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Window of opportunity for estrogen and progestin intervention in brain aging and Alzheimer's disease

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In 1966, Robert Wilson published the controversial book “Feminine Forever”, in which he listed memory loss as a symptom of menopause (Wilson, 1966). While at the time this claim was not backed with methodical scientific verification, many studies now support the assertion that memory changes occur in women concordant with menopause, relating to accompanying ovarian hormone changes. The U.S. Census Bureau estimates that by 2020, the population of women between 45 and 64 years old will reach approximately 41 million, and will represent 25% of the entire female population in the U.S. This is a marked increase from the 32 million reported for the year 2000 (U.S. Census Bureau. 2004, “U.S. Interim Projections by Age, Sex, Race, and Hispanic Origin,” (http://www.census.gov/ipc/www/usinterim proj/) Internet release date: March 18, 2004). This increasing number of menopausal women will consequently need to make decisions about the use of hormone therapy to treat not only menopausal symptoms, but potentially, to maintain a healthy brain. Recognizing this is critically important, now more than ever, given that women are living approximately one-third of their lives in a menopausal hypo-ovarian hor mone state. Indeed, women are living longer, yet age of spontaneous menopause has remained stable. While

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research thus far has yielded important insights into rela tions between endogenous and exogenous female steroid effects on the brain and its functions, it is nonetheless true that we have much to learn about the neurobehavioral consequences of the ovarian hormone loss associated with menopause, as well as effects of subsequent hormone ther apy use. Many researchers are working steadfast toward their goal of identifying under what conditions hormone therapies are beneficial, null, or detrimental to cognitive function, as well as mechanisms of these potential impacts. Although numerous basic science studies, epidemiological studies, and some clinical trials have supported the potential benefit of hormone therapy in reducing the incidence of age-associated brain dysfunction, including reducing the risk for Alzheimer's disease, results from the Women's Health Initiative (WHI) have suggested the contrary and left the field unsettled as to the future of hormone therapy. While the latter findings were initially quite unexpected and perhaps even disconcerting to many, the salience of the basic science studies persevered and it is now recognized that many factors that could be interpreted as “caveats” to the WHI (particularly the WHI memory study, WHIMS) are actually critical turning points in the neurobehavioral efficacy of hormone therapy. These putative critical turning points are now being systematically and methodically tested in the preclinical and clinical realm. These include the possibility that both aging and the duration of post-menopausal hormone deprivation diminish the pro tective brain response to steroid hormones (1, 2). This begs the question of whether a finite period of responsivity to estrogens and/or progestins exists; that is, is there a limited window of opportunity around menopause during which hormone therapy can exert positive effects? In order to offer an authoritative perspective on this issue, we invited leaders in the field of steroid hormone neurobiology to offer their insight into five questions: (1) Is there a window of opportu nity for brain protection with hormone therapy in post-menopausal women? (2) Is there evidence for better estrogens and progestins than the estrogen combination conjugated equine estrogens and the progestin medroxypro gesterone acetate, which are the most commonly utilized hormone therapies used to date, and were used in the WHIMS? (3) What are the parameters impacting whether hormone therapy acts as an enhancer or a detriment to the brain and cognition? (4) Are there alternatives to estrogens/ progestins in protecting women from cognitive decline after the menopause? (5) What are the mechanisms underlying the cognitive efficacy of hormone treatment, especially as related to a critical window around menopause?

The chapters included in this Special Issue of Brain Research address these five questions through discussion of such topics as the importance of considering the experimental variables, design, and baseline characteristics of the study population in humans, or how the choice of an animal model and tools used to assess such endpoints as cognitive function in rodents can influence outcome and interpretation of the effects of estrogens and progestins, how potential alternatives to estrogens exert their effects on cognitive function and mechanisms related to cognitive function, and the implication of specific receptors and signaling mechanisms in defining the response of the brain to estrogens and/or progesterone. Collectively, we believe that these chapters provide critical information that not only reviews our current understanding of the neurobiology of estrogens and proges-tins, but also offers important insight into the biological basis for the window of opportunity.

Identifying the various components of the complex interactions between menopause, hormone therapy, and the brain and its function, including experimental protocols using basic science and clinical evaluations, is the optimal approach to converge the many findings that might currently appear contradictory. In fact, with the continued emergence of new data, including data presented herein, it will likely become clear that the various findings are not contradictory at all. Rather, the variability in effectiveness of hormone therapy is likely dependent on numerous factors that are just starting to be understood, or are not yet taken into account in many studies because they are not yet discovered. As we continue to converge the many perspectives of one scientific problem, such as with the current Special Issue wherein we embody a multidimensional approach to the critical question of a window of opportunity for the neurocognitive effects of hormone therapy, we will align basic science discoveries with clinical findings and interpretations. The hope is that this approach will capitalize on opportunities to make new discoveries, thereby providing subsequent intervention strategies so that women can maximize their potential for healthy brain aging. It is our goal that the window of opportunity for optimal hormone therapy efficacy will expand as new findings emerge and we are able to more explicitly define hormone therapy parameters that enhance brain plasticity, neuroprotection, and cognitive function during aging.