



Sex Differences in Brain and Translational Research in Neuroscience

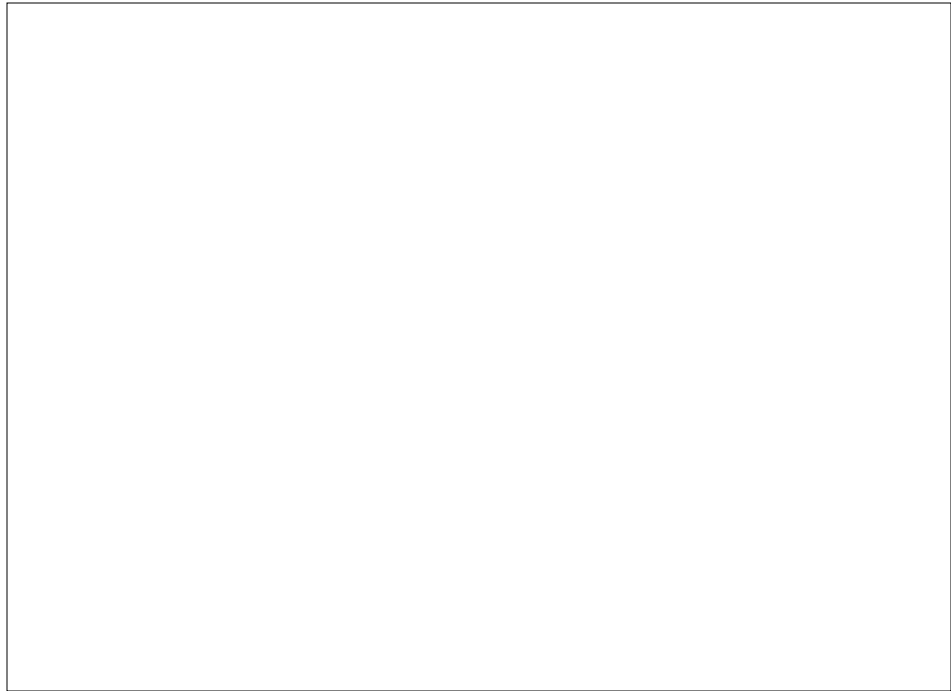
- Women and men have different risks for developing certain neurological, psychiatric, neuroendocrine, neuroimmunological, and injury/trauma-related disorders
- Certain disorders of brain and behavior are specific to one sex
- Certain disorders of brain and behavior exhibit a sex-specific etiology, presentation, course, severity, and/or responsiveness to therapeutic interventions

Overarching issues/problems to address:

- Translation of findings in basic neuroscience research to clinical research and practice
- Absence of focus on sex differences in brain function and dysfunction in basic and clinical neuroscience research

Factors contributing to these problems:

- Political hot button, public misunderstanding
- Overhyping and trivializing of sex differences in brain function that have very serious implications for the understanding of sexually differentiated brain function and disease



Basic science
research on sex
differences in brain
function



Clinical
research/drug testing

The culture of neuroscience research on sex differences

- Absence of sex differences in brain function as an integral topic in neuroscience graduate programs and medical school neuroscience courses
- Lack of recognition of the importance of sex differences in brain function and disease within the scientific community at large and as it relates to grant reviews and funding decisions

Sex Differences in Brain Disorders

<i>Disorder</i>	<i>Prevalence</i>	<i>Sex-specific onset, course, or manifestation</i>
Parkinson's Disease	M > F	Females older at onset, slower progression
Alzheimer's Disease	F > M	Female risk increased in advanced age
Huntington's Disease	M > F	Female > age of onset, course more moderate
Multiple Sclerosis	F > M	2:1; Earlier onset, more relapsing-remitting
Traumatic brain injury	F = M	M > level of injury, F > therapeutic responses
Stroke	M > F	Incidence in females greater after age 85
Autism	M > F	Boys affected more frequently, 4:1
Schizophrenia	M = F	M onset earlier; second increase in F 45-54yr
Depression	F > M	2:1 F/M during adolescence
Anxiety Disorders	F > M	F > Panic disorder, PTSD, social phobia, GAD
Eating Disorders	F > M	Anorexia nervosa and bulimia >> women
Peripheral Neuropathy	F > M	Multiple causation: some influenced by sex

Neuroendocrine Function is Sexually Differentiated

<i>Neuroendocrine function</i>	
Reproductive behavior	Greater influence of psychosocial variables in humans versus experimental animals
Gonadal hormone actions in CNS	T, E2, P4, Organizational actions in fetus, neonate
Gonadal hormone actions in CNS	T, E2, P4, Activational effects in adolescent, adult
Gonadal hormone actions in CNS	E2, Synaptic plasticity
Gonadal hormone actions in CNS	E2, T, P4, Neuroprotection
Pubertal maturation	Earlier onset in girls
Stress responses	Higher basal and stress-induced glucocorticoid release
Energy homeostasis	Ovarian hormones potent regulators of energy balance; food intake and energy expenditure

Recommendations:

1. Promote recognition and understanding of sex differences in brain function and brain disorders in neuroscience graduate and medical school training curricula
2. Convene a panel of experts to make recommendations to NIH Peer Review administration on the inclusion of female subjects and/or focus on sexually differentiated brain function and disease in basic neuroscience research

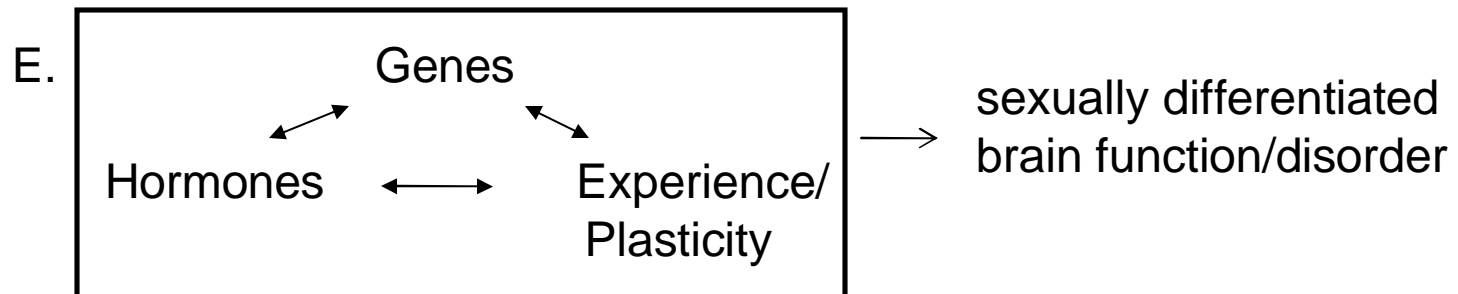
A Paradigm Shift is Needed!

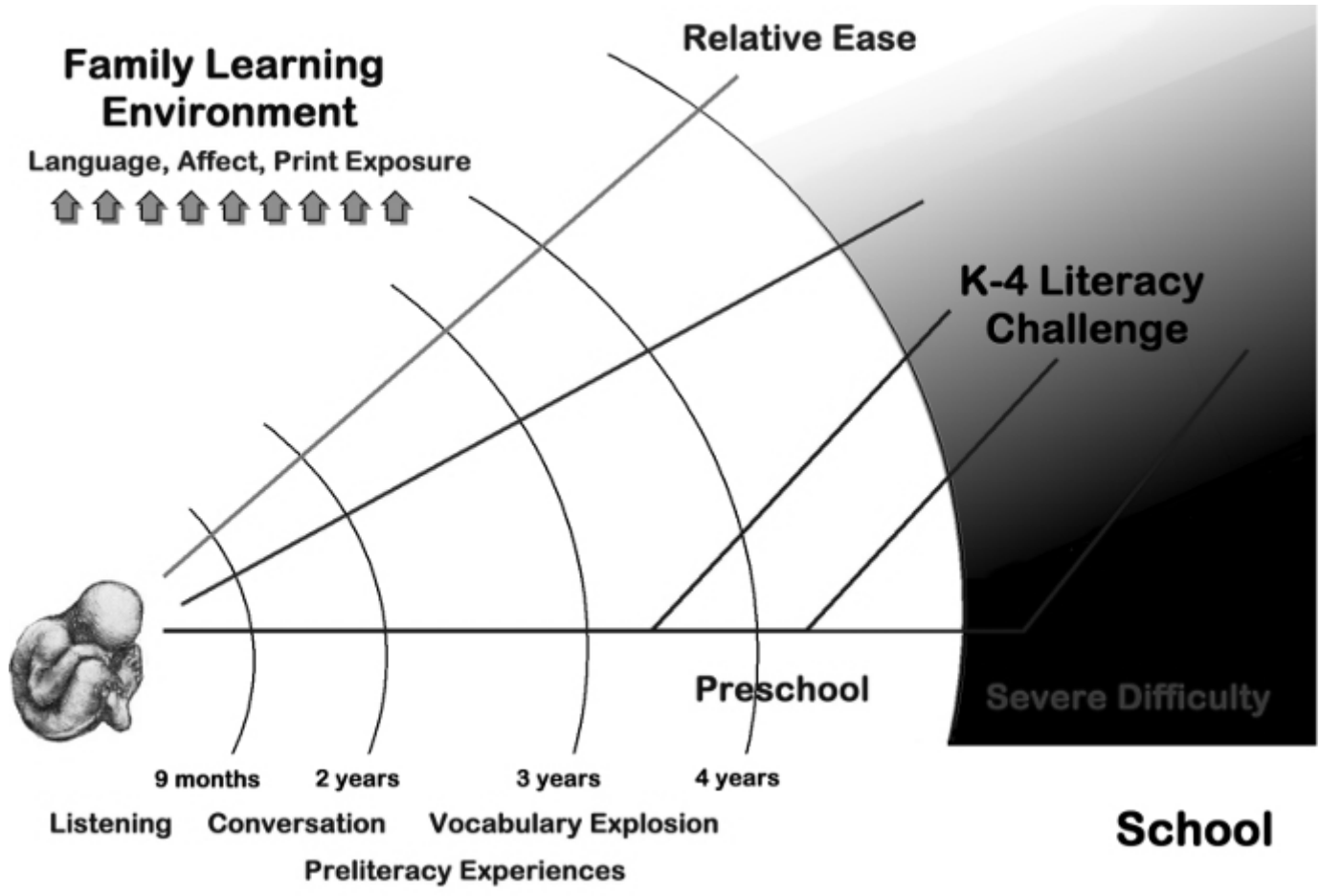
A. Structure \longrightarrow sexually differentiated neurophysiology/behavior

B. +/- hormones* \longrightarrow structure \longrightarrow sexually differentiated neurophysiology/behavior

C. +/- Hormones \longrightarrow genes \longrightarrow sexually differentiated brain function/disorder

D. Genes \longrightarrow +/- hormones \longrightarrow sexually differentiated brain function/disorder
+/- experience/plasticity

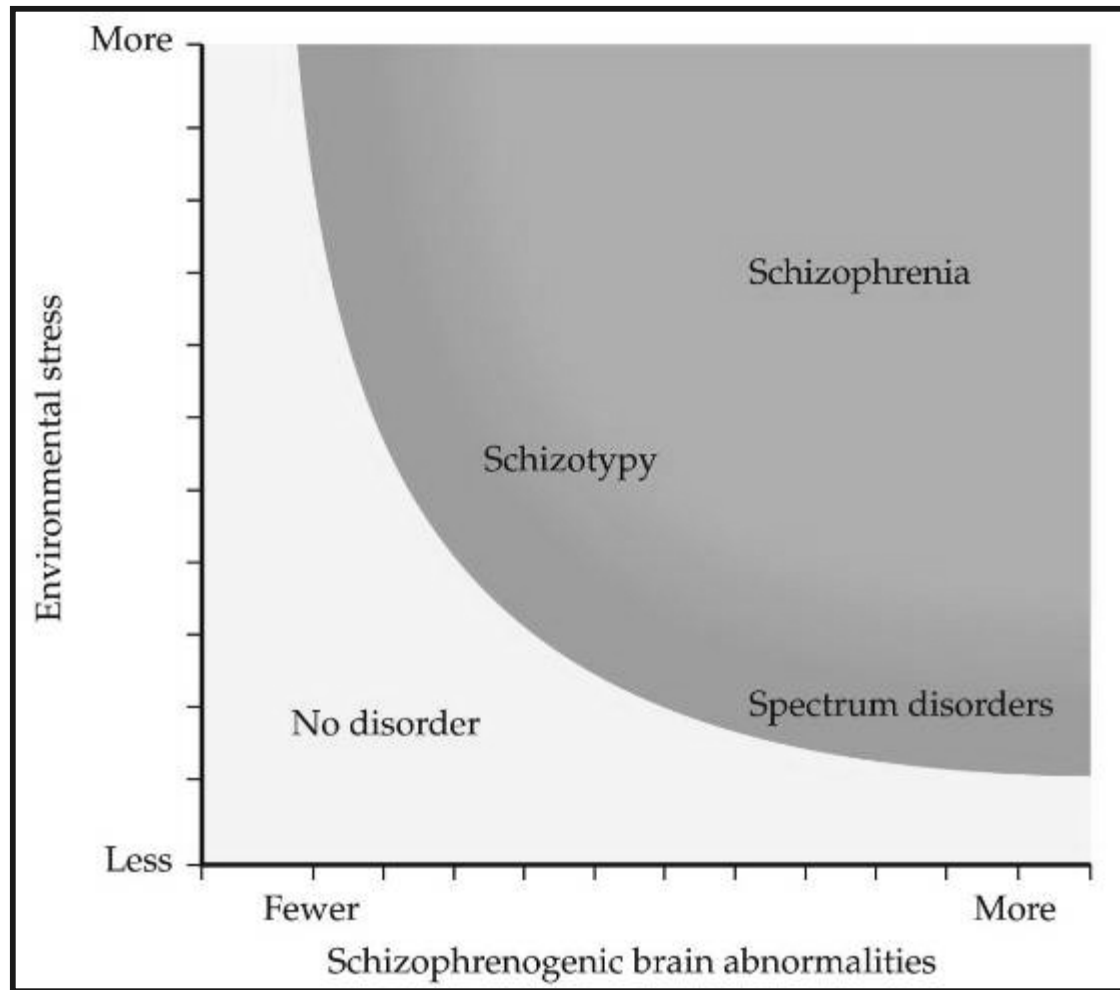




Diathesis-Stress Models

- Diathesis=genetic predisposition to disease
- Stress=environmental precipitator of disease manifestation
- The greater the underlying predisposition, the less stress it takes for disease manifestation
- Stressors are different for women and men

Diathesis-Stress Model Applied to Schizophrenia



Neuroscience Research and Women's Health: New approaches, New paradigms

Recommendations:

3. New paradigms to study the **epigenetic influences** impacting development of neurological and psychiatric disorders. What determines sex-specific or sex-biased brain disease vulnerability, course, and/or response to therapeutics?
 - Experimental paradigms that model sex-specific or sex-biased experiential, hormonal, and psychosocial effects on gene expression, and intra- and inter-cellular signaling properties in brain.
 - Develop and utilize high-throughput epigenomic approaches to characterize the large-scale epigenetic alterations associated with experience and related to sexually differentiated brain function and disease
4. Develop new paradigms and molecular genetic approaches to study the impact of experience, hormones, developmental stage, and aging on sex differences in steroid hormone signaling *in vivo*; new generations of transgenic and gene targeting approaches

. Recommendations (cont.)

5. Develop and support new approaches to define similarities and differences in sexually differentiated brain function and disease in human and animal models, e.g. through the use of comparative imaging (e.g. fMRI, etc.) of sexually differentiated brain function.
6. Develop new methodologies for targeted imaging, application of pharmacological agents to sexually differentiated cell populations in brain