of sex on the reproductive system. We then summarize different lines of evidence that contradict aspects of the analogy between the effects of sex on the reproductive organs and the effects of sex on brain structure and function. On the basis of these data, we call for a paradigm shift in our conceptualization of the relations between sex and brain, to one that focuses on the interactions of sex with other factors and

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processes. We demonstrate the need for such a paradigm shift in the field of animal models of psychiatric disorders. We conclude by explaining how the new conceptualization can account for sex differences in psychopathology. We would like to note that a review of the data on the mechanisms by which sex affects the brain (e.g. sex chromosomes vs. gonadal hormones effects, organizational vs. activational effects of gonadal hormones) is beyond the scope of this review. Extensive reviews of these issues can be found elsewhere (Arnold, 2009; McCarthy *et al.*, 2009b; McCarthy and Arnold, 2011; Arnold *et al.*, 2013).

Sex and the reproductive system

Our current conceptualization of the effects of sex on the reproductive organs depicts sex as a divergence process that exerts a unitary, overriding and serial effect on the form of other tissues, so that a difference at the 'origin' of sex (i.e. the sex chromosome complement) leads sequentially to the emergence of differences in additional tissues (first, the gonads and then the internal and external genitalia). This process culminates in the creation of two distinct systems – the male reproductive system and the female reproductive system (see Arnold and Chen, 2009; McCarthy and Arnold, 2011). That this indeed happens in most individuals depends on the fact that sex (genetic and gonadal) is *the most important factor* in determining the form of the gonads and genitalia respectively. Thus, although there is within-sex variation in the form of the gonads and the genitalia (reflecting the effects of factors other than sex), there is very little overlap between the form of these tissues in men and women, that is, these tissues are sexually dimorphic. Moreover, there is almost always a perfect consistency between the form of the different components of the reproductive system within a single individual, that is, most humans are born with either ovaries, uterus, fallopian tubes, vagina, labia minora and majora *and* clitoris, *or*, testes, prostate, seminal vesicles, scrotum *and* penis (and a similar division is evident in other mammals) (see Joel, 2011; 2012; 2014, for further exposition and discussion).

Sex and the brain

Using this model of sex to conceptualize sex effects on the brain, leads to the implicit assumption that sex similarly acts serially and uniformly, exerting an overriding and diverging effect, ultimately leading to the creation of two distinct systems, a 'male' brain and a 'female' brain. Current data, however, do not support these implicit assumptions (Joel, 2012; 2014).

Several lines of evidence contradict the assumption that sex acts serially and uniformly always driving divergence in other systems. Specifically, already at the most basic levels of sex, there are sex-dependent processes that act to reduce sex differences downstream rather than to create such differences (see, De Vries, 2004; De Vries and Sodersten, 2009). The best known of these is X inactivation, which occurs only in female (or more accurately, in subjects with at least two copies of the X chromosome) and compensates for the sex difference in the composition of the sex chromosome complement (i.e. XX vs. XY) (see De Vries, 2004; De Vries and Sodersten, 2009). More recently discovered is the sometimes opposite effects of sex chromosomes and gonadal hormones on body and brain, which act to reduce sex differences in these systems (see De Vries, 2004; Arnold and Chen, 2009; De Vries and Sodersten, 2009; Arnold *et al.*, 2013). The existence of antagonistic effects of sex chromosomes and gonadal hormones not only contradicts the view of sex as a solely divergent mechanism, but also refutes the assumption that sex is a uniform process (Arnold and Chen, 2009; Arnold *et al.*, 2013). Two additional phenomena that may be grouped under the term 'compensation mechanisms' (De Vries, 2004; De Vries and Sodersten, 2009) are the local synthesis of steroids, including oestradiol, in several brain regions, which may compensate for sex differences in the blood levels of these hormones (see McCarthy and Konkle, 2005; McCarthy, 2009), and sex differences in the brain that act to reduce or prevent sex differences in behaviour, that would otherwise be caused by sex differences at earlier levels (e.g. hormonal) (see De Vries and Boyle, 1998; De Vries, 2004; De Vries and Sodersten, 2009).

Another dramatic change in our view of the relations between sex and brain comes from data showing that in marked contrast to the overriding importance of sex in determining the form of the reproductive organs, sex is just one of several factors that affect the form of the brain. The effects of other factors (i.e. developmental, environmental, genetic) increase the variability within each sex and consequently the overlap between the sexes (McCarthy *et al.*, 2009a), and may also completely reverse the effects of sex, that is, what is typical in one sex under some conditions may be typical in the other sex under other conditions (Joel, 2011; 2012; Cahill, 2012). Specifically, there is ample evidence from animals that environmental events, such as prenatal and postnatal stress, rearing conditions, maternal deprivation and exposure to drugs, may create, enhance, reverse or eliminate sex differences in different characteristics (size, number of neurons, number of glia cells, dendritic morphology, number and size of axons, and density of receptors) of many brain regions (the frontal and occipital cortex, hippocampus and related cortical areas, amygdala, cerebellum, brain stem, hypothalamus, corpus callosum) and neurotransmitter systems, such as. the glutamatergic, GABAergic, serotonergic, dopaminergic, noradrenergic and endocannabinoid systems (Juraska, 1991; Vathy and Katay, 1992; McCormick *et al.*, 1995; Galea *et al.*, 1997; Shors *et al.*, 2001; Vathy, 2001; 2002; Mitsushima *et al.*, 2003; Drossopoulou *et al.*, 2004; Richardson *et al.*, 2006; Wilber *et al.*, 2007; Rothstein *et al.*, 2008; Zuena *et al.*, 2008; Fumagalli *et al.*, 2009; Garrett and Wellman, 2009; Lin *et al.*, 2009; McLaughlin *et al.*, 2009; Oomen *et al.*, 2009; Reich *et al.*, 2009; Rhodes *et al.*, 2009; Suarez *et al.*, 2009; Viveros *et al.*, 2009; also see Joel, 2011; 2012).

Taken together, the different lines of research refute each of the components of the analogy between the reproductive organs and the brain. Moreover, they provide a new understanding of sex beyond the genitalia, according to which sex is a complex system whose different components interact with one another (Arnold and Chen, 2009; McCarthy and Arnold, 2011) and with other systems (Joel, 2011; 2012; 2014) to affect the brain. As a result of these complex interactions, the form of brain features is highly variable within sex and highly overlaps between sexes, and there is little

consistency in the form of different brain features within a single organism (Joel, 2011; 2012). Therefore, although the reproductive system of most subjects fits into one of two categories, male or female, their brain does not. Rather, brains often posses both 'male' and 'female' features, as well as features with an intermediate form (Joel, 2011; 2012). The paradigm shift that this understanding calls for is from thinking of sex in terms of sexual dimorphism and sex differences, to thinking of sex in terms of its interactions with other factors and processes.

Sex, brain and psychopathology

The need for such a paradigm shift is clearly evident in the field of animal models of psychopathology. This is because complex interactions within-sex and between-sex and other factors also affect brain function, that is, behaviour.

Recent years have seen an increase in the number of studies using the four core genotypes mouse model as well as other genetic models that allow assessment of the specific contribution of sex chromosomes and gonadal hormones to behaviour. Although a thorough review and analysis of these studies is beyond the scope of the present review, these studies are revealing the effects of complex interactions between sex chromosomes and gonadal hormones (prenatally and at adulthood) on a wide array of behaviours, including activity level, social and sexual behaviours, and anxiety- and depression-like behaviours (Gatewood *et al.*, 2006; Grgurevic *et al.*, 2008; McPhie-Lalmansingh *et al.*, 2008; Cox and Rissman, 2011; Bonthuis *et al.*, 2012; Kuljis *et al.*, 2013; Seney *et al.*, 2013). Moreover, there is some evidence that the behavioural outcome of these interactions may be different under different environmental conditions. For example, the interaction between chromosomal and gonadal effects yielded opposite patterns of social and play behaviours in the four core genotypes mouse model when these behaviours were assessed during an interaction with siblings compared with non-siblings (Cox and Rissman, 2011).

The effects of interactions of sex with other factors on behaviour are clearly revealed in studies testing genetically intact males and females in animal models of psychopathology. Table 1 presents results of studies using animal models of depression and antidepressant response and animal models of anxiety and anxiolytic response, as well as behavioural assays commonly used to study several types of learning. Most of the assays in the Table have been used in a large number of studies to allow comparisons among studies; a few assays that were not used in many studies have also been included to allow comparisons among different measures of the same construct (e.g. anxiety-like behaviour) (for a comprehensive review of animal models of depression, anxiety, drug response and cognition, see Dalla, this issue). The general conclusion of recent reviews of such studies, also evident from inspection of Table 1, is that the effects of sex (that is, whether a sex difference exists and its direction) depend on the interaction of genetic (i.e. strain), developmental and environmental factors (such as, specific test employed, prior experience with the task, housing conditions, exposure to stress and the specific parameters of the stress paradigm, time of testing, temperature, etc.) (Crawley *et al.*, 1997; Barros and Ferigolo, 1998; Palanza, 2001; Jonasson, 2005; Hughes, 2007; Weinstock, 2007; Rasakham and Liu-Chen, 2011; ter Horst *et al.*, 2012; Simpson and Kelly, 2012).

For example, the existence and direction of sex differences in animal models of depression and antidepressant response depend on strain [e.g. the opposite sex difference in immobility time in the forced swim test (FST) in Wistar and Long-Evans rats], prior history (the observation of a sex difference in Long-Evans rats in the FST depends on prior exposure to the assay), the type of assay used to measure depression-like behaviour (e.g. learned helplessness vs. FST), as well as additional non-specified variables, as shown by the variety of results obtained using the same strain, assay and behavioural measure, such as the inconsistent findings with Sprague-Dawley rats in the FST and with Wistar rats in sucrose preference.

Even in fields where results seem to be more consistent across studies, a closer look reveals complex interactions between sex and other factors. For example, although many studies in rodents report more anxiety-like behaviours in male compared with female rodents (contrary to what is assumed to be the case in humans), also, here, the existence and direction of sex differences depend on strain – the direction of the sex difference in time spent in the open arms of the elevated plus maze (EPM) in Sprague-Dawley is opposite that observed in Wistar and Long-Evans rats –, on prior history – the existence and direction of a sex difference in Sprague-Dawley rats in the EPM depend on prior exposure to stress, – on the specific measure used – in Sprague-Dawley rats the direction of the sex difference in the EPM is opposite in time in the open arms vs. number of entries to these arms) – on the type of assay used -Wistar rats show a sex difference in the EPM, but not in the free-choice paradigm, and on other non-specified variables, as shown by the inconsistent results obtained using the same strain, assay and behavioural measure (e.g. the inconsistent findings with Sprague-Dawley rats in the percent of time spent in the open arms of the EPM).

Complex interactions between sex and other factors are also evident in studies tapping what may be thought of as more basic processes, that is, learning and memory. For example, the existence and direction of a sex difference in tests of classical conditioning depends on procedure (e.g. fear conditioning vs. taste aversion), environmental factors (e.g. water deprivation, prior stress), and method of assessment of the extent of learning (e.g. during acquisition or extinction) (see Simpson and Kelly, 2012 for a similar conclusion). Similarly, in tests of spatial abilities in rodents, the existence and direction of a sex difference depends on strain, age, apparatus (radial maze vs. water maze), environmental factors (e.g. stress, previous familiarization with the task) and the specific requirements of the task (only working memory or both working and reference memory) (see Simpson and Kelly, 2012 for a similar conclusion).

It is clear from the above, that sex is just one of many factors that interact to produce normal and abnormal behaviours. As with brain structure, the effects of other factors may completely reverse the effects of sex on brain function. Moreover, the interactions between the different factors are complex, that is, whether there is a sex difference in a specific behaviour and its direction are often not predictable by the

Table 1

Complex sex × environment × genes interactions in widely used behavioural assays

Model	Test	Measurement	Sex	Manipulation	Strain	Species	Reference
Depression	FST	Immobility	F < M	–	B6: C57BL/6J	Mice	Mineur *et al.*, 2006
			F = M	UCMS	B6: C57BL/6J	Mice	Mineur *et al.*, 2006
			F = M	–	C: BALB/cJ	Mice	Mineur *et al.*, 2006
			F = M	UCMS	C: BALB/cJ	Mice	Mineur *et al.*, 2006
			F = M	–	D2: DBA/2J	Mice	Mineur *et al.*, 2006
			F > M	UCMS	D2: DBA/2J	Mice	Mineur *et al.*, 2006
			F < M	One day of testing	Flinders Sensitive Line	Rats	Kokras *et al.*, 2009
			F < M	Chronic melatonin treatment	Long-Evans	Rats	Brotto *et al.*, 2000
			F < M	–	Long-Evans	Rats	Brotto *et al.*, 2000
			F = M	One day of testing	Long-Evans	Rats	Frye & Walf, 2002
			F < M	–	Sprague–Dawley	Rats	Alonso *et al.*, 1991
			F = M	One day of testing	Sprague–Dawley	Rats	Kokras *et al.*, 2009
			F = M	–	Sprague–Dawley	Rats	Pitychoutis *et al.*, 2009
			F > M	–	Wistar	Rats	Dalla *et al.*, 2008a
			F > M	–	Wistar	Rats	Drossopoulou *et al.*, 2004
		Struggling	F > M	One day of testing	Flinders Sensitive Line	Rats	Kokras *et al.*, 2009
			F > M	Chronic melatonin treatment	Long-Evans	Rats	Brotto *et al.*, 2000
			F > M	–	Long-Evans	Rats	Brotto *et al.*, 2000
			F = M	One day of testing	Sprague–Dawley	Rats	Kokras *et al.*, 2009
			F = M	–	Sprague–Dawley	Rats	Pitychoutis *et al.*, 2009
			F < M	–	Wistar	Rats	Drossopoulou *et al.*, 2004
			F < M	–	Wistar	Rats	Dalla *et al.*, 2008a
		Swimming	F = M	One day of testing	Flinders Sensitive Line	Rats	Kokras *et al.*, 2009
			F > M	Chronic melatonin treatment	Long-Evans	Rats	Brotto *et al.*, 2000
			F > M	–	Long-Evans	Rats	Brotto *et al.*, 2000
			F = M		Long-Evans	Rats	Frye & Walf, 2002
			F = M	One day of testing	Sprague–Dawley	Rats	Kokras *et al.*, 2009
			F < M	–	Sprague–Dawley	Rats	Pitychoutis *et al.*, 2009
			F = M	–	Wistar	Rats	Dalla *et al.*, 2008a
			F = M	–	Wistar	Rats	Drossopoulou *et al.*, 2004
	Sucrose preference	Sucrose intake	F > M	Mild pro-inflammatory challenge with LPS	Sprague–Dawley	Rats	Pitychoutis *et al.*, 2009
			F > M	Chronic mild stress	Wistar	Rats	Dalla *et al.*, 2005
			F > M	–	Wistar	Rats	Dalla *et al.*, 2005
			F = M	Chronic mild stress	Wistar	Rats	Dalla *et al.*, 2008a
			F = M	–	Wistar	Rats	Dalla *et al.*, 2008a
			F > M	Chronic mild stress	Wistar	Rats	Kamper *et al.*, 2009
			F > M	–	Wistar	Rats	Kamper *et al.*, 2009
	Learned helplessness	Escape latency	F < M	Foot shock	Holtzman	Rats	Padilla *et al.*, 2009
			F < M	Sham–operated	Sprague–Dawley	Rats	Dalla *et al.*, 2008b
			F < M	–	Sprague–Dawley	Rats	Shors *et al.*, 2007
			F = M	Longer sessions of stress	Sprague–Dawley	Rats	Shors *et al.*, 2007
			F < M ($P = 0.08$)	–	Wistar	Rats	Steenbergen *et al.*, 1990
Anxiety	EPM	Time spent in the open arms	F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F > M	–	Long-Evans	Rats	Zimmerberg & Farley, 1993
			F > M	Predator scent stress	Sprague–Dawley	Rats	Mazor *et al,*. 2009
			F < M	–	Sprague–Dawley	Rats	Mazor *et al,*. 2009

Table 1

Continued

Model	Test	Measurement	Sex	Manipulation	Strain	Species	Reference
			F > M	Early weaning	Wistar	Rats	Ito *et al.*, 2006
			F > M	–	Wistar	Rats	Ito *et al.*, 2006
		Percentage of time spent in the open arms	F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F > M	–	Flinders Sensitive line	Rats	Kokras *et al.*, 2011
			F > M	–	Hooded lister	Rats	Johnston & File, 1991
			F = M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
			F > M	Social isolation	Sprague–Dawley	Rats	Weintraub *et al.*, 2010
			F > M	–	Sprague–Dawley	Rats	Weintraub *et al.*, 2010
			F = M	Neonatal treatment with clomipramine	Sprague–Dawley	Rats	Andersen *et al.*, 2002
			F = M	–	Sprague–Dawley	Rats	Andersen *et al.*, 2002
			F > M	Sham operated in adulthood and exposed to short stress	Wistar	Rats	Leret *et al.*, 1994
		Number of open arm entries	F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F > M	–	Flinders Sensitive line	Rats	Kokras *et al.*, 2011
			F > M	Neonatal handling	Long-Evans	Rats	Duchesne *et al.*, 2009
			F > M	–	Long-Evans	Rats	Duchesne *et al.*, 2009
			F > M	Predator scent stress	Sprague–Dawley	Rats	Mazor *et al*,.2009
			F = M	–	Sprague–Dawley	Rats	Mazor *et al*,.2009
			F > M	After stress (restraint)	Sprague–Dawley	Rats	Bowman *et al.*, 2009
			F > M	–	Sprague–Dawley	Rats	Bowman *et al.*, 2009
			F > M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
			F > M	Sham operated in adulthood and exposed to short stress	Wistar	Rats	Leret *et al.*, 1994
			F > M	Early weaning	Wistar	Rats	Ito *et al.*,2006
			F > M	–	Wistar	Rats	Ito *et al.*,2006
		Percentage of number of open arms entries	F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F = M	Neonatal handling	Long-Evans	Rats	Duchesne *et al.*, 2009
			F = M	–	Long-Evans	Rats	Duchesne *et al.*, 2009
			F > M	–	Hooded lister	Rats	Johnston & File, 1991
			F > M	–	Wistar	Rats	Lucion *et al.*, 1996
		Total arm entries	F < M	–	DBA/2	Mice	Rodgers & Cole, 1993
			F < M	–	TI	Mice	Rodgers & Cole, 1993
			F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F > M	–	Flinders Sensitive line	Rats	Kokras *et al.*, 2011
			F > M	Neonatal handling	Long-Evans	Rats	Duchesne *et al.*, 2009
			F > M	–	Long-Evans	Rats	Duchesne *et al.*, 2009
			F > M	Environmental enrichment	Sprague–Dawley	Rats	Pena *et al.*, 2006
			F > M	–	Sprague–Dawley	Rats	Pena *et al.*, 2006
			F > M	Stress (restraint)	Sprague–Dawley	Rats	Bowman *et al.*, 2009
			F > M	–	Sprague–Dawley	Rats	Bowman *et al.*, 2009
			F > M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
			F > M	Sham operated in adulthood and exposed to short stress	Wistar	Rats	Leret *et al.*, 1994
			F > M	–	Wistar	Rats	Lucion *et al.*, 1996

Table 1

Continued

Model	Test	Measurement	Sex	Manipulation	Strain	Species	Reference
	Free choice paradigm	Latency to explore the outside of the home cage	F < M	–	Sprague–Dawley	Rats	Bert *et al.*, 2013
			F = M	–	Wistar	Rats	Bert *et al.*, 2013
		Numbers of visits outside the home cage	F > M	–	Sprague–Dawley	Rats	Bert *et al.*, 2013
			F = M	–	Wistar	Rats	Bert *et al.*, 2013
		Percentage of rats exploring the outside the home cage	F > M	–	Sprague–Dawley	Rats	Bert *et al.*, 2013
			F = M	–	Wistar	Rats	Bert *et al.*, 2013
Anxiety/ Activity	Open field test	Horizontal locomotor activity	F > M	–	Flinders Sensitive line	Rats	Kokras *et al.*, 2011
			F > M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
		Vertical activity	F > M	–	Flinders Sensitive Line	Rats	Kokras *et al.*, 2011
			F > M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
		Distance moved-overall activity	F = M	–	B6: C57BL/6J	Mice	Mineur *et al.*, 2006
			F = M	UCMS	B6: C57BL/6J	Mice	Mineur *et al.*, 2006
			F = M	–	C: BALB/cJ	Mice	Mineur *et al.*, 2006
			F = M	UCMS	C: BALB/cJ	Mice	Mineur *et al.*, 2006
			F = M	–	D2: DBA/2J	Mice	Mineur *et al.*, 2006
			F = M	UCMS	D2: DBA/2J	Mice	Mineur *et al.*, 2006
			F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
		Average rearing duration/number of rearing	F > M	–	F2-generation rats derived from the inbred RHA/Verh and RLA/Verh strains	Rats	Aguilar *et al.*, 2003
			F > M	–	Holtzman	Rats	Padilla *et al.*, 2009
			F > M	Chronic melatonin treatment	Long-Evans	Rats	Brotto *et al.*, 2000
			F > M	–	Long-Evans	Rats	Brotto *et al.*, 2000
			F > M	Chronic stress	Sprague–Dawley	Rats	Beck & Luine, 2002
			F = M	–	Sprague–Dawley	Rats	Beck & Luine, 2002
			F > M	–	Sprague–Dawley	Rats	Alonso *et al.*, 1991
			F > M	–	Wistar	Rats	Dalla *et al.*, 2005
		Crossing behaviour	F > M	Chronic melatonin treatment	Long-Evans	Rats	Brotto *et al.*, 2000
			F > M	–	Long-Evans	Rats	Brotto *et al.*, 2000
		Central entries	F > M	–	Long-Evans	Rats	Frye & Walf, 2002
		Time in centre	F > M	–	Flinders sensitive line	Rats	Kokras *et al.*, 2011
			F < M	–	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F < M	Neonatal isolation	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F = M	–	Sprague–Dawley	Rats	Kokras *et al.*, 2011
		Latency to enter the field	F = M	Chronic stress	Sprague–Dawley	Rats	Beck & Luine, 2002
			F < M	–	Sprague–Dawley	Rats	Beck & Luine, 2002
Classical conditioning	Fear conditioning	Percentage of time freezing	F < M	–	Fischer	Rats	Pryce *et al.*, 1999
			F < M	–	Lewis	Rats	Pryce *et al.*, 1999
			F = M	Neonatal isolation	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F = M	–	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F = M	Brief maternal separation	Sprague–Dawley	Rats	Kosten *et al.*, 2006
			F = M	Prolonged maternal separation	Sprague–Dawley	Rats	Kosten *et al.*, 2006
			F = M	–	Sprague–Dawley	Rats	Kosten *et al.*, 2006
			F < M	–	Sprague–Dawley	Rats	Maren *et al.*, 1994
			F < M ($P = 0.06$)	–	Wistar	Rats	Pryce *et al.*, 1999

Table 1

Continued

Model	Test	Measurement	Sex	Manipulation	Strain	Species	Reference
		Ultrasonic vocalizations duration	F < M	Neonatal isolation	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F < M	–	Sprague–Dawley	Rats	Kosten *et al.*, 2005
			F < M	Brief maternal separation	Sprague–Dawley	Rats	Kosten *et al.*, 2006
			F < M	Prolonged maternal separation	Sprague–Dawley	Rats	Kosten *et al.*, 2006
			F < M	–	Sprague–Dawley	Rats	Kosten *et al.*, 2006
		Latency to re-enter the shock compartment	F < M	Neonatal handling	Sprague–Dawley	Rats	Kosten *et al.*, 2007
			F < M	–	Sprague–Dawley		Kosten *et al.*, 2007
		Mean number of magazine visits	F = M	–	Wistar	Rats	Maes, 2002
		Acoustic startle response	F > M	Stress (tail shock)	Sprague–Dawley	Rats	Beck *et al.*, 2002
			F > M	–	Sprague–Dawley	Rats	Beck *et al.*, 2002
	Taste aversion	Acquisition (amount of sucrose consumed with aversive stimuli)	F = M	Fluid deprived	Deer Mouse	Mice	Robbins, 1980
			F < M	–	Deer Mouse	Mice	Robbins, 1980
			F = M	Fluid deprived	Sprague–Dawley	Rats	Randall-Thompson & Riley, 2003
		Extinction (amount of sucrose consumed)	F = M	Fluid deprived	Deer mouse	Mice	Robbins, 1980
			F = M	–	Deer mouse	Mice	Robbins, 1980
			F > M	–	Long-Evans	Rats	Brot *et al.*, 1992
			F = M	–	Long-Evans (VP-deficient heterozygous)	Rats	Brot *et al.*, 1992
			F = M	–	Long-Evans (VP-deficient homozygous)	Rats	Brot *et al.*, 1992
			F > M	Fluid deprived	Sprague–Dawley	Rats	Randall-Thompson & Riley, 2003
			F > M	One-week isolation	Sprague–Dawley	Rats	Chambers & Sengstake, 1976
			F = M	Six-week isolation	Sprague–Dawley	Rats	Chambers & Sengstake, 1976
			F > M	–	Wistar	Rats	Sengstake *et al.*, 1978
			F = M	Fluid deprived	Wistar	Rats	Sengstake *et al.*, 1978
Spatial abilities	Water maze	Path length	F = M	–	C57BL/6	Mice	Berger-Sweeney *et al.*, 1995
			F = M	Five months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
			F > M	Seventeen months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
			F = M	Twenty-five months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
			F > M	Six months old	Fischer 344	Rats	Markowska, 1999
			F > M	Twelve months old	Fischer 344	Rats	Markowska, 1999
			F > M	Eighteen months old	Fischer 344	Rats	Markowska, 1999
			F > M	Twenty-four months old	Fischer 344	Rats	Markowska, 1999
			F = M	–	Long-Evans	Rats	Bucci *et al.*, 1995
			F > M	–	Long-Evans	Rats	Perrot-Sinal *et al.* 1996
			F = M	Previous familiarization with non-spatial aspects of the task	Long-Evans	Rats	Perrot-Sinal *et al.* 1996
			F (oestrus) < M F (proestrus) = M	Aged rats (22–24 months old)	Long-Evans	Rats	Warren and Juraska., 2000
			F > M	Alcohol on PND 4–10	Sprague–Dawley	Rats	Kelly *et al.*, 1988
			F = M	Artificially reared	Sprague–Dawley	Rats	Kelly *et al.*, 1988
			F = M	–	Sprague–Dawley	Rats	Kelly *et al.*, 1988
			F = M	Seven months old	Wistar	Rats	Lukoyanov *et al.*, 1999
			F = M	Sixteen months old	Wistar	Rats	Lukoyanov *et al.*, 1999
			F = M	Twenty-six months old	Wistar	Rats	Lukoyanov *et al.*, 1999

Table 1

Continued

Model	Test	Measurement	Sex	Manipulation	Strain	Species	Reference
		Latency to find the hidden platform	F = M	–	C57BL/6	Mice	Berger-Sweeney *et al.*, 1995
			F = M	–	NMRI	Mice	Lamberty and Gower., 1988
			F = M	–	Lister hooded	Rats	Healy *et al.*, 1999
			F = M	Sham operated in the frontal cortex	Long-Evans	Rats	Kolb and Cioe, 1996
			F (oestrus) < M F (proestrus) = M	–	Long-Evans	Rats	Warren and Juraska, 2000
		Time in the peripheral	F = M	–	C57BL/6	Mice	Berger-Sweeney *et al.*, 1995
		Swim speed	F = M	–	C57BL/6	Mice	Berger-Sweeney *et al.*, 1995
			F > M	Seventeen months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
			F = M	Five months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
			F = M	Twenty-five months old	C57BL/6NIA	Mice	Frick *et al.*, 2000
		Mean swim time to the platform	F > M	–	Long-Evans	Rats	Beiko *et al.*, 2004
	Radial maze-working memory	Mean working memory errors	F = M	–	CD-1	Mice	LaBuda *et al.*, 2002
			F > M	–	ddY	Mice	Mishima *et al.*, 1986
			F = M	Young animals (3–4 months)	Fischer 344	Rats	Kobayashi *et al.*. 1988
			F = M	Aged animals (22–27 months)	Fischer 344	Rats	Kobayashi *et al.*. 1988
			F = M	Complex environment	Lister hooded	Rats	Juraska *et al.*, 1984
			F = M	Isolated environment	Lister hooded	Rats	Juraska *et al.*, 1984
			F > M	Reared in complex environment	Littermate hooded	Rats	Seymoure *et al.*, 1986
			F > M	Reared alone	Littermate hooded	Rats	Seymoure *et al.*, 1986
			F > M	Light reared	Long-Evans	Rats	Tees *et al.*, 1981
			F > M	Dark–reared	Long-Evans	Rats	Tees *et al.*, 1981
			F = M	Sham operated in the frontal cortex	Long-Evans	Rats	Kolb and Cioe, 1996
			F = M	–	Sprague–Dawley	Rats	Maier and Pohorecky, 1986
			F > M	Ethanol exposure	Sprague–Dawley	Rats	Maier and Pohorecky, 1986
			F = M	–	Sprague–Dawley	Rats	Roof, 1993
			F > M	–	Wistar	Rats	Einon, 1980
			F = M	Social isolation	Wistar	Rats	Einon, 1980
			F = M	–	Wistar	Rats	Endo *et al.*, 1994
			F > M	–	Wistar	Rats	Endo *et al.*, 1994
	Radial maze-working and reference memory	Mean reference memory errors	F = M	–	CD-1	Mice	LaBuda *et al.*, 2002
			F > M	Reared in complex environment	Littermate hooded	Rats	Seymoure *et al.*, 1986
			F > M	Reared alone	Littermate hooded	Rats	Seymoure *et al.*, 1986
			F = M	Sham operated in the frontal cortex	Long-Evans	Rats	Kolb and Cioe, 1996

A comparison between the behaviour of males and females in behavioural assays commonly used to assess depression-like and anxiety-like behaviours, classical conditioning and spatial abilities.
= < > relate to the existence/direction of a sex difference in the behavioural measurement specified.
– means that the animals did not undergo any specific manipulation and that the behavioural procedure was carried out in its standard form.
F, female; M, male; VP, vasopressin.

existence (or lack) of sex differences in this behaviour under other environmental conditions or in a different strain/species, nor by the existence (or lack) of sex differences in other behaviours.

Whereas the conclusions mentioned earlier are based primarily on comparing data obtained in different experiments, there are also studies that demonstrate these principles in a single experiment (Aguilar *et al.*, 2003; Mineur *et al.*, 2006; Monteggia *et al.*, 2007; Andersen *et al.*, 2010). For example, Mineur *et al.* (2006) tested sex differences in the effects of unpredictable chronic mild stress (UCMS) on several behaviours relevant to anxiety and depression in three genetically distinct inbred mice strains. They found a large number of double and triple interactions between strain, treatment and sex, as well as different patterns of effects in different behavioural tests (Mineur *et al.*, 2006). That behavioural output depends on the interaction between sex and genetic and environmental factors (strain and stress, respectively, in this study) is evident when looking, for example, at immobility time in the FST (Figure 1A, reproduced with permission on the basis of figure 6 in Mineur *et al.*, 2006). This figure also demonstrates the unpredictability of the effects of sex on a specific behaviour. For example, there is no sex difference in immobility time of DBA/2J mice in the FST under control conditions, but a marked sex difference following exposure to UCMS (UCMS increases immobility time in female DBA/2Js, but does not affect immobility time in male DBA/2Js). This marked sex difference under UCMS in DBA/2J mice could not be predicted on the basis of (i) the existence of a sex difference in the control condition, because there was no sex difference; (ii) the existence of sex differences under UCMS in other strains, because there were no sex differences under UCMS in the C57BL/6J and Bagg albino (BALB)/cJ strains; and (iii) some type of a general relation between sex differences in the control condition and under UCMS, because there was also no sex difference under control conditions in the C57BL/6J strain, yet this strain did not show a sex difference under UCMS. In this example, the sex difference in DBA/2J mice following UCMS in immobility time in the FST could have been predicted on the basis of a sex difference in a related task (immobility time in the tail suspension test, Figure 1B, reproduced with permission on the basis of figure 6 in Mineur *et al.*, 2006). Please note, however, that in the tail suspension test, there was also a sex difference in the control condition, which was not evident in the FST; therefore, the similar effect of sex in the two procedures following UCMS does not generalize to other environmental conditions.

One conclusion from these studies is that it is misleading to talk about sexual dimorphism of behaviours that show a sex difference, because what is typical for males and for females is different under different environmental conditions as well as under the same conditions, but on a different genetic background (i.e. in different strains). Moreover, as with brain structure, even if one used some criterion to distinguish between a 'masculine' and a 'feminine' form of behaviour, each subject would exhibit a unique set of both 'masculine' and 'feminine' behaviours, as a result of its unique combination of genetic background and preceding and current environmental events. For example, in Mineur *et al.*'s (2006) study, control C57BL/6J mice showed a sex difference in immobility time in the FST (Figure 1A), immobility time in the tail suspension test (Figure 1B) and percent time in the open arms of the plus maze (figure 1 in Mineur *et al.*, 2006). Following UCMS, C57BL/6J males exhibited the 'feminine' form of behaviour in the FST and tail suspension test but maintained their 'masculine' form of behaviour in the plus maze.

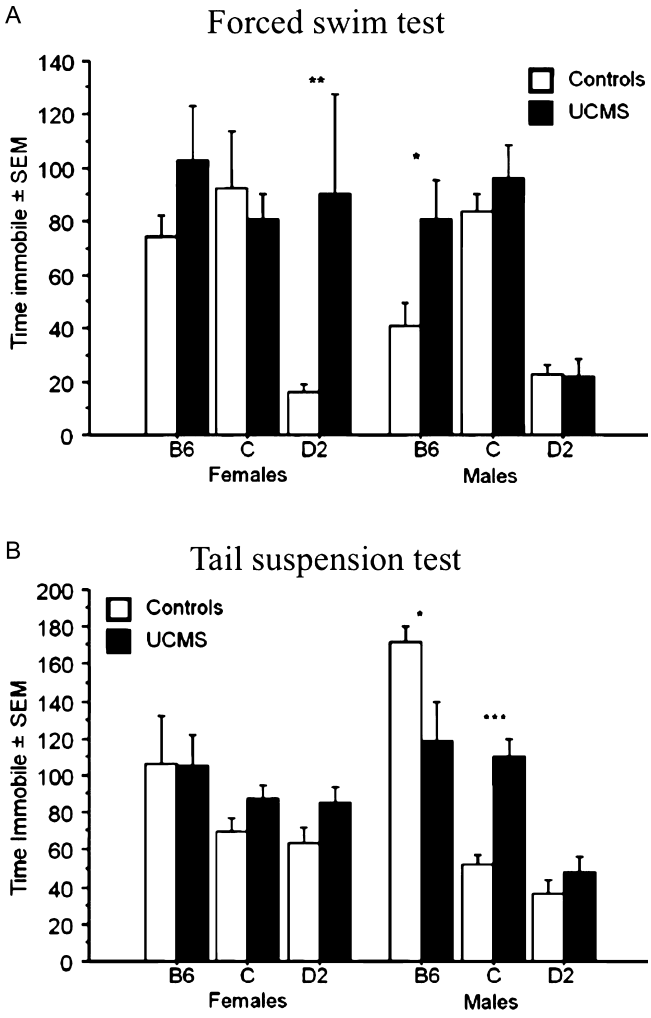

Figure 1

Mean and SEM time spent immobile in (A) the FST and (B) the tail suspension test of male and female BALB/cJ (B6), C57BL/6J (C) and DBA/2J (D2) mice that did or did not undergo UCMS (and control respectively). Adapted with permission, from figures 5 and 6 in Mineur *et al.* (2006).

It follows that we should study the effects of sex, but do so without *a priori* and implicitly assuming that these effects will be dimorphic and consistent. Two changes in terminology that may help this endeavour are the abandonment of the term 'sexual dimorphism', because behaviours (including sexual behaviours, Goy and Goldfoot, 1975) are not sexually dimorphic, and the replacement of the term 'sex differences' with the term 'sex interactions' (e.g. instead of stating that one studies sex differences in response to stress, we can state that one studies the interactions of sex and stress).

The review and discussion above also have implications for our conceptualization of sex differences in psychopathology (for recent reviews of the latter see Mathis *et al.*, 2011; Mendrek and Stip, 2011; Vega *et al.*, 2011; Hasson and Fine, 2012; Jogia *et al.*, 2012; Nolen-Hoeksema, 2012). It is widely accepted that psychopathology is a result of specific combinations of environmental events and genetic susceptibility factors (Rutter *et al.*, 2006; Rutter, 2007; Thapar *et al.*, 2007; Dick, 2011; Hyde *et al.*, 2011; Bellani *et al.*, 2012; Jaffee and Price, 2012; Kim-Cohen and Turkewitz, 2012). As the studies mentioned earlier demonstrate, these combinations may have different effects in men and in women (Eley *et al.*, 2004; Verona *et al.*, 2006; Uher and McGuffin, 2008; Schwandt *et al.*, 2010), and this may lead to sex differences in psychopathology (Joel, 2011). This account of sex differences in psychopathology is nicely demonstrated in Mineur *et al.*'s (2006) study discussed earlier. In this study, UCMS was found to increase immobility time in the FST in female, but not in male DBA/2J mice, while concomitantly decreasing time spent in the lit side in the light/dark box in male, but not in female members of this species. Assuming that immobility in the FST and time in the lit side have some relevance to the mechanisms of depression and anxiety, respectively, this study demonstrates how sex differences in psychopathology may result from the complex interactions of sex, genes and environment. Note that this is a different account for the existence of sex differences in psychopathology than the one attributing such differences to sex differences in the structure of the normal brain (e.g. the 'extreme male brain' hypothesis, Baron-Cohen *et al.*, 2005).

As brain pathology is a result of complex interactions of sex, environment and genes, studies of psycho- and neuropathology, whether in humans or in animal models, should be conducted using both male and female models. This practice is necessary for the advancement of the health of both women and men (Barros and Ferigolo, 1998; Hughes, 2007; Monteggia *et al.*, 2007; Dalla and Shors, 2009; Dalla *et al.*, 2010; ter Horst *et al.*, 2012; Simpson and Kelly, 2012).

A comment on the myth of males being free of fluctuating gonadal hormones

As outlined by McCarthy *et al.* (2012) and Cahill (2012), the call to study both males and females often meets with scientifically unjustified objections. We want to relate here to only one of them, the myth of the homogenous males as opposed to the highly variable females. Specifically, it is widely recognized that in females, the level of gonadal hormones fluctuates and that these hormones have behaviour-modulating effects. Thus, changes in the level of oestrogen and/or progesterone during the oestrous cycle, pregnancy and lactation have been shown to modulate anxiety- and depression-like behaviours, spatial behaviour, learning and memory in female rats and mice (see Barros and Ferigolo, 1998; Jonasson, 2005; Dalla and Shors, 2009; Simpson and Kelly, 2012; ter Horst *et al.*, 2012). Although there are studies that demonstrate similar behaviour-modulating effects of testosterone in males (e.g. Frye *et al.*, 2001; Aikey *et al.*, 2002; Edinger *et al.*, 2004; Edinger and Frye, 2004; 2005; 2007; Fernandez-Guasti and Martinez-Mota, 2005; Giammanco *et al.*, 2005; Toufexis *et al.*, 2006; Toufexis, 2007; Nyby, 2008; Choleris *et al.*, 2009), these effects are typically being ignored because testosterone levels in males, who obviously do not have an oestrous cycle, are implicitly assumed to be non-fluctuating. This implicit assumption is clearly reflected in using the fluctuations in female gonadal hormones as a justification for using only male subjects. However, there is a large intra- and inter-individual variability in the level of gonadal hormones in males (Bartke and Dalterio, 1975; Coquelin and Desjardins, 1982; Ellis and Desjardins, 1982; Nyby, 2008). This is caused by the pulsatile nature of testosterone release in males, resulting in high peaks of testosterone that are superimposed on a low basal level (Nyby, 2008). The timing of peaks, which can occur every few hours, as well as their amplitude, which can reach up to 40-folds of basal levels, are highly variable within an individual and between individuals (Coquelin and Desjardins, 1982). While it is well documented that mating interactions as well as exposure to mating-related stimuli lead to pulsatile release of testosterone (termed, reflexive release), it is spontaneous release, occurring several times a day, that accounts for much of circulating testosterone (Bartke and Dalterio, 1975; Coquelin and Desjardins, 1982; Ellis and Desjardins, 1982; Nyby, 2008). Although social factors (e.g. dominance) have been shown to affect testosterone level (e.g. Harding, 1981; Stefanski, 2000; Giammanco *et al.*, 2005; Chichinadze *et al.*, 2012), spontaneous pulsatile release also occurs in individually housed males (Nyby, 2008). Nyby (2008) estimated that 'at any given time, 75% of the males are experiencing baseline levels while the other 25% are experiencing a testosterone pulse, although not necessarily at peak levels'. (p. 206). Thus, *not only does testosterone level vary in males, its variability is much greater than the variability of estradiol and progesterone during the oestrous cycle* (up to seven and 10-fold increase respectively; Haim *et al.*, 2003; Harte-Hargrove *et al.*, 2013).

The most straightforward method to overcome the fluctuations of gonadal hormones in both males and females is random assignment to experimental groups. Although clearly, if circulating hormones affect the dependent measure, then not accounting for their fluctuations will add variability to the study; gonadal hormones are not different from any other variable that may affect the dependent measure, but is not under study in a given experiment. Thus, if a researcher is not specifically interested in studying the effects of gonadal hormones on the phenomena under investigation, there is no need to assess testosterone level in males or stage of the oestrous cycle in females. Similarly, there is no need to castrate or ovariectomize animals, as these manipulations lead to changes in many neural systems (Singh *et al.*, 1995; Sumner *et al.*, 1999; Mohamed and Abdel-Rahman, 2000; Danzer *et al.*, 2001; Rose'Meyer *et al.*, 2003; De Castilhos *et al.*, 2008; Nyby, 2008; Chen *et al.*, 2009; 2013) making inference to the intact condition very difficult. Yet, the researcher may use current knowledge about factors that affect gonadal hormones for the allocation of animals to the different experimental conditions. Thus, in some species (e.g. mice), housing females together may lead to the cessation or synchronization of the oestrous cycle (the Lee-Boot effect and the Whitten effect, respectively; Gangrade and Dominic, 1984; Jemiolo *et al.*, 1986; Ma *et al.*, 1998). Therefore, in such species, it may be recommended to allocate each of the female mice in a given home cage to a different experimental condition, as they are all expected to have a similar hormonal

profile. In contrast, in male mice, it may be better to allocate all male mice in a given home cage to the same experimental condition, because the testosterone level is affected by dominance (Harding, 1981; Stefanski, 2000; Giammanco *et al.*, 2005; Chichinadze *et al.*, 2012), and is therefore expected to differ between male mice housed in the same cage.

Conclusions

There is ample evidence that the effects of environmental events and genetic variation on the brain depend on sex, and vice versa – that the effects of sex on the brain depend on environment and genetic variation. It is these complex interactions between sex, genes and environment that determine brain structure and function. These interactions lead both to brains that do not have sex (as they are composed of both 'male' and 'female' features) and to sex differences in psychopathology. Changing our conceptualization of sex from one of dimorphism to one of interaction will enable us to capture this complexity and advance the health of the human species.

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Conflict of interest

None.

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