NEURAL REGENERATION RESEARCH
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Sex differences in aging and injured brain

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Background: The prevalence, age of onset, and symptomatology of traumatic brain injury, stroke, and neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease) differ substantially between males and females. The higher prevalence of these brain disorders has been attributed to females having a greater longevity compared with males. Since one of the greatest risk factors of acquired brain injury (such as stroke, traumatic brain injury caused by fall) and neurodegenerative disease is age, it would be reasonable to state that more females would live long enough to develop a brain disorder. However, a recent systematic review and meta-analysis shows that even when baseline data is adjusted for demographic covariates such as age, females continue to have worse rehabilitation outcomes and account for more deaths compared to males (Ali, 2022). Increasing evidence suggests other factors are contributing to the sex-specific risk of brain diseases for females. These may include hormonal differences, genetics, menopause, pregnancy, and productivity, as well as gender differences in social and cultural roles, such as depression, education level, family burden, and sleep. Studying these sex differences is important because if sex is a crucial biological variable in disease heterogeneity, understanding these differences provides the potential for the generation of alternative approaches to identify the cause and provide treatment. This aids in the development of more precise medical interventions and better outcomes.

Sex difference in neurodegeneration: Regarding neurodegeneration, females have a greater incidence rate of any dementia, and current evidence suggests that they suffer greater cognitive deterioration than males in the same disease stage. A recent research has linked these sex differences to neuroimaging markers of brain pathology, specifically related to the hippocampus (Burke et al., 2019). The rate of hippocampal atrophy affects the progression of Alzheimer's disease (AD) in females more than males, as well as functionally. Disrupted functional connectivity from the hippocampus to other neural populations fundamental for cognitive processing and memory has been implicated. Our recent study shows that in mild cognitive impairment, which is the prodromal stage of AD, the functional connectivity from the hippocampus to the precuneus cortex and brain stem is significantly stronger in males than in females (Williamson et al., 2022). When extending to AD, our new study revealed males had a significantly stronger interhemispheric functional connectivity between the left and right hippocampus, compared with females (Williamson et al., 2024a). These sex differences may be direct or there could be other factors playing a role in the reduced hippocampal functional connectivity in females. One theory is the apolipoprotein E (ApoE) ε4 gene, a well-known risk factor for AD. ApoE ε4 carriers have reduced hippocampal functional connectivity and the presence of this gene affects females differently than males. Williamson et al. (2024b) found that intrahippocampal functional connectivity only differs by sex in AD participants who have at least one ε4 allele. One potential explanation for this is that ApoE ε4 is affecting tau protein aggregates or amyloidogenic processes differently between sexes, which is then playing a role in disconnecting the hippocampus from specific memory systems resulting in worse neuropsychological task performance seen in females. In addition to AD, the ApoE genotype is related to the severity of other proteinopathies and neurodegenerative diseases characterized by overt neuroinflammation (i.e., multiple sclerosis, Parkinson's disease, dementia with Lewy bodies, and amyotrophic lateral sclerosis). These conditions also have shown sex differences in both development and progression as reported by Gamache et al. (2020). A focus in the study of neurodegeneration, and specifically AD, should be a continued examination of complexities and connections between sex, genetics, protein tau, and neural functional connectivity. This study has the potential for sex-specific biomarkers for improved AD treatment.

Sex difference in neuroplasticity: Aging and neurodegeneration, such as AD, cause micro- and macro-structural and functional changes in the brain. The pathophysiological progression of AD and aging are associated risk factors of having a brain injury, such as stroke. Research has shown that the state of degeneration in the brain also affects the long-term functional recovery in patients with stroke (Gupta et al., 2022). The ability of the human brain to recover from brain injury relies on neuroplasticity. Neuroplasticity is the change or rewiring of the neural network. After a stroke, the plasticity process is initiated to attempt to compensate for the lesion itself and its remote effects. Females account for more stroke deaths, consistently suffer from worse stroke outcomes, and are more often institutionalized and permanently disabled than males. The recent systematic review and meta-analysis from Ali et al. (2022) shows that this disparity is independent of treatment or management of acute stroke – meaning there must be a sex difference in the neuroplastic recovery. Much attention has been given to the effect of estragon on stroke, since the extent of stroke damage has been linked to hormonal fluctuations during the reproductive cycle and the menopausal transition is when many women develop cardiovascular risk factors. Therefore, it is critical to consider these sex differences when examining interventions for stroke recovery. Future work should include a subgroup analysis by sex in clinical studies and account for whether females included in the study are pre- or postmenopausal or are on hormone therapy.

Neuroimaging as a precision diagnosis to detect sex difference in the brain: Neuroimaging is a useful tool for understanding sex differences in the brain from both structural to functional level, and from the whole brain to the molecular level. Structural neuroimaging techniques such as computed tomography or magnetic resonance imaging (MRI) can be used to observe sex differences in brain volume loss and structure changes caused by aging and brain injuries as demonstrated by Burke et al (2018). More detailed structural changes in the brain including fiber loss and sex-specific neuroplasticity can be examined by diffusion tensor imaging that uses anisotropic diffusion of water molecules to reveal the axonal (white matter) organization of the brain as reported by Xin et al. (2019). In addition to structural information, one can also track sex-specific functional changes in the brain using functional MRI (fMRI). Our recent fMRI study found that inter-hemispheric hippocampus connectivity decreases more in females than males in AD as compared to cognitively normal controls (Williamson et al, 2024). Studies evaluating both the structural and functional differences in the brain during aging and within disease and injury can provide insight into why there is a disparity between sexes (Xin et al., 2019; Edwards et al., 2021). Positron emission tomography is another imaging technique that measures the concentration of specific molecules in the brain and can help understand sex differences of mechanistic changes in the brain post injuries and during neurodegenerative processes as shown in Edwards et al. (2021). This data can be used to make interpretations about central processing mechanisms and how molecular changes impact brain circuitries and their functions. Furthermore, machine learning models can be trained using longitudinal neuroimages to predict the progression of disease as indicated in Xin et al. (2019). These progression curves may be tracked for males and females separately to account for the differences between sexes. These can serve as sex-specific biomarkers that can estimate pathological changes occurring in the brains that could predict clinical outcomes, which would aid in more individualized treatment. This type of approach is visualized in **Figure 1**.

Non-invasive brain stimulation as precision medicine for sex-specific treatment: For many acquired chronic neurological conditions, such as neurodegeneration and post injury brain damage, neuromodulation remains a promising treatment. Non-invasive brain stimulation technologies, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are safe and easy-to-manage neuromodulation approaches to modulate cortical excitability, however, these technologies have a high degree of variability between individuals. Sex-related response variability to non-invasive brain stimulation has been previously reported. A recent study found an age-related sex difference in tDCS current intensity mediated by differences in cortical anatomy; older females (aged 64+ years old) should receive a higher intensity of tDCS compared to males, while young females (18–41 years old) should receive less than males for the same amount of current density (Bhattacharjee

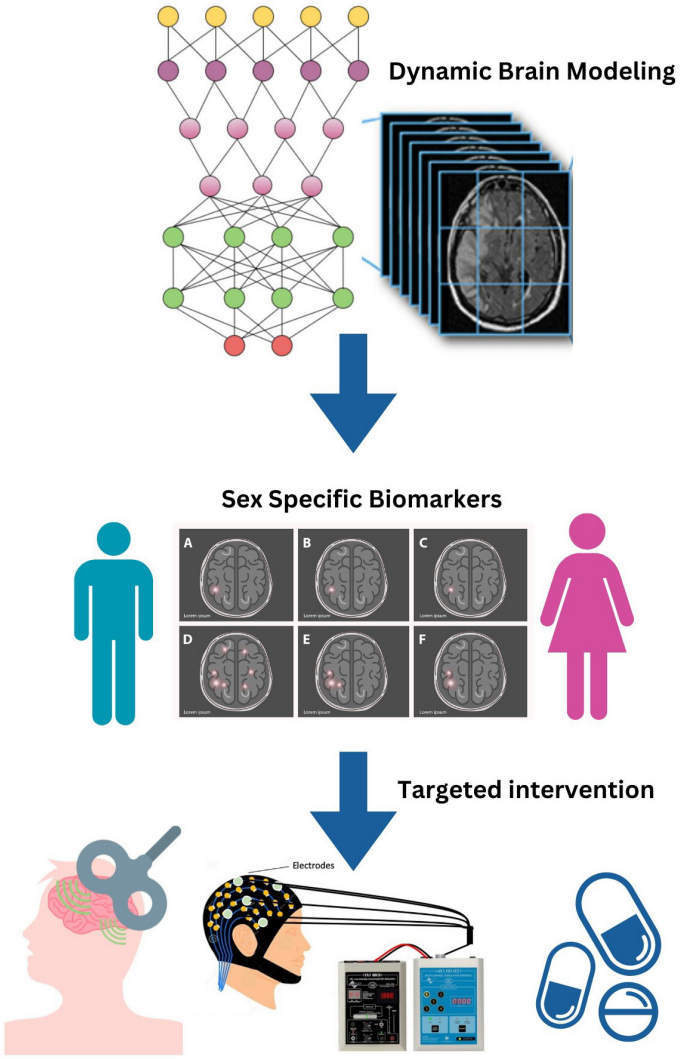

Figure 1 | **Framework of combining neuroimaging and deep learning techniques to extract sex-specific biomarkers for targeted interventions.**
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et al, 2021). Furthermore, sex differences in neuroplasticity, aging, neurodegenerative disease, and recovery from brain injuries have also been widely reported in previous studies (Ali et al, 2022; Gupta et al, 2022). Therefore, considering sex variation is critically important for maximizing the effect of non-invasive brain stimulation and achieving better clinical outcomes. To do this, there are emerging techniques of targeted high-definition tDCS proposed by Williamson et al. (2023) using a few small electrodes, navigated by subject-specific MRI and TMS localization to specifically modulate a cortical region. Further, neuromodulation intervention involving repetitive TMS has incorporated simultaneous fMRI-electroencephalogram-TMS systems developed by Bergmann et al. (2021) to provide proof of target engagement in the cortex during stimulation. These recent precision interventions are likely able to account for the variation in sex for an enhanced treatment effect, though more future studies are needed to verify such new technologies.

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