metabolize and store fat. A critical goal of future research is to determine how dietary lifestyle, overconsumption and obesity development alters the DA neuron lipidome, intracellular FA metabolism and neuronal function. Indeed, human obesity is linked to increased brain FA uptake [6], a consequence which may underlie the psychiatric and neurodegenerative risks associated with obesity.

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Amyloid oligomer interactions and polymorphisms: disease-relevant distinct assembly of α-synuclein and tau

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Neurodegenerative diseases are complex diseases characterized by set of disease-specific clinical symptoms with one or more characteristic protein aggregates. However, there has been considerable overlap between multiple diseases, both in terms of clinical manifestations and protein accumulation [1]. The co-occurrence of α-synuclein and tau protein pathologies in several brain diseases implies a toxic relationship and has become an active area of research. Two of the major challenges faced in the neurodegeneration field are the formation and biological relevance of amyloid polymorphisms (strains) and the toxic interactions between amyloidogenic proteins [2]. Previously, we demonstrated that, in addition to the meta-stable oligomeric α-synuclein, tau oligomers are also present in Parkinson's disease and Dementia with Lewy bodies [3].

In our recent study, we presented novel evidence supporting the role of α-synuclein potentiating the harmful effects of tau [4]. We demonstrated that tau aggregates induced by pre-formed α-synuclein oligomers evade larger aggregate or fibril formation, thus, prolonging their oligomeric state compared to the self-aggregated tau. We evaluated the seeding propensity of tau oligomers prepared with or without pre-formed α-synuclein oligomers by exogenously adding them in three different cell models: YFP-tau expressing CV-1 cells, differentiated human neuroblastoma cell line SH-SY5Y and primary cortical neurons from embryos of Htau mouse, a transgenic tauopathy mouse model. Pre-formed α-synuclein oligomers induced tau aggregates were more potent in altering cell morphology and increasing cell death in CV-1 and SH-SY5Y cells. Moreover, these aggregates caused significant dendritic spine retraction in primary neurons when compared to the self-aggregated tau, indicating the differences in their seeding properties and toxic effects. Therefore, to gain more insight into the toxic interaction between α-synuclein and tau, we isolated complexes of oligomeric α-synuclein and tau from post-mortem Parkinson's disease (PD) brain tissues, and tau oligomers from brain tissues of progressive supranuclear palsy (PSP), a pure tauopathy without any documented α-synuclein pathology. Upon administration of these brain-derived aggregates into Htau mice, α-synuclein-tau complexes accelerated endogenous tau aggregation, caused memory deficits and spread disease pathologies as compared to pure tau oligomers.

Our study demonstrates the combined deleterious effects of α-synuclein and tau, suggesting a toxic mechanism of interaction. The ability of oligomeric α-synuclein to induce tau aggregation also points to the mechanism of cross-seeding, which has been observed among several amyloidogenic proteins, including Aβ in multiple neurodegenerative diseases [5]. This is in accordance with our previous observation, where oligomeric aggregates of Aβ, PrP, α-synuclein and TDP-43 proteins are shown to co-localize in AD pathology [6]. In conclusion, our study represents the first step to elucidate the toxic interplay between α-synuclein and tau altering the aggregation profiles and nature of amyloid deposits, possibly, resulting in the formation of unique aggregates that can cause specific loss of functions of important proteins and impairment of cellular machineries. Insights into the pathogenic interaction between α-synuclein and tau will lead to further investigation of their upstream or downstream interacting proteins that may also

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have potential roles in disease pathologies. This will lay the groundwork for more successful therapeutic interventions by targeting multiple candidate molecules, such as α-synuclein and tau in diseases.

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Ovarian hormones, genes, and the brain: the case of estradiol and the brain-derived neurotrophic factor (BDNF) gene

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The need for novel therapeutics has fueled the burgeoning impetus to uncover biological mechanisms that contribute to sex and individual differences in the manifestations of neuropsychiatric disorders. Investigating interactions between sex hormones and genetic makeup holds promise for this quest.

Animal studies have clearly established that sex hormones impact brain organization and function at critical developmental periods, including gestation and puberty; the neuromodulatory effects of ovarian steroids are well documented across the lifespan. However, little is known about the genesis of individual differences in cognitive and behavioral response to these hormones in humans. For example, why do some women develop postpartum depression while others do not, even in the face of the same hormonal events? Because ovarian hormones are important transcriptional regulators, their actions on the brain may vary according to individual differences in genetic make-up, suggesting an important research direction that could provide information regarding this and similar clinical questions.

The potential importance of such investigations is supported by preclinical studies in female transgenic mice harboring the uniquely human *BDNF* Val^{66}Met variant. The *BDNF* gene is of particular interest for investigating gene–hormone interaction because estradiol induces *BDNF* expression that mediates hippocampal function [1]. Likely as a consequence, in female $BDNF_{Met}$ knock-in mice, the estrus cycle critically interacts with the Val^{66}Met variant to modulate anxiety-related behaviors [2] as well as hippocampally dependent function and behavior [3].

Building on these preclinical experiments, we used two different but complementary neuroimaging modalities, the blood-oxygen-level depndent functional magnetic resonance imaging and positron emission tomography regional cerebral–blood flow techniques, to measure working memory-dependent brain function in healthy, regularly menstruating women during a 6-month hormone-manipulation protocol with three hormone conditions: ovarian suppression induced by the gonadotropin-releasing hormone agonist leuprolide acetate (Lupron), Lupron + estradiol replacement, and Lupron + progesterone replacement. We found a genotype–hormone interaction in the hippocampus, a region that is typically not recruited and is often even deactivated during working memory: in women carrying the $BDNF_{Met}$ variant, the hippocampus was atypically activated (i.e., abnormally recruited), but only in the presence of estradiol [4]. The results were consistent between both imaging platforms, providing important confirmatory data. Our findings demonstrate an estrogen sensitivity in the context of the Met variant in women, and thus provide an important translational step by demonstrating that the *BDNF* genotype–ovarian steroid interaction impacts neural function.

These studies offer evidence that harboring a genetic predisposition regulated in part by sex hormones in the brain, such as the $BDNF_{Met}$ allele, may have clinical implications [5]. Additionally, a recent preclinical study showing $BDNF_{Met}$ variant-specific elimination of hippocampal function during peri-adolescence [6] suggests the importance of future studies examining gene–hormone interactions during this critical period of brain development and hormonal change.

Delineating how the interplay between genes and sex hormones influences the brain has important relevance for women's mental health, for understanding individual differences

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