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Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system

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Abstract

The brain is an endocrine organ whose day-to-day function is tied to the rhythmic production of neuromodulatory hormones. Yet, traditional approaches to studying brain–hormone relationships in humans are often coarse in scope. By contrast, dense-sampling neuroimaging offers the unique ability to probe dynamic interactions between the nervous and endocrine systems. This review summarizes recent evidence of sex hormones' influence on structural and functional properties of the human brain. In particular, findings from the '28andMe' project suggest that estradiol modulates the topology of large-scale functional brain networks and progesterone rapidly shapes medial temporal lobe morphology across the menstrual cycle. This nascent body of work sets the stage for additional studies in larger cohorts. We end by discussing the potential of dense-sampling designs to further elucidate endocrine modulation of the brain, with implications for personalized medicine.

Keywords

deep imaging; sex hormones; personalized medicine; MRI

Since its inception, the field of neuroendocrinology has provided cross-species evidence for the tightly-coupled relationship between the nervous and endocrine systems [1,2]. Sex steroid hormones act as critical neuromodulators, influencing the brain from the level of microscopic intracellular and synaptic events [3,4] to macroscopic structural [5–7] and functional [8,9] brain networks. Two major sex steroid hormones, 17β-estradiol and progesterone, are critical components of cell survival and plasticity, exerting excitatory and inhibitory effects that are evident across multiple spatial and temporal scales [10].

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Scientists have routinely pushed the bounds of experimental creativity to tease apart the inherently complex nature of brain–hormone interactions. Here, we address a new set of methodological innovations for probing estrogen and progesterone action in the human brain. A central feature of the mammalian endocrine system is that hormone secretion varies over time, and this rhythmicity is essential for sustaining many physiological processes. Traditional approaches to studying brain–hormone interactions rely largely on cross-sectional designs that, by nature, cannot capture fluctuations in sex hormone production. A growing trend in human neuroimaging is to flip the cross-sectional model, densely-sampling individuals over timescales of days, weeks, months, or years to provide greater insight into the dynamic properties of the human brain. Dense-sampling neuroimaging studies extend longitudinal designs by collecting multiple phenotypic measurements at a higher frequency or over a larger number of sessions (> 10 time points) in individuals [11,12].

In this review, we discuss how dense-sampling methods can be adopted within the field of human neuroendocrinology. A handful of recent human neuroimaging studies have begun leveraging dense-sampling techniques to uncover the dynamic endocrine modulation of the nervous system across novel timescales, including the ‘28andMe’ Project from the University of California, Santa Barbara. After reviewing key findings from this emerging literature, we discuss how these methods could be leveraged to improve personalized medicine for endocrine-related neurological disorders.

I. Traditional experiments reveal brain–hormone relationships

Cross-sectional investigations

In cognitive neuroscience, a classic approach for studying the brain involves collecting data from a number of individuals at a *single* time point and then group-averaging, thus increasing the ability to generalize findings to a broader population. Similarly, testing differences between cross-sections of the population has been valuable for brain–hormone investigations. For example, differences in brain structure and function have emerged when comparing groups of women at different stages of the menstrual cycle [13] or menopausal transition [14,15] and similar comparisons are useful for investigating the brain’s response to exogenous hormone exposure [16]. In a recent study, Zeydan and colleagues (2018) compared the effects of reproductive stage on brain structure among middle-aged women [17]. Those that had undergone surgical menopause before the age of 50 had thinner parahippocampal/entorinhal cortices, smaller amygdala volumes, and lower entorhinal white matter fractional anisotropy values compared to women who underwent spontaneous menopause later in life. One strength of this cross-sectional approach is that it allows researchers to isolate how reproductive stage, over and above chronological age, shapes the brain [18].

Large-scale ‘population neuroscience’ datasets are also being leveraged to test brain–hormone associations. Recently, de Lange and colleagues used the UK Biobank database to examine the association between a woman’s reproductive health history and brain age [19,20]. Using machine learning on data from over 12,000 middle-aged women, they found that multiparous women were classified as having ‘younger-looking’ brains relative to nulliparous women, particularly within striatal and limbic regions—an effect that held after

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accounting for age, ethnicity, education, body mass index, age at first birth, and number of reproductive years.

Longitudinal investigations—insights from 'sparse-sampling' designs

Longitudinal studies provide insight into the degree of stability or change within groups of individuals over time, a particularly powerful approach for revealing hormone-related changes in the brain. Recent longitudinal brain–hormone studies have sampled individuals before and after major neuroendocrine events such as pregnancy [21] and across discrete stages of the menopausal transition [22]. One such study examined first-time mothers prospectively, finding reductions in gray matter volumes post-pregnancy in regions largely overlapping with theory-of-mind circuitry. These changes were not observed in age-matched nulliparous women or male counterparts scanned over the same time-period [21]. Longitudinal studies like these offer valuable clues about how the brain responds to periods of significant hormonal change. A number of recent studies have also applied this approach to the menstrual cycle, sampling women several (e.g. 2–4) times in order to compare brain structure and function by cycle stage [8,23,24]. However, inconsistences emerge due to the inherent limitation of applying a static sampling rate to the study of a dynamical system. For example, Schmalenberger and colleagues (2020) argue that exploring within-person menstrual cycle effects requires, *at minimum,* sampling three time points across one cycle [25]. Still, three time points are insufficient to explore how the brain responds to *transient changes* in sex hormones, a critical feature of the endocrine system [9,26,27].

Together, findings from cross-sectional and traditional longitudinal studies support a role for ovarian hormones in shaping the brain across the life course [1–2,4,10]. However, new approaches with improved temporal resolution are needed to illuminate the time-sensitive coupling between hormone fluctuations and the functional and structural architecture of the human brain.

II. Dense-sampling as a new avenue for probing brain–hormone interactions

Neuroimaging studies that densely sample the individual connectome are beginning to transform our understanding of human brain organization over time [11,12]. This method is particularly well-suited for examining relationships between brain dynamics and physiological variables that vary over relatively short time scales, such as ovarian hormone production over the human menstrual cycle. To that end, a small but emerging body of work has begun to reveal sex hormones' ability to drive changes in the brain's structure and function [5,7,9,27–30].

Densely-sampling the functional connectome across the menstrual cycle

Arélin and colleagues densely-sampled a naturally-cycling female every 2–3 days over a four-month period, collecting brain imaging and blood hormone data across 32 sessions [5,29]. Using resting-state fMRI, the authors observed a positive relationship between progesterone and functional connectivity between the hippocampus, dorsolateral prefrontal cortex (PFC), and sensorimotor cortex, suggesting that changes in inter-regional connectivity

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are tied to hormone fluctuations across the cycle [29]. This sampling rate provided novel evidence for a relationship between functional connectivity and hormone fluctuations, while accounting for potential intra-individual hormone variation across multiple cycles. However, the study was unable to address whether changes in sex hormones *drive* variation in brain states, which requires a higher within-person measurement frequency (e.g. day to day assessments) and time-lagged analyses.

To that end, our group completed the '28andMe' project, in which a participant underwent brain imaging and venipuncture over 30 consecutive days across a complete menstrual cycle (Study 1), followed by 30 consecutive days on an oral hormonal contraceptive regimen (0.02 mg ethinyl-estradiol, 0.1 mg levonorgestrel, Aubra, Afaxys Pharmaceuticals) (Study 2) one year later. To probe time-synchronous and time-lagged effects of ovarian hormones on functional brain networks, we sampled the participant every 24 hours. The unique strength of these studies derives from their ability to capture, with high spatial and temporal resolution, the brain's response to a central feature of the mammalian endocrine system: hormonal rhythmicity.

To begin, we tested the hypothesis that whole-brain, resting-state functional connectivity (rs-fc) is associated with intrinsic fluctuations in estradiol and progesterone in a time-synchronous (i.e. day-by-day) fashion. Based on enriched expression of estrogen receptors in frontal cortex [31], we predicted that the Default Mode, Frontoparietal Control, and Dorsal Attention Networks would be most sensitive to hormone fluctuations across the cycle. We observed robust increases in coherence across the brain as a function of increasing estradiol (Fig. 1A) [9]. In contrast to estradiol's proliferative effects, progesterone was primarily associated with reduced coherence across the whole brain. Next, we used time-lagged methods from dynamical systems analysis to test the temporal directionality of these associations, finding that estradiol enhances within-network integration (i.e. global efficiency) in several large-scale brain networks, with the strongest effects in Default Mode (DMN) (Fig. 1B) and Dorsal Attention (DAN) Networks. These results replicated across Study 2 (where progesterone, but not estradiol, was selectively suppressed), further strengthening the notion that estradiol drives changes in network connectivity. In fact, across both studies, estradiol often predicted brain states better than previous states of the brain itself.

However, questions remained regarding how hormones shape large-scale functional brain network reorganization: *which* nodes are driving this network reorganization and *how* do they reorganize? To address this, we applied methods from complex systems analysis —dynamic community detection (DCD)—to identify periods of time when functionally coupled regions began to shift the network communities with which they were affiliated: so-called network 'flexibility' [27]. Despite a large degree of network stability over the menstrual cycle, a striking reorganization event occurred within the DMN, coincident with the peaks in serum estradiol (Fig. 1C). During the 3-day ovulatory window, the DMN core split into two smaller groups, leading to the transient formation of a new functional community. This was one of only two large-scale reorganization events—the other occurring during the luteal phase's secondary peak in estradiol, which involved an overlapping set of nodes located predominantly within the PFC.

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While DCD expanded upon our earlier finding by highlighting cycle-dependent alterations in DMN organization, unique effects emerged when comparing naturally-cycling (Study 1) and oral contraceptive (Study 2) conditions. Our original investigation [9] revealed that estradiol's ability to drive global efficiency within the DMN was invariant to condition (i.e. evident under naturally cycling conditions and when progesterone was selectively suppressed). In contrast, a closer look with DCD revealed increased DMN network flexibility only during ovulation: networks were largely *stable* under the oral contraceptive regimen, with no major reorganizations despite the fact that fluctuations in estradiol were on par with those observed under naturally cycling conditions. It is possible that hormone-driven changes in sub-network organization are specific to conditions in which gonadotropins and ovarian hormones (e.g. luteinizing hormone, follicle stimulating hormone, estradiol, and progesterone) exert coordinated action in the brain, as occurs across the menstrual cycle.

Together, these dense-sampling studies provide initial evidence that transient fluctuations in ovarian hormones over the cycle drive coordinated reorganization across the functional connectome, especially within the DMN. Interestingly, a major DMN subnetwork encompasses theory-of-mind circuitry [32], a cognitive process that underlies the ability to infer another individual's mental state [33]. Given that pregnancy leads to select structural changes in this circuit [21], there may be a specific functional significance of cycle-related changes in DMN connectivity – i.e. to support social cognitive processes. This hypothesis could be tested in future dense-sampling experiments in which theory-of-mind performance, resting-state fMRI, and endocrine evaluations are assessed in diverse cohorts of women across the menstrual cycle. Further, examining DMN properties across other major endocrine transition periods (e.g. puberty, menopause) and in response to direct pharmacological manipulation will strengthen our understanding of sex hormones' role in this circuit.

Densely-sampling brain structure across the menstrual cycle

In addition to sex hormone–driven changes in the functional connectome, dense-sampling studies are also beginning to reveal hormone-related changes in *morphology* over short timescales. Animal studies provide powerful evidence that sex hormones play a critical role in the synaptic organization of the hippocampus. In rodents, peak levels of estradiol during the estrous cycle induce a 30% increase in dendritic spine density in the CA1 region of the hippocampus, while progesterone rapidly reverses this effect. On average, women experience an 8-fold increase in estradiol and an 80-fold increase in progesterone across a menstrual cycle; yet, few studies have investigated the relationship between endogenous hormone fluctuations and hippocampal subfield morphology in humans [34]. Furthermore, prior to 28andMe, none had sampled at sufficiently high temporal and spatial (submillimeter) resolutions to probe whether the pronounced effects of sex hormones observed at the microscopic scale in rodents [35] are evident at the mesoscopic scale detectable with human MRI.

Using high-resolution hippocampal subfield imaging, we discovered that endogenous hormone fluctuations and exogenous hormone manipulations alter medial temporal lobe

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morphology [7]. Across the menstrual cycle, intrinsic fluctuations in progesterone were associated with volumetric changes in CA2/3, entorhinal, perirhinal, and parahippocampal cortex. Chronic progesterone suppression (with 0.02 mg ethinyl-estradiol, 0.1 mg levonorgestrel, Aubra, Afaxys Pharmaceuticals) abolished these cycle-dependent effects. These results suggest progesterone has the ability to dynamically shape medial temporal lobe morphology over rapid timescales.

Considerations from *28andMe*

A major limitation of the 28andMe project is that it densely tracked one individual, limiting our ability to generalize findings to a more diverse sample of women. Indeed, the pattern of results we observed may vary across women depending upon the duration of a woman's ovulatory window, sensitivity to hormone fluctuations, or sex hormone receptor expression (to name a few). Rather, findings from the 28andMe Project should be treated as indicative of the type that might emerge when applying dense-sampling methods to reveal endocrine modulation of the human brain. We hope that this project motivates future dense-sampling studies that investigate the dynamic role endogenous/exogenous sex hormones play in shaping the brain of both sexes across the lifespan. For example, future work using dense-sampling to characterize the brain's response to sex hormone fluctuations in men (e.g. androgens) and other steroid hormones (e.g. cortisol) will improve our understanding of the time-course through which hormones influence brain structure and function. Critically, the extent to which hormone fluctuations *cause* mesoscopic brain variability remains rich for exploration. Models of interactions lagged in time (such as VAR) may offer a promising first step, but they require strong *ad hoc* specification and make considerable assumptions about the temporal structure of brain-hormone dynamics. Ovarian hormones are more likely a nonlinear system, for which other modeling techniques are better-suited. Ultimately, although dense-sampling studies in neuroendocrinology remain rare, this approach could elucidate general principles of brain-hormone interactions in the human brain at an unprecedented temporal resolution.

III. Relevance for personalized medicine

Personalized medicine is the development of therapeutic approaches catered to the individual through phenotypic and genotypic characterization. Increasing the frequency of within-person measurements (i.e. dense-sampling) in neuroimaging provides a new opportunity to identify neural biomarkers that can lead to individualized inferences, detection, and treatment of psychiatric and neurologic conditions—personalized neuroscience. Throughout the life course, major hormonal transition periods (including puberty, pregnancy, initiation of oral contraceptive use, and perimenopause) coincide with an increased risk for major depressive disorder [36]. Modeling dynamic *changes* in these tightly-coupled systems (e.g. brain networks, ovarian hormones) in the healthy brain could help us better predict the likely consequences of their disruption in the disordered brain. Doing so could afford unique insight into why symptoms emerge in some individuals but not others.

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Disruptions in functional brain networks are implicated in a number of neurodegenerative disorders, including Alzheimer's Disease (AD). The DMN is particularly vulnerable to AD progression, demonstrating distinct abnormalities in functional connectivity compared to healthy controls [37] and hypoactivity due to amyloid-β aggregation [38]. Notably, DMN connectivity is also altered in MDD [39], a known risk factor for AD [40]. At the morphological level, the entorhinal cortex is one of the first cortical regions of the brain to develop neuropathology in the progression of AD, followed by surrounding medial temporal lobe regions (MTL) [41,42]. A distinct characteristic of these AD-sensitive circuits (e.g. the DMN and MTL) is that they are heavily populated by sex hormone receptors and are regulated by sex hormones [7–10,13,17,18,21,31]. In 28andMe, we discovered that estradiol is a major driver of global efficiency within DMN [9], a network that also exhibited the most striking reorganization event (transiently splitting into two distinct subnetworks) coincident with peaks in estradiol. Next, our dense-sampling study revealed that the most pronounced effects of chronic progesterone suppression occurred in entorhinal cortex [7], demonstrating strong regulatory effects of progesterone on entorhinal cortex volume, which adds to a growing body of work underscoring the need for clinical studies to investigate the neuroendocrine basis of cognitive decline and dementia risk [43–46]. Few studies of the aging brain consider the midlife period, and even fewer consider the neural effects of reproductive aging [43]. Given that women are disproportionately affected by AD [44,45], applying dense-sampling methods to the menopausal transition (a neurological transition state when ovarian hormone production declines by >90% [46]) would allow us to observe how an individual's brain—especially DMN and MTL architecture— responds to a changing hormonal milieu decades before disease onset. Such studies may yield important clues about what constitutes normative reproductive aging versus a prodromal period of heightened disease risk.

IV. Conclusions

While human neuroimaging studies that densely sample the individual connectome have begun to transform our understanding of the dynamics of human brain organization, they routinely omit sex steroid hormones as variables of interest. This approach is uniquely well-suited, however, to test hypotheses and build models of nervous and endocrine system interactions across the lifespan, capturing details of brain–hormone coupling that may be overlooked by traditional cross-sectional or sparse-sampling approaches. Advancing our understanding of how hormones shape the brain is imperative for our basic understanding of the brain and for women's health.

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Highlights

- Sex steroid hormones influence the brain across multiple spatiotemporal scales
- Dense-sampling can uncover brain–hormone interactions at higher temporal resolution
- Transient increases in estradiol enhance global efficiency of several large-scale networks
- Progesterone shapes medial temporal lobe volume across the menstrual cycle
- Incorporating endocrine factors into neuroimaging could improve personalized medicine

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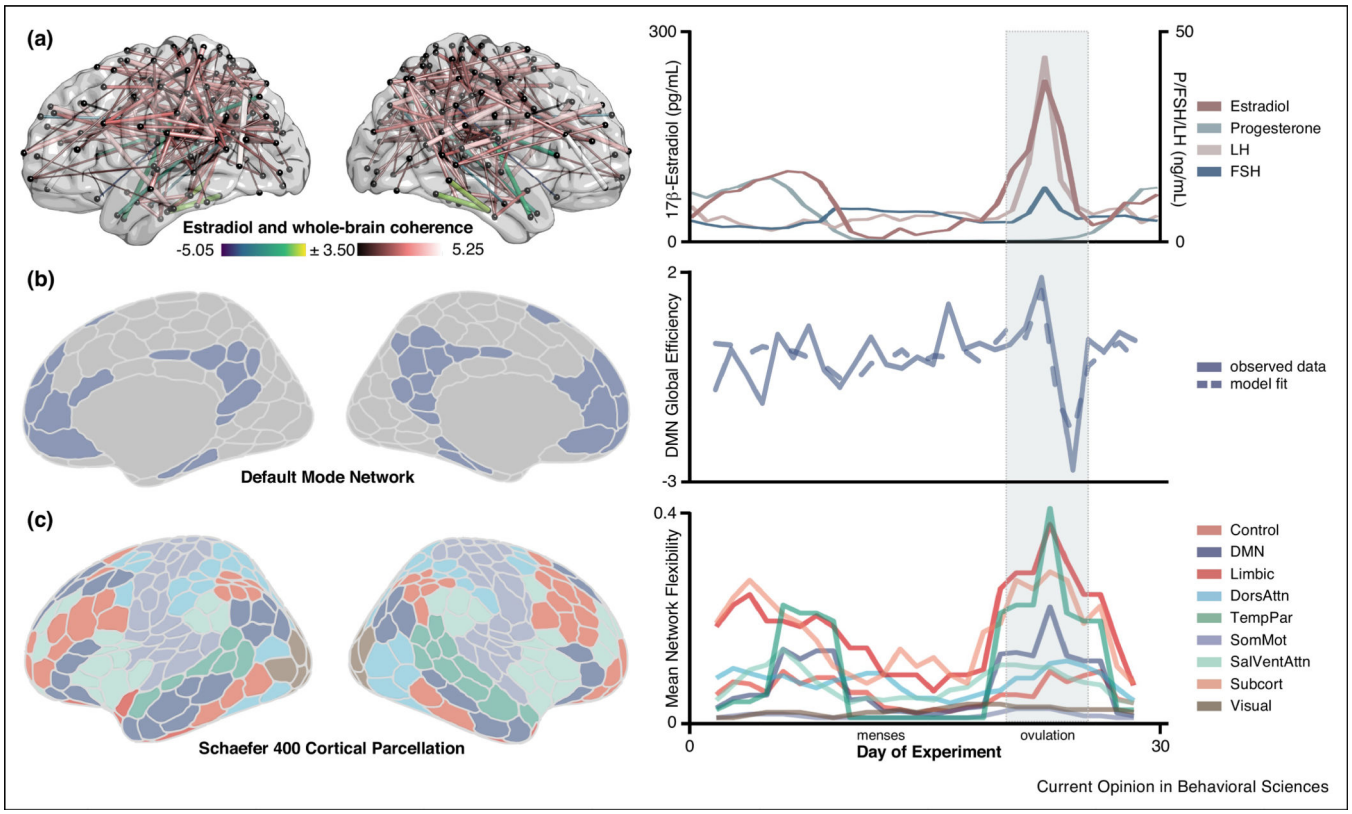

Figure 1. Estradiol has a robust impact on intrinsic brain network properties in a densely sampled female.

A) Transient changes in estradiol across the menstrual cycle were associated with whole-brain coherence at rest (*left*) [9]. Warmer colors indicate increased coherence with higher concentrations of estradiol; cool colors indicate the reverse. Nodes without significant edges are omitted for clarity. Ovarian steroid hormones (estradiol, progesterone) and gonadotropin (LH, FSH) concentrations are plotted across the 30-day study *(right).* **B)** Time-lagged analyses suggest that estradiol *drives* Default Mode Network topology (*left*). Observed data (solid lines) vs. Vector Autoregressive model fits (dotted lines) are depicted for within-network efficiency (*right*). Note that the peak/trough of DMN network efficiency coincides with estradiol's characteristic rise and fall across the ovulatory window (*gray band*) [9]. **C)** Network flexibility (calculated over a 5-day sliding window [27]) was also noticeably higher in many regions of the Temporal Parietal, Limbic, and Default Mode Networks during the ovulatory phase of the cycle. Peaks in flexibility were coincident with the ovulatory window (days 22–25) and the secondary peak in estradiol (days 5–10) (*right*). These findings are based on a densely-sampled female and should be examined in a larger cohort to assess generalizability. Abbreviations: DMN, Default Mode Network; DorsAttn, Dorsal Attention Network; FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; SalVentAttn, Salience/Ventral Attention Network; SomMot, SomatoMotor Network; TempPar, Temporal Parietal Network.