iPSC-Derived Neurons: Advantages and Applications for Studying Human Gene Regulation, Stress Biology, and Personalised Wellbeing

Introduction

Personalised wellbeing is increasingly understood not as the product of a single organ, gene, or pathway, but as the emergent outcome of dynamic regulation across interconnected biological systems. Stress biology illustrates this especially well. Endocrine, neural, immune, and metabolic processes interact continuously over time, and relatively small regulatory shifts can produce markedly different outcomes across individuals (McEwen & Stellar, 1993; McEwen, 1998; Ménard et al., 2017). Such a systems-level perspective challenges older one-cause explanations of health and disease and underscores the need for human-relevant models that can capture regulatory mechanisms with greater precision. Induced pluripotent stem cells (iPSCs) have transformed this field by enabling researchers to investigate human cellular processes in more physiologically relevant ways (Cerneckis et al., 2024).

Reprogrammed from adult somatic cells into a pluripotent state, iPSCs can be differentiated into a wide range of cell types, including neurons and glial cells, while preserving the donor's genetic background (Takahashi & Yamanaka, 2016; Cerneckis et al., 2024). This makes them especially valuable for modelling human neurobiology, disease mechanisms, and inter-individual variation (Soliman et al., 2017; Cerneckis et al., 2024). In neuroscience, iPSC-derived neurons are particularly important because access to living human neural tissue is extremely limited, while animal models and immortalised cell lines do not always reproduce the complexity of human-specific regulation (Soliman et al., 2017; Cerneckis et al., 2024).

These considerations are especially relevant to the study of stress-sensitive biology. Human well-being does not arise from genes alone, nor from environment alone, but from the continuous interaction between biology and experience (McEwen & Stellar, 1993; McEwen, 1998). Genes shape how cells respond to environmental input, including glucocorticoids, inflammatory signals, and neurochemical fluctuations (de Kloet & Meijer, 2024; Ménard et al., 2017). In turn, those responses influence neuronal plasticity, cognition, and vulnerability to dysregulation (McEwen, 1998; Ménard et al., 2017). iPSC-derived neurons offer a practical means of observing some of these cellular processes under controlled conditions, thereby helping bridge molecular investigation with broader questions about health and resilience (Seah et al., 2022; Franks et al., 2024).

This essay argues that iPSC-derived neurons provide a powerful human-relevant platform for studying gene regulation and stress-sensitive neurobiological mechanisms relevant to personalised wellbeing. Their major strengths lie in preserving donor-specific genetic background, enabling mechanistic study of neuronal pathways, and supporting

CRISPR-based modulation of gene expression. However, limitations including cellular immaturity, experimental variability, and incomplete systemic complexity mean that they are best understood as part of an integrative multi-level research framework rather than as a complete model of human wellbeing (Cerneckis et al., 2024; Van Lent et al., 2024; Gaffey et al., 2025).

What are iPSC-derived neurons?

Induced pluripotent stem cells are generated by reprogramming differentiated somatic cells, such as skin fibroblasts or blood cells, back into a pluripotent state. Since the pioneering work of Yamanaka and colleagues, this technology has become one of the most influential advances in biomedical science, enabling the generation of patient-specific human cells without the need for embryonic tissue (Takahashi & Yamanaka, 2016). Once reprogrammed, iPSCs can self-renew and can be directed into specific cellular lineages, including cortical neurons, dopaminergic neurons, astrocytes, microglia, and more complex neural organoid systems (Cerneckis et al., 2024; Soliman et al., 2017).

In neuroscience, this capability is especially valuable. Living human neural tissue is rarely accessible for experimental study, and post-mortem tissue cannot capture dynamic cellular responses. iPSC-derived neurons overcome part of this limitation by providing access to live human neural cells *in vitro* (Soliman et al., 2017; Cerneckis et al., 2024). They can be used to examine neuronal differentiation, synaptic development, electrophysiological behaviour, transcriptional responses, and disease-relevant phenotypes under controlled laboratory conditions (Soliman et al., 2017; Cerneckis et al., 2024).

A major strength of these models is that they retain the donor's genetic background. This means they can capture aspects of patient-specific vulnerability and biological variation that standardised immortalised cell lines often miss (Soliman et al., 2017; Cerneckis et al., 2024). For this reason, iPSC-derived neurons are increasingly used not only to study neurological disease but also to explore how human neurons respond differently to hormones, drugs, inflammatory signals, and gene perturbations (Seah et al., 2022; Franks et al., 2024).

This relevance extends to questions of stress and well-being. Wellbeing itself is not a cellular trait in any narrow sense; it is a broad and multidimensional state shaped by biological, psychological, and social influences (McEwen & Stellar, 1993; McEwen, 1998). However, important components of wellbeing-related vulnerability, including stress responsivity, neuroplasticity, and regulatory flexibility, depend in part on cellular and molecular processes that can be examined experimentally (de Kloet & Meijer, 2024; Ménard et al., 2017). iPSC-derived neurons, therefore, do not model well-being directly, but they provide a valuable platform for investigating some of the neurobiological mechanisms that contribute to it (Seah et al., 2022; Franks et al., 2024).

Advantages of iPSC-derived neurons

One of the greatest advantages of iPSC-derived neurons is their human relevance. Traditional animal models remain indispensable in many areas of science, yet species differences in neurodevelopment, stress responsiveness, immune signalling, and gene regulation can limit the translation of findings into humans (Soliman et al., 2017; Cerneckis et al., 2024). iPSC-derived neurons, by contrast, originate from human donors and therefore offer a system that is genetically and biologically closer to the processes under investigation (Cerneckis et al., 2024; Van Lent et al., 2024).

A second major advantage is their preservation of individual genetic variation. Because iPSCs can be derived from specific individuals, they enable examination of how different genetic backgrounds influence cellular phenotypes and experimental responses (Soliman et al., 2017; Cerneckis et al., 2024). This is highly relevant to personalised medicine and to any scientific framework seeking to explain why the same stimulus, risk factor, or treatment can lead to different outcomes across people (McEwen, 1998; Cerneckis et al., 2024). In this sense, iPSC-derived neurons support a shift away from average-based biology toward person-sensitive biology (Cerneckis et al., 2024).

A third important strength is their experimental flexibility. Once differentiated into neural lineages, these cells can be exposed to hormones, inflammatory mediators, drugs, or targeted gene perturbations in tightly controlled conditions (Seah et al., 2022; Franks et al., 2024). Researchers can examine transcriptional changes, signalling cascades, synaptic function, or electrophysiological properties with a level of mechanistic precision that is often difficult to achieve in whole-organism studies (Soliman et al., 2017; Franks et al., 2024). This makes iPSC-derived neurons especially useful for dissecting specific pathways involved in stress responsiveness and neural adaptation (Seah et al., 2022; de Kloet & Meijer, 2024).

A fourth advantage lies in their compatibility with more advanced model systems. Early iPSC research often relied on two-dimensional monocultures, which remain useful but simplified. More recent developments have expanded the field to include co-cultures with astrocytes and microglia, three-dimensional organoids, and assembloid systems that better reflect cellular interaction and tissue architecture (Cerneckis et al., 2024; Marton & Pașca, 2020). These advances are important because neuronal function is shaped not only by neurons themselves but also by surrounding support cells and the environment in which they develop (Marton & Pașca, 2020). As a result, iPSC-derived systems increasingly enable researchers to move beyond isolated cell behaviour toward more integrated, human-relevant modelling (Marton & Pașca, 2020; Cerneckis et al., 2024).

Taken together, these strengths explain why iPSC-derived neurons have become such influential tools in neuroscience. They combine human specificity, donor-relevant biology, mechanistic accessibility, and expanding experimental sophistication in ways few previous model systems could achieve (Soliman et al., 2017; Cerneckis et al., 2024; Marton & Pașca, 2020).

Applications in studying stress-sensitive neurobiology

The applications of iPSC-derived neurons extend far beyond disease modelling into broader areas of biology, including stress, adaptation, and resilience. Stress-responsive systems operate through the interaction of multiple pathways, including glucocorticoid signalling, neurotransmitter regulation, inflammatory crosstalk, and neuroplastic processes (McEwen, 1998; Ménard et al., 2017; de Kloet & Meijer, 2024). Although these pathways are often discussed separately, their effects are deeply interconnected. This is one reason why human responses to stress vary so substantially between individuals (McEwen & Stellar, 1993; McEwen, 1998).

Neurons are particularly important in this context because they sit at the interface between molecular regulation and behaviour. Stress hormones such as cortisol influence neuronal gene expression, synaptic plasticity, and network function, especially in brain regions associated with executive control, emotional regulation, and memory (McEwen, 1998; de Kloet & Meijer, 2024). When these regulatory processes become disrupted, the consequences may extend beyond cellular change to altered cognition, mood, and resilience (McEwen, 1998; Ménard et al., 2017).

iPSC-derived neurons provide a useful platform for investigating such mechanisms under controlled conditions. *In vitro* stress-related models have been used to examine how glucocorticoids alter neuronal survival, transcriptional regulation, plasticity-associated pathways, and inflammatory signalling (Seah et al., 2022; de Kloet & Meijer, 2024). These approaches are valuable because they allow specific variables to be manipulated and observed more clearly than is usually possible *in vivo*, where multiple systems are changing simultaneously (Seah et al., 2022; Franks et al., 2024).

This matters because dysregulation rarely emerges from a single isolated defect. Rather, it often reflects cumulative shifts across interacting pathways (McEwen & Stellar, 1993; McEwen, 1998; Ménard et al., 2017). A systems-informed approach, therefore, does not treat any single gene or cell type as the whole explanation. Instead, it uses focused models to understand how particular components contribute to wider patterns of regulation. iPSC-derived neurons are especially useful in this regard because they provide access to one crucial part of the network: the human neural response (Seah et al., 2022; Franks et al., 2024).

Genes such as NR3C1, which encodes the glucocorticoid receptor, and SLC6A4, which encodes the serotonin transporter, illustrate this well. These genes are not sufficient to explain well-being in themselves, yet they occupy important positions within broader stress-sensitive networks (de Kloet & Meijer, 2024). Variation in glucocorticoid signalling may affect how neurons respond to stress hormones, while variation in serotonergic regulation may influence emotional processing and adaptive flexibility (de Kloet & Meijer, 2024; McEwen, 1998). By studying these pathways in human neuronal models, researchers can begin to clarify how

modest regulatory changes may scale into wider differences in vulnerability or resilience (Seah et al., 2022; Franks et al., 2024).

Thus, iPSC-derived neurons are particularly well suited to a systems-level research strategy: not because they capture the whole organism, but because they allow precise investigation of specific mechanisms that contribute to broader biological outcomes (McEwen, 1998; Seah et al., 2022; Franks et al., 2024).

CRISPR-based modulation of gene regulation in iPSC-derived neurons

If iPSC-derived neurons are among the most promising model systems in modern neuroscience, CRISPR-based tools are among the most powerful ways to interrogate them. The field of genome engineering has moved well beyond simple gene disruption and now includes CRISPR interference (CRISPRi), CRISPR activation (CRISPRa), and epigenome-editing approaches that can tune gene expression without permanently altering DNA sequence (Franks et al., 2024).

This distinction is especially important for research on stress-sensitive neurobiology. Many processes relevant to wellbeing do not involve complete gene loss. Instead, they involve changes in expression level, regulatory state, or context-dependent transcriptional control. In such cases, reversible or graded modulation may be more informative than permanent gene knockout. CRISPRi and CRISPRa are therefore particularly attractive because they allow researchers to control gene expression in a targeted manner while preserving the cell's overall genomic structure (Franks et al., 2024).

Within iPSC-derived neurons, these tools enable more refined mechanistic questions. What happens when the expression of a stress-sensitive gene is dialled down rather than eliminated? How does a donor-specific neuronal background respond to glucocorticoid exposure after targeted transcriptional modulation? Which downstream inflammatory or plasticity-related pathways shift when the regulatory balance of a key node is altered? These questions are central to understanding regulation as a dynamic process rather than a static state (Franks et al., 2024; de Kloet & Meijer, 2024).

Here, genes such as NR3C1 and SLC6A4 are conceptually valuable examples. Modulating NR3C1 expression could help clarify how changes in glucocorticoid receptor availability affect neuronal responses to stress hormone exposure (de Kloet & Meijer, 2024). Similarly, graded modulation of SLC6A4 could be used to investigate how serotonergic regulation influences downstream signalling and cellular adaptation. In both cases, the goal is not to reduce well-being to a single gene, but to use targeted experimental control to understand how regulatory shifts propagate through wider networks (McEwen, 1998; Franks et al., 2024).

For a field such as gene editing, this application is particularly important. It demonstrates that contemporary genome engineering is not limited to cutting DNA but increasingly functions as a toolkit for biological modulation. When combined with iPSC-derived neurons,

CRISPR-based regulation offers a powerful strategy for modelling complex human traits that is both mechanistically precise and biologically relevant (Franks et al., 2024).

Limitations and challenges

Despite their promise, iPSC-derived neurons are not without limitations. One of the most widely discussed challenges is cellular immaturity. Differentiation *in vitro* is accelerated and occurs outside the full physiological environment of the human brain, leading many derived neurons to resemble earlier developmental stages rather than fully mature adult neurons (Soliman et al., 2017; Van Lent et al., 2024). This can limit the extent to which findings generalise to adult neurobiology, especially in studies concerned with late-onset or experience-shaped regulation (Van Lent et al., 2024).

A second major challenge is variability. Differences can arise from donor background, reprogramming methods, differentiation protocols, laboratory handling, and batch effects. Such variability may threaten reproducibility and complicate interpretation, particularly when conclusions are drawn from small samples or single-cell lines. While standardisation continues to improve, this remains a major issue in the field (Gaffey et al., 2025; Van Lent et al., 2024).

A third limitation is reduced systemic complexity. Even sophisticated neuronal cultures do not fully reproduce the wider gut-immune-endocrine-brain axis that contributes to human wellbeing *in vivo*. Although organoids, co-cultures, and assembloids improve physiological realism, they still represent partial systems. They cannot yet capture the full embodied context in which hormones, immune mediators, environmental exposures, and lived experience interact over time (Marton & Pașca, 2020; Ménard et al., 2017).

These limitations do not negate the value of iPSC-derived neurons. Rather, they clarify how such models should be used. Their greatest strength lies in enabling detailed study of specific human cellular mechanisms within a broader multi-level research programme. In that sense, they are not complete replicas of human biology, but strategically powerful tools within an integrative framework (Van Lent et al., 2024; Gaffey et al., 2025).

Conclusion

iPSC-derived neurons have become an essential platform in contemporary neuroscience because they combine human relevance, donor-specific biology, and experimental flexibility (Cerneckis et al., 2024; Soliman et al., 2017). They are particularly valuable for studying gene regulation and stress-sensitive neurobiological mechanisms relevant to personalised wellbeing, as they allow researchers to investigate human neuronal responses in ways that standard animal or immortalised cell models often cannot (Seah et al., 2022; Franks et al., 2024).

Their usefulness is further enhanced when combined with CRISPR-based tools that modulate gene expression in graded, reversible ways (Franks et al., 2024). Together, iPSC-derived

neurons and CRISPRi/a approaches allow researchers to move beyond simple knockout thinking toward a more nuanced understanding of regulation, plasticity, and individual biological variation. This is especially important in fields concerned with stress, resilience, and vulnerability, where outcomes often emerge from shifts in regulatory balance rather than from single catastrophic defects (McEwen, 1998; de Kloet & Meijer, 2024).

At the same time, iPSC-derived neurons should not be presented as complete models of well-being. Their immaturity, variability, and incomplete systemic context mean that they are best understood as one highly informative part of an interdependent research strategy (Van Lent et al., 2024; Gaffey et al., 2025; Marton & Pașca, 2020). Seen in this way, they occupy a central place in the shift from reductionist explanations toward more personalised and systems-level biology. They do not explain the whole garment of human wellbeing, but they allow researchers to examine some of its most important fibres with far greater clarity.

Looking ahead, organoid and assembloid models derived from human pluripotent stem cells may further expand this methodological toolkit by enabling researchers to investigate cellular crosstalk, regional integration, and early circuit formation in ways that more closely reflect human neurodevelopment than traditional reductionist models (Marton & Pașca, 2020). Such advances may help move stress research closer to the biological complexity required for a more precise and genuinely personalised understanding of wellbeing.

References

Cerneckis, J., Cai, H., & Shi, Y. (2024). Induced pluripotent stem cells (iPSCs): Molecular mechanisms of induction and applications. *Signal Transduction and Targeted Therapy, 9*, Article 112. https://doi.org/10.1038/s41392-024-01809-0

de Kloet, E. R., & Meijer, O. C. (2024). Glucocorticoid hormone as regulator and readout of resilience. *Current Opinion in Behavioral Sciences, 59*, Article 101439.

Franks, S. N. J., et al. (2024). CRISPRi: A way to integrate iPSC-derived neuronal models. *Trends in Molecular Medicine*.

Gaffey, F., et al. (2025). Examining iPSC-derived motor neuron variability and reproducibility. *Scientific Reports*.

Marton, R. M., & Pașca, S. P. (2020). Organoid and assembloid technologies for investigating cellular crosstalk in human brain development and disease. *Trends in Cell Biology, 30*(2), 133–143. https://doi.org/10.1016/j.tcb.2019.11.004

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*(1), 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S., & Stellar, E. (1993). Stress and the individual: Mechanisms leading to disease. *Archives of Internal Medicine, 153*(18), 2093–2101. https://pubmed.ncbi.nlm.nih.gov/8379800/

Ménard, C., Pfau, M. L., Hodes, G. E., et al. (2017). Immune and neuroendocrine mechanisms of stress vulnerability and resilience. *Neuropsychopharmacology, 42*(1), 62–80. https://doi.org/10.1038/npp.2016.90

Seah, C., et al. (2022). Modeling gene × environment interactions in PTSD using human iPSC-derived glutamatergic neurons and peripheral blood mononuclear cells. *Nature Neuroscience*.

Soliman, M. A., et al. (2017). Pluripotent stem cells in neuropsychiatric disorders. *Molecular Psychiatry, 22*, 1241–1249.

Takahashi, K., & Yamanaka, S. (2016). A decade of transcription factor-mediated reprogramming to pluripotency. *Nature Reviews Molecular Cell Biology, 17*(3), 183–193. https://doi.org/10.1038/nrm.2016.8

Van Lent, J., et al. (2024). Advances and challenges in modeling inherited peripheral neuropathies using iPSCs. *Experimental & Molecular Medicine*.