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Building a science of human pleasure, meaning making, and flourishing

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"Supporting human flourishing" is a goal of governments and societies, yet the construct may appear hard to define. We discuss the emerging science of pleasure and flourishing, insights into the brain mechanisms of meaning making and thriving, and the potential for interdisciplinary studies to advance this promising scientific field.

Introduction

> What is the meaning of life? That was all—a simple question; one that tended to close in on one with years, the great revelation had never come. The great revelation perhaps never did come. Instead, there were little daily miracles, illuminations, matches struck unexpectedly in the dark; here was one.
>
> —Virginia Woolf (*To the Lighthouse*)

Like many great artists, Virginia Woolf wrestled with the big questions of life and provided often-surprising insights on the complexity of existence. Although her question may sound simple, it is anything but. Searching for the meaning of life relates directly to existential questions of how best to conduct our lives to maximize the chance that we, other species, and our tiny blue planet can flourish together. Over the course of human history, many have looked for answers to these deep questions, which arguably gave birth not only to art but also to philosophy and science. Sadly, finding the right answers is becoming more and more urgent in these difficult times of severe mental health problems, mass extinction, and climate catastrophe.

A few decades ago, some of us began to use scientific methods to explore how the human brain creates deeply subjective states—including the underlying meaning-making processes that give us a sense of purpose and are fundamental to our flourishing. It has been an exciting journey, one that has already generated significant insights into the underlying brain mechanisms and networks for highly subjective phenomena, such as emotion and pleasure. These topics were traditionally considered outside the realm of science: over the years, some of our colleagues have repeatedly asked, "Are you sure this is science?"

Refuting this skepticism, we reached back to Aristotle's proposal that a meaningful life consists of both hedonia (pleasure, from "hedus," the sweet taste of honey) and eudaimonia (a life well lived, embedded in meaningful values). We created a neuroscience of hedonia by using indisputable sensory pleasures—food and sex—to investigate subjective brain states, such as emotion, pleasure, and pain.[1] These investigations have become increasingly interdisciplinary and more subtle, combining science with disciplines like music, which can evoke strong emotions.

This interdisciplinary science has matured to where we may finally be reaching an understanding of some of the core principles of meaning making and flourishing in the human brain. For example, we have now developed a fuller understanding of what goes awry in neuropsychiatric disorders: how a lack of pleasure, "anhedonia," combined with a lack of motivation, "avolition," causes a malignant orchestration of brain dynamics that wreak havoc on our mental health. Sophisticated causal whole-brain models have moved us significantly closer to discovering what a healthy orchestration of brain dynamics looks like, which helps facilitate finding better ways of rebalancing disease, from direct-brain stimulation, which can reduce or even eliminate chronic pain, to psychedelics, which can mitigate treatment-resistant addiction and depression.

Personal histories of flourishing

The journey has not been easy, and all three authors have had unusual career trajectories. We had to pursue careers outside mainstream science and focus on creating a science devoted to truly difficult problems such as pleasure, meaning making, and flourishing in the human brain.

When M.L.K. wanted to start his university studies in the early 1990s, neuroscience was not taught in Denmark. He chose a degree in computer science, determined to find the best way to reverse engineer the brain. Unlike a digital computer with a classic von Neumann bottleneck architecture, the brain is massively parallel and distributed. Yet the brain is also surprisingly slow compared to computers, taking around 10–30 ms to move information between two neurons. How can such a slow machine perform the

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necessary computations fast enough for survival?

M.L.K. realized that the brain might have heuristics that allow it to ignore irrelevant parts of the input and focus only on what contributes to survival. After all, survival has remained the main goal of evolving brains. Inspired by pioneering emotion scientists such as Joseph LeDoux and Antonio Damasio, M.L.K. focused on how emotion could act as such a filter by assigning value and the prediction of value to ensure that our relatively slow brains can make the right decisions for us to survive.

After completing his graduate work in computer science at the University of Copenhagen and architecture at the Royal Danish Academy of Fine Arts, M.L.K. began gathering the empirical data necessary for reverse engineering the brain. This work culminated in a novel model of the orbitofrontal cortex (OFC) that illuminated the multitude of functions this brain region has in emotional and hedonic processing.[2] During his two postdocs, M.L.K. also learned how to use magnetoencephalography (MEG) and deep brain stimulation. In 2007, M.L.K. started his own Hedonia lab at the Department of Psychiatry at the University of Oxford and at the Center of Functionally Integrative Neuroscience (CFIN) at the University of Aarhus, Denmark, where he also accepted a full professorship.

During his doctorate, M.L.K. met G.D., who already had three doctorates under his belt. G.D. began in Argentina, where he obtained a doctorate in atomic physics, working on the three-body problem. He then moved to Germany, where he earned two more in computer science and psychology. In 2006, G.D. became a professor of neuroscience at ICREA and Pompeu Fabra University, Barcelona, where he created his pioneering whole-brain model framework, which has become a cornerstone of using neuroimaging data to understand causal mechanisms of brain function, allowing the field to move beyond correlational neophrenology. M.L.K. and G.D. have spent many years developing this framework to better understand the brain in health, disease, and flourishing.[3]

In Aarhus, M.L.K. met P.V., who was already a well-known jazz musician, composer, and professor at the Royal Academy of Music Aarhus/Aalborg. After earning degrees in mathematics, French, and music, P.V. completed a doctorate on the neuroscience of jazz at CFIN. When they met, he had just started building his group, and they quickly discovered a shared love of music. Building on P.V.'s seminal predictive-music-coding model, they realized that music's uniqueness could be used as a tool for understanding the brain. In 2014, they convinced the Danish National Research Foundation to support the establishment of the Center for Music in the Brain, which, with P.V. as its founding director, has grown into one of the largest centers of its kind in the world.[4]

A science of pleasure: A new field of scientific inquiry

In 2007, when M.L.K. established his lab, he decided it was premature to study eudaimonia, instead focusing on the pleasure and hedonic processing foundational to emotion. This option was only available because of American neuroscientist Kent Berridge's pioneering research at the University of Michigan. With sheer, dogged persistence, Berridge tested his intuition that although pleasure may appear to be a highly subjective phenomenon, objective "liking" can be studied even in human infants and nonhuman animals by measuring their behavioral affective expressions to pleasurable stimuli.[5] Using rodent orofacial expressions in response to sweet and bitter tastes, Berridge demonstrated that hedonic "liking" reactions to sweetness were enhanced by stimulation with opioid and endocannabinoid neurotransmitters in specific nucleus accumbens' "hedonic" hotspots. He also found that the motivational aspect, "wanting"—the incentive salience of reward—can be measured by how much a rodent will work. This motivation was affected by mesolimbic dopamine—effects that do not extend to "liking" reactions. In a series of elegant studies, Berridge went on to show that "liking" and "wanting" have different underlying brain circuits. These findings have been foundational for establishing the science of pleasure upon which scientific insights into flourishing can be made.

Still, it took time for these findings to be accepted, and many research pioneers are forced to adopt a "siege mentality." For many years, Berridge was unable to get funding for this seminal work, so he had to use funding from other projects to pursue his dream.

Using human neuroimaging, M.L.K. worked with Berridge to investigate whether brain mechanisms of pleasure and wanting are similar in rodents and humans. This sampled activity in the whole brain and used subjective ratings that revealed the subjective components of liking and wanting. The research used robust hedonic stimuli—the taste of sugar, the smell of strawberries, the appearance of a baby face, the sound of baby giggles—to reliably identify the main brain networks involved in hedonic processing. These networks are the affective core of regions evaluating positive and negative stimuli that are selectively captured by attentional processes and made available for appraisal.[5] This research became the foundation for a science of hedonia. We have been able to demonstrate how hedonic brain processing changes over time, going through a "pleasure cycle," with appetitive, consummatory, and satiety phases that are intimately linked to the learning mechanisms needed for survival (Figure 1A). The dissociable brain networks and mechanisms responsible for reward wanting, liking, and learning have been linked to increasingly specific regions and neurotransmitters, which help to orchestrate the phase transitions within the pleasure cycle (Figure 1B).

Their research has now advanced to where we can directly manipulate rodents' brain circuitry to even make them behave in counterproductive ways, like wanting what hurts. Using optogenetics, Berridge and colleagues stimulated the central nucleus of the amygdala to make the animal voluntarily approach and repeatedly touch a laser-paired shock rod despite receiving multiple electric shocks as a prototype of addictive motivation where excessive "wanting" becomes independent of "liking."[7] These findings highlight the maturity of and potential for the underlying neuroscience.

A science of flourishing: An emerging field

An important take-home message from this new science of pleasure is that our increasingly detailed scientific understanding of the roles of and transitions in the pleasure cycle between brain regions

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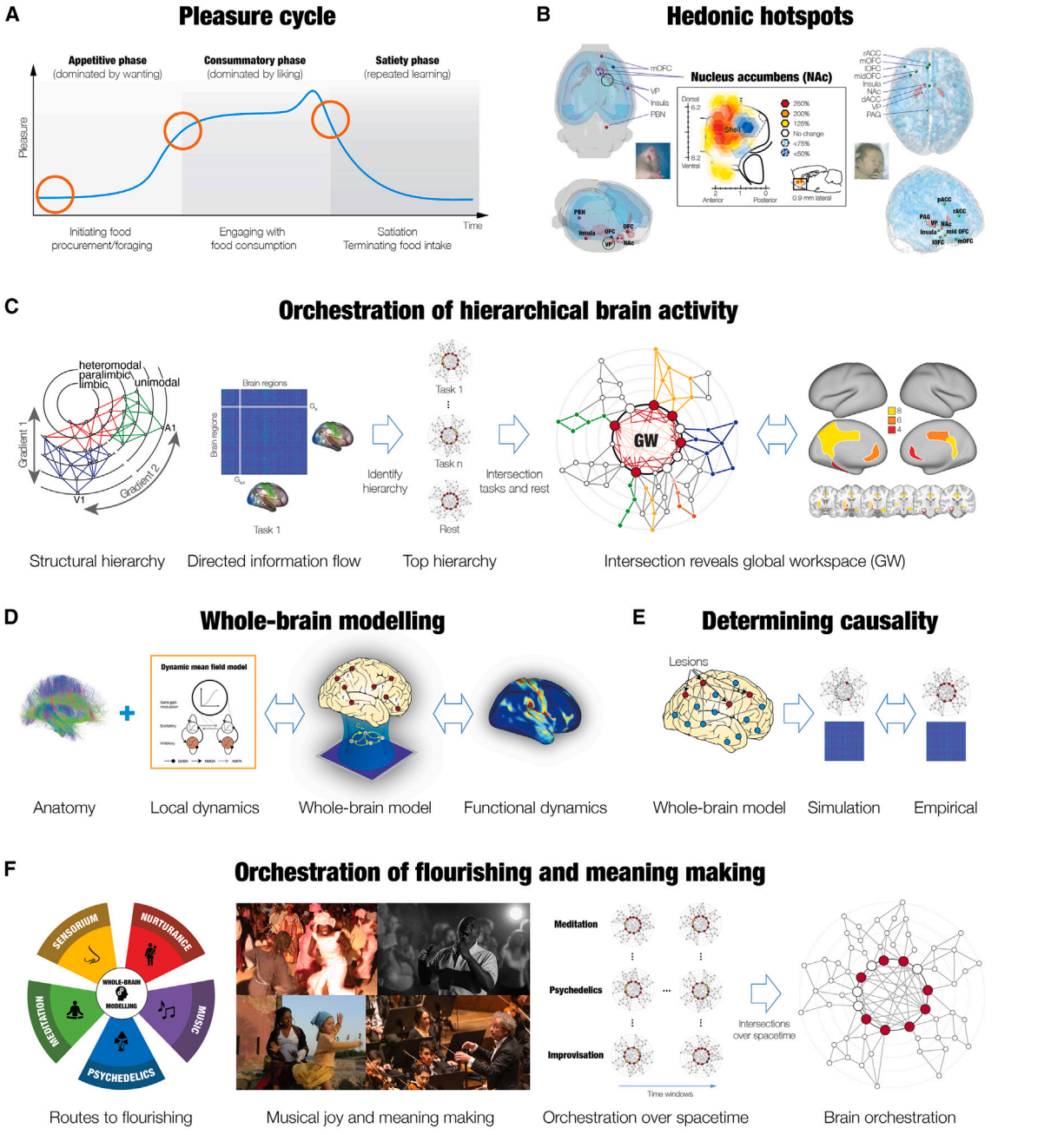

Figure 1. The neuroscience of pleasure and flourishing

(A) The pleasure cycle is driven by pleasurable stimuli such as food or music. Rewarding moments begin with a wanting phase, followed by consummation, often with a peak level of pleasure, and then satiety, with learning and updating predictions for the reward in the future—although learning can take place throughout the whole cycle.

(B) The liking phase is dependent on specific hedonic hotspots (blue) and coldspots (red) that can enhance or suppress pleasure and are found in regions of rodent brains such as the ventral pallidum (VP), orbitofrontal cortex (OFC), and nucleus accumbens (NAc).[5] The NAc (medial shell) contains a map of hotspots and coldspots established with opioid agonist microinjections.

(C) Moving beyond the pleasure engine to whole-brain orchestration, careful anatomical studies have found that the brain is hierarchical, with gradients from unimodal sensory processing (in blue and green) to heteromodal cognitive processing (in red). This anatomical connectivity provides the routes for functional hierarchy, determined from the bidirectional flow of information between any two brain regions, leading to an asymmetric whole-brain matrix of the information flow. From this information flow, the functional rich club (FRIC) sits on top, orchestrating dynamics in a brain state. The general "global workspace" orchestrating brain function was determined as the intersection of FRICs from cognitive tasks and rest.[6]

(D) Whole-brain modeling combines structural connectivity (obtained with diffusion MRI) with local dynamics to fit empirical neuroimaging data.

(E) Similar to animal models, lesioning the orchestrators in this *in silico* model can be used to provide causal evidence of the underlying mechanisms.

(legend continued on next page)

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and networks can be leveraged to produce novel treatments of disease. Indeed, any breakdown in the pleasure cycle's orchestration can lead to anhedonia and avolition, core features of neuropsychiatric disorders such as depression and schizophrenia. It is also important, however, to remember that the links between pleasure and well-being are not straightforward.[8] More pleasure is not the same as more well-being, and the obsessive pursuit of pleasure too often leads to addiction and great unhappiness. States of well-being still do clearly require a fully functioning pleasure system—an engine to run the necessary, orderly transitions through the pleasure cycle. A key problem is that targeted treatment of a malfunctioning pleasure system may move the brain closer to a healthy state but not help with meaning making.

Although meaning making is a hallmark of true states of flourishing, we still lack a full understanding of how a healthy brain makes meaning. Meaning making is hard to capture, as it often occurs only during relatively rare visits to states of flourishing. Some progress has been made in positive psychology. Over the past few decades, researchers have used questionnaires to gather evidence on subjective self-reports of happiness and life satisfaction. They then turned this evidence into a country-based "happiness index" where the top countries have the highest levels of "happiness." Such work has helped define many domains of flourishing. It has not, however, yielded new insights into the underlying brain mechanisms. The high happiness scores also do not correlate consistently with the frequency of severe mental health problems measured through reports of depression and suicide. As such, subjective self-reports may not be particularly accurate.

Perhaps, as has been suggested, we truly are strangers to ourselves or, at the very least, perhaps not willing to—or sure how to—use these scales truthfully. Similarly, when we sing "if you're happy and you know it, clap your hands" and are forced to introspect, we all too easily lose such happy moods. It has proven rather difficult to reliably induce meaningful flourishing states both outside and inside neuroimaging scanners.

In spite of these seemingly insurmountable obstacles, after having spent decades studying pleasure and worrying that eudaimonia might be too hard to study, over time, we came to realize that there are certain classes of stimuli and experiences that can reliably lead to meaningful states. Music can elicit joy, meaning, and a whole host of related, complex emotions. Moreover, musical paradigms can be precisely controlled and repeated, which provides a reliable scientific route for studying deeply subjective flourishing experiences.[4]

Social interaction—particularly with babies—can also elicit joyful and deeply meaningful states. During his first postdoc, M.L.K. used the high temporal resolution of MEG to study adults' positive reactions to cute infants. He discovered a brain mechanism for "cuteness ignition": our brains give privileged access to both the sight and sound of babies. They ignite activity in the OFC at around 130 ms, long before we become consciously aware that we are seeing or hearing a baby.[9]

Creating the Centre for Eudaimonia and Human Flourishing

Still, truly making progress in understanding meaning making, flourishing, and eudaimonia requires an interdisciplinary quest rather than just neuroscience experiments arising from the conservative peer review process utilized by grant funding bodies. In 2020, this dream was made possible by generous philanthropic funding from the Pettit Foundation and the Carlsberg Foundation, enabling the creation of an endowment in honor of the late psychologist Erel Shalit used to establish the Centre for Eudaimonia and Human Flourishing (http://hedonia.kringelbach.org) at Linacre College. Although the Centre is closely affiliated with Oxford's Department of Psychiatry, being part of Linacre College lets us benefit from the inherent interdisciplinarity of an Oxford college, where the students and fellows come from all the different knowledge branches of the university.

The members of the Centre bring their own unique perspectives that are synergistically enhanced through conversations and collaborations. Our weekly seminars (https://www.kringelbach.org/talks/) are from writers and artists-in-residence discussing their practices, philosophers and anthropologists providing theoretical perspectives on flourishing, and scientists discussing their latest breakthroughs in complexity research. After the seminars, we promote collaborations over delicious coffee and chocolates, both important constituents of true flourishing.

We are creating a neuroscience of flourishing that explores the possibility of establishing how different brain states orchestrate the hierarchical activity that generates meaning. We use state-of-the-art computational frameworks to help determine the hierarchy of the functional processing that unfolds on the underlying hierarchical brain structure. This functional processing orchestrates the coordination of essential segregated and integrated information-processing mechanisms that promote our survival and thriving.

To study conscious brain orchestration, we recently used large-scale human neuroimaging to identify the common "global workspace."[6] With an information theoretic framework, we discovered the common "conductors" across different brain states (Figure 1C) by determining the intersection of the brain regions at the top of the hierarchy in resting state, then in seven tasks designed to cover human cognitive flexibility. We validated the causal significance of this global workspace by lesioning our whole-brain model, which showed that the regions are causally important to proper orchestration (Figures 1D and 1E).

A key idea in the Centre is to use a similar strategy to identify the orchestration of flourishing. We use five main types of stimuli that reliably elicit meaning

(F) The Centre uses five main experimental routes (sensorium, nurturance, music, psychedelics, and meditation) to robustly elicit flourishing and meaning making in human neuroimaging experiments. One key strategy for revealing the orchestration of flourishing could be to create whole-brain models of flourishing states evoked through these routes, identify the main orchestration for each experiment, and then establish the shared orchestration for all these experiences.

making and flourishing in humans: sensorium, nurturance (social interactions), music, meditation, and psychedelics (Figure 1F). As an example of how these interact, one psychedelic participant reported that "to 'let go' and become enveloped in the beauty of—in this case—music was enormously spiritual."

But many questions remain, such as how this meaning making is orchestrated over time, independently of state. To identify the orchestrating conductors of these transient states of flourishing, we continue to develop cutting-edge scientific frameworks of thermodynamics, turbulence, and harmonics. Integrating these tools with whole-brain modeling has already yielded new insights. We used a thermodynamics-inspired paradigm to reveal that—contrary to expectations—compared to resting and tasks, movie watching results in a flattening of the brain hierarchy. This temporary eudaimonic relief from the rat race of existence could be a key reason why film watching is a relaxing pastime for many of us.[10]

Conclusion

We have spent well over two decades trying to establish an interdisciplinary science of pleasure and flourishing. We had to overcome many obstacles along the way, but establishing the Centre provides the stability and autonomy we need to make more rapid progress in our mission to help find ways to make better lives.

The many outstanding questions will require much more than just research in a center based in a small city at the confluence of seven rivers. We have therefore established the International Centre for Flourishing, which brings together our research in Oxford, Barcelona, and Aarhus, conducted in the flourishing spirit of "nit nitay garabam" ("people are people's medicine," a Wolof proverb).

Recently, rereading *The Log from the Sea of Cortez* by writer John Steinbeck and marine biologist Ed Ricketts, it is difficult not to despair of the "tragic miracle of consciousness" central to human existence, and as they write, our "species is not set, has not jelled, but is still in a state of becoming." Yet, we choose to cling on to the hopeful "state of becoming" rather than worry about the unchangeable past and uncertain future. We must seek better ways of finding meaning in the now, and we hope that many of you will join us in this interdisciplinary endeavor given that our very future—and that of other species and our tiny blue planet—will depend on it.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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