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Cover Art

Cover Image: A tranquil autumn landscape in Northern Idaho reveals the restorative power of nature in supporting mental health and well-being. This photograph captures a rocky mountain stream bed with large volcanic boulders reflecting in still pools, framed by golden aspens and evergreen conifers against a backdrop of forested mountains and clear blue sky. The scene exemplifies the therapeutic environments that Professor Helen Lavretsky describes as essential for maintaining balance between academic demands and personal wellness, as discussed in her Genomic Press Interview (pages [23–26]).

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Cardiac rhythms as windows into brain stimulation response: Promise and pitfalls in precision psychiatry

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The challenge of depression

Depression remains one of the most pressing challenges in psychiatry, with a heterogeneous presentation and incomplete response to current treatments. In recent years, an increasing body of work has pointed to multiple disturbances as modulators of depressive phenotypes. Within this evolving framework, in this issue of *Brain Medicine*, Goya-Maldonado and colleagues made novel contributions that highlight the roles of distinct systems (1). By situating depressive disorders within a systems-level context, their work exemplifies how mechanistic insights can inform the search for novel, biologically grounded treatment strategies.

Study design and core questions

Their study tackles two critical questions in contemporary neuromodulation research. First, can functional connectivity guide optimal stimulation site selection? Second, do immediate physiological responses predict long-term clinical outcomes? The investigators enrolled 75 patients with major depressive disorder in a quadruple-blind crossover trial, comparing personalized stimulation sites based on individual resting-state connectivity with standard F3 positioning. Throughout stimulation sessions, continuous electrocardiogram monitoring captured heart rate dynamics, with a focus on beat-to-beat deceleration and heart rate variability measures.

The results paint a nuanced picture of treatment prediction. Patients who showed greater heart rate deceleration within the first 45 seconds of initial stimulation demonstrated superior clinical improvement at the six-week follow-up. This relationship held specifically for active stimulation, suggesting that immediate autonomic responses reflect meaningful target engagement rather than nonspecific effects. The correlation between early cardiac modulation and eventual symptom reduction offers tantalizing evidence that the frontal-vagal pathway serves as a real-time indicator of therapeutic neural circuit activation (1).

Promising biomarker: Heart rate deceleration

This finding builds on emerging evidence linking prefrontal stimulation to downstream autonomic effects through subcortical relay stations. The proposed mechanism involves signal propagation from the dorsolateral prefrontal cortex through the subgenual anterior cingulate cortex to brainstem nuclei controlling vagal tone (see Figure 1) (2). When iTBS successfully engages this network, the resulting cardiac deceleration may signal effective neuromodulation of mood-regulatory circuits. Previous work in healthy volunteers has demonstrated that F3 stimulation optimally induces such heart rate changes (3), and preliminary studies in depression have shown trends toward associations between cardiac modulation and clinical response (4).

The implications extend beyond simple prediction. If validated, cardiac biomarkers could enable real-time optimization during treatment sessions. Clinicians can adjust coil positioning, stimulation intensity, or other parameters based on immediate physiological feedback, potentially improving response rates, which currently hover around 30–50% for

standard protocols (5). This approach sidesteps the limitations of motor threshold determination, which relies on anatomical assumptions that may not translate to prefrontal targets. Instead, cardiac monitoring provides direct evidence of relevant circuit engagement.

Unexpected complexity in heart rate variability

However, the study by Wilkening et al. reveals unexpected complexity in heart rate variability responses (1). While the root mean square of successive differences (RMSSD) increased during active stimulation compared to sham, higher increases paradoxically predicted poorer outcomes at one-week assessment. That was unexpected! This counterintuitive finding challenges prevailing assumptions about autonomic flexibility in depression. It is particularly striking, as it highlights the significant gaps in our understanding of the temporal dynamics of brain–heart interactions during neuromodulation. The authors suggest that effective frontal-vagal engagement may initially reduce variability during stimulation, followed by compensatory increases that align with clinical improvement. However, this explanation remains speculative, highlighting gaps in understanding the temporal dynamics of brain–heart interactions during neuromodulation.

The personalized targeting paradox

Equally unexpected is the failure of personalized connectivity-based targeting to outperform standard F3 positioning. Despite sophisticated neuroimaging protocols identifying individual sites with maximal anticorrelation between the left dorsolateral prefrontal cortex and the default mode network, personalized stimulation yielded no clinical advantage (1). This null finding contradicts influential studies suggesting that connectivity-guided targeting improves outcomes (6, 7).

Technical limitations warrant consideration. Despite neuronavigation, the actual stimulation sites deviated from ideal targets by more than 10 millimeters in some participants from the personalized group. Those discrepancies, while reflecting real-world implementation challenges, could dilute the potential benefits of individualized targeting.

The discrepancy nonetheless raises fundamental questions about the reliability and generalizability of imaging connectivity biomarkers for depression treatment using TMS. That said, the need for precision targeting is increasingly recognized as a necessary component for optimal response to other neuromodulation treatments, notably deep brain stimulation (8) and focused ultrasound (9). Beyond the precise delivery of the intended treatment, the state of the targeted network itself may be a contributing factor that impacts both biomarker behavior and response trajectories (10).

Methodological considerations

The crossover design, while strengthening internal validity, introduces interpretive complexities. A parallel-group comparison might have clarified whether personalized targeting benefits emerge at specific therapeutic windows. The authors acknowledge this limitation, noting that averaging



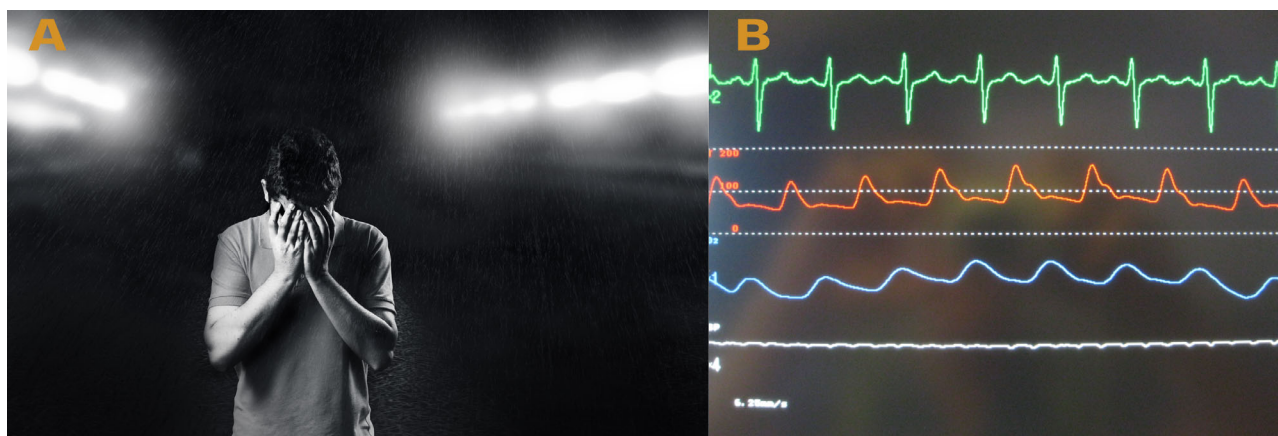


Figure 1. Depression and cardiac biomarkers in brain stimulation therapy. (A) Depression affects millions worldwide, with at least one-third of patients not responding well to conventional treatments. (B) Electrocardiogram patterns during brain stimulation showing heart rate deceleration within 45 seconds (increased intervals between beats) that predicts treatment success at 6 weeks. Image sources: (A) Fotorech, Pixabay, 2015; (B) John Campbell, Flickr, 2016. Both CCO via Wikimedia Commons.

across intervals provides conservative estimates but may obscure temporal patterns of response (1).

Future studies employing parallel-group designs with consistent follow-up periods could clarify whether personalized targeting (or accelerated protocols) benefits emerge at specific therapeutic windows.

Methodological considerations also extend to the cardiac measurement approach. The study assessed RMSSD during stimulation rather than at rest, capturing stimulation-induced entrainment rather than baseline autonomic tone. This difference matters because iTBS likely induces transient heart-brain coupling that differs mechanistically from tonic vagal activity (11). Other mechanisms have also been posited using changes in heart rate evoked potentials over the course of subcallosal cingulate region deep brain stimulation (12). While Wilkening and colleagues appropriately acknowledge this nuance, the field lacks consensus on optimal cardiac assessment protocols during neuromodulation.

Moving forward, standardization of measurement approaches will prove essential for cross-study comparisons and clinical translation. That said, the focus on new metrics that can index critical interoceptive features at the core of major depression is an important advance.

Symptom-specific biomarker limitations

The selective association with Montgomery-Åsberg Depression Rating Scale (MADRS) scores, but not with the Hamilton Depression Rating Scale (HAMD) or Beck Depression Inventory (BDI), highlights another challenge (1). Different scales emphasize distinct symptom domains, with the MADRS loading heavily on observed mood, the HAMD on neurovegetative features, and the BDI on cognitive symptoms (see Table 1) (13). The finding that cardiac biomarkers predict mood changes but not other symptom clusters suggests a specific underlying mechanism that warrants further investigation. Future research should examine whether different biomarkers predict improvements in specific symptom dimensions, potentially enabling more targeted treatment selection (14).

Several additional factors might explain this negative result. The heterogeneity of depression likely obscures group-level effects, with different symptom profiles responding to specific stimulation targets (15). An alternative consideration is that brain state, rather than symptoms, may more reliably stratify patients into the treatment option most likely to be effective, while also avoiding those that will not (16). Brain state signatures that guide treatment selection at all stages of illness, as well as identify markers of illness progression, are a critical need, particularly with the increasing availability of new treatment options for increasingly difficult-to-treat patients (17).

Challenges in precision psychiatry translation

The findings also underscore broader challenges in precision psychiatry. It remains a failure of research translation that, despite decades of biomarker research and several putative treatment selection biomarkers, clinical practice still relies heavily on trial-and-error prescribing. The field continues searching for the psychiatric equivalent of HER2 testing in breast cancer or EGFR mutations in lung cancer, biomarkers that fundamentally alter treatment decisions. Cardiac monitoring during iTBS represents progress toward this goal; however, substantial implementation hurdles remain. Equipment costs, training requirements, and workflow integration pose practical barriers even if the science proves robust.

Future research directions

As we look forward, several research priorities emerge. Replication in larger, more diverse samples will establish generalizability across demographic and clinical populations. Head-to-head comparisons of different biomarker approaches: cardiac, electroencephalographic, and neuroimaging, could identify optimal prediction strategies or complementary marker combinations. Mechanistic studies using concurrent neurophysiological recordings might clarify how cardiac responses relate to neural

Table 1. Depression rating scales and their primary symptom domains

Scale	Primary Focus	Key Domains	Cardiac Biomarker Association
MADRS	Observed mood	Clinical observation of mood symptoms	Significant correlation with HR deceleration and clinical improvement
HAMD	Neurovegetative features	Sleep, appetite, physical symptoms	No significant association
BDI-II	Cognitive symptoms	Thought patterns, self-perception	No significant association

MADRS = Montgomery-Åsberg Depression Rating Scale; HAMD = Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory-II; HR = heart rate.



circuit dynamics. Clinical trials directly comparing biomarker-guided treatment protocols with standard treatment protocols will ultimately determine whether physiological monitoring improves patient outcomes.

Reconsidering depression neurobiology

The work also raises philosophical questions about psychiatric nosology and treatment targets. If cardiac responses predict improvement better than sophisticated neuroimaging, what does this imply about depression neurobiology? Peripheral physiological markers capture integrative processes that focal brain measures miss. Alternatively, the focus on prefrontal-subcallosal cingulate connectivity might be replaced by more autonomic- or interoceptive-specific functional connectivity pathways (18). Alternatively, cardiac monitoring may provide more reliable and less noisy signals than current neuroimaging approaches. Resolving these possibilities requires continued integration of central and peripheral measurement strategies.

Conclusions: Practical over sophisticated

The study by Wilkening, Jungeblut, Goya-Maldonado, and colleagues advances the field by demonstrating that readily obtainable physiological measures predict brain stimulation outcomes (1). Their rigorous methodology and transparent reporting of both positive and negative findings exemplify good scientific practice. While personalized targeting based on connectivity may be disappointing, cardiac biomarkers offer a new and practical path toward treatment optimization. As the field continues to pursue precision psychiatry, this work reminds us that the most sophisticated approach may not always prove the most effective. Sometimes, listening to the heart provides more explicit guidance than mapping the brain.

Taken together, the work of Goya-Maldonado and his team underscores the importance of looking at depression not merely as a set of symptoms, but as a complex condition shaped by multiple systems. This integrative perspective moves the field away from narrow categorical models and toward a biologically informed framework that is both mechanistic and clinically relevant. By framing depression through a systems-level lens, his team's contributions challenge us to move beyond symptom clusters toward mechanistically guided therapies, a direction that may redefine the field in the years ahead.

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Andrea Ballesio: Mechanisms of sleep-mood interactions

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Keywords: sleep, insomnia, mood, depression, biomarker

Dr. Andrea Ballesio is a tenure-track researcher (RTT) in Clinical Psychology at the Faculty of Medicine and Psychology, Sapienza University of Rome. He works in the Clinical Psychology & Psychophysiology Lab of the Department of Psychology, where he investigates the causes and consequences of poor sleep and insomnia and the clinical efficacy of psychotherapeutic interventions for sleep disorders. Dr. Ballesio's research aims to shed light on the psychophysiological and psychoneuroimmunological mechanisms linking insomnia and mood disturbances, particularly depression. To serve this aim, he mostly employs longitudinal and experimental models in humans. He is a member of the European Sleep Research Society (ESRS), the European Insomnia Network (EIN), the European Academy of Cognitive Behaviour Therapy for Insomnia, the European Psychoneuroimmunology Network, and the International Society of Psychoneuroendocrinology (ISPNE). He received the 2023 ISPNE Early Career Scholar Award. Dr. Ballesio is also a licensed psychotherapist, working in the clinical centre of the Department of Psychology, Sapienza University of Rome. We are delighted that Dr. Ballesio shares his insights from the Genomic Press Interview with our community.

Part 1: Andrea Ballesio – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I became interested in science during my first year of university when I attended lectures that showed how psychotherapy could be proven scientifically effective. Previously, I had studied Freud in high school and attended some seminars on Rorschach, and until then, I only had a nebulous idea of the scientific application of psychological theories.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

I gained all my formal university degrees in my hometown, at Sapienza University of Rome, Italy. I received a master's degree in clinical health psychology in 2015. During my Master's, I spent a semester in Budapest for the Erasmus program and some months at the Freiburg University Medical Centre, where I worked with Dieter Riemann's team on my Master's thesis on sleep and emotions. I also met a terrific mentor and trusted friend, Chiara Baglioni, who taught me how to use meta-analysis. I will always be grateful to her for that. Then, I had the opportunity to win a grant to spend some months at the Sleep and Circadian Neuroscience Institute of Oxford in 2018, where I had the privilege to work with another fantastic mentor, Simon D. Kyle, who was and still is the academic I aspire to be. These experiences consolidated my eagerness to attempt a career in sleep research. I got the PhD in 2019, with a project on executive functions in insomnia, then a post-doc in psychometrics (2019), a position as a researcher in clinical psychology (2021), the habilitation as an associate professor in clinical psychology (2022), and ultimately my current position (2023).



Figure 1. Andrea Ballesio, PhD, Sapienza University of Rome, Italy.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

I have always been captivated by the idea that sleep could integrate mind and body, representing a key feature of psychophysiology. Sleep shows us how the mind can physically modulate the body. Moreover, when I was choosing the topic of my specialisation, I considered epidemiological aspects: insomnia is complained about by most individuals with mental disorders, and it is also frequent in physically ill patients. From this perspective, studying sleep could have been a model for understanding mind-body interactions and a powerful tool for improving people's health.

What impact do you hope to achieve in your field by focusing on specific research topics?

I wish I could clarify the specific mechanisms leading people reporting poor sleep and insomnia to a higher risk of suffering from emotional disorders. Also, I wish I could contribute to making treatments for sleep conditions more effective and accessible to the public.

Please tell us more about your current scholarly focal points within your chosen field of science?

Several projects I am currently running involve ecological momentary assessment of sleep and mood in different populations, such as adolescents,





Figure 2. Dr. Andrea Ballesio in Rome at the Zaha Hadid-designed MAXXI (Italian: Museo Nazionale delle Arti del XXI Secolo, "National Museum of 21st-century Arts"), with a photo panel of Sapienza University of Rome in the background.

workers, and patients with neurological disorders. These intense longitudinal assessments allow us to estimate "real-life" associations between sleep, mood, and underlying factors. Other projects focus on how sleep can be related to (e.g., modulate) psychoneuroimmunological aspects of mood disorders, especially depression. More broadly, I aim to integrate two areas of research that have been chiefly investigated separately for a long time: the immunology of sleep and the immunology of depression. In the latter, for example, the study of sleep has been chiefly relegated to the response to sickness behaviour. The work of Michel Irwin and his group exemplifies the integration between the two fields, and I find it remarkably inspiring.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

Freedom, independence, and collaboration are fundamental values for me. Recognising and supporting the personal propensities and ambitions of each lab member while working towards joint goals is the perfect match for me.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I strive to make friendship and kindness my compass in my work. I spend much time with my colleagues and students and would like to cultivate meaningful and pleasant relationships. This is independent of individual or cultural characteristics.

What do you most enjoy in your capacity as an academic or research rising star?

Creating new possibilities, whether it is a successful research grant with my team members or a dissertation project, students can be thrilled to carry out. We all need to work, chill, and have fun simultaneously.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I cannot help staying still. I love nature and sports, but I also enjoy admiring Italian and European design shops with furniture and artworks from the 1930s and 1940s.

Part 2: Andrea Ballesio – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Tzatziki in Amorgos, Greece.

What is your greatest fear?

Rejection.

Which living person do you most admire?

This is hard to rate: probably Fabiola Gianotti, in science and a Buddhist monk in spirituality.

What is your greatest extravagance?

I spend much time thinking about poetic or funny titles for my papers. So far, the sympathy of editors has yet to be found.

What are you most proud of?

I am proud to be able to help people sleep and feel emotionally better.

What is your greatest regret?

I should have undertaken a post-doc training opportunity in a foreign lab, but it was incompatible with my job then. Maybe one day...

What is the quality you most admire in people?

Dignity in grief.

What is the trait you most dislike in people?

Overtalking.

What do you consider the most overrated virtue?

Self-control.

What is your favorite occupation (or activity)?

Swimming and running.

Where would you most like to live?

Rome, London, and Florence, in hierarchical order.

What is your most treasured possession?

The books I received from my parents.

When and where were you happiest? And why were so happy then?

Last Sunday, in Tuscany, having my first swim of the year.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



What is your current state of mind?

Tired but peaceful.

What is your most marked characteristic?

Independence.

Among your talents, which one(s) give(s) you a competitive edge?

Self-discipline.

What do you consider your greatest achievement?

Having the friends that I have.

If you could change one thing about yourself, what would it be?

I wish I were more extroverted.

What do you most value in your friends?

Forgiveness and understanding.

Who are your favorite writers?

Ernest Hemingway, Kazuo Ishiguro, and Raymond Carver.

Who are your heroes of fiction?

Shantaram!

Who are your heroes in real life?

Dad.

What aphorism or motto best encapsulates your life philosophy?

"Let the boat of your life travel lightly, lest your possessions sink you." A Chinese proverb that I heard from a sage English friend.

Andrea Ballesio¹

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Hermona Soreq: Revolutionizing neuroscience by elucidating the roles of poly(A) tails, mRNA stability, and acetylcholine in brain-body communication throughout the lifespan

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Keywords: cholinergic pathway, small non-coding RNAs, traumatic stress responses, transfer RNA fragments

Hermona Soreq, PhD, holds the Endowed Slesinger Professorship of Molecular Neuroscience at the Hebrew University of Jerusalem. She is an internationally recognized molecular neuroscientist known for her research into the cholinergic system and the small RNA regulators driving the parasympathetic system in men and women under daily and acute stress responses and neurodegenerative diseases like Alzheimer's and Parkinson's diseases (AD, PD). Her studies have long been focused on the roles of acetylcholine in the mammalian nervous system. In the 1980s, Professor Soreq and coworkers cloned the human cholinesterase genes, identified several disease-related mutations and single nucleotide polymorphisms (SNPs) that may impair their functions, and described the unusual features these mutations conferred on carriers under acute stress, exposure to anticholinesterase poisons and diverse disease conditions, including but not limited to myasthenia gravis, ischemic stroke, schizophrenia, bipolar disorder, AD and PD as well as daily stress responses. Soreq further identified microRNA-132 as a principal controller of the cholinergic pathway and studied its impact as well as of other cholinergic-targeted microRNAs as regulators of parasympathetic brain and body functions and neuroinflammation. More recently, she has shifted her interest to the re-discovered transfer RNA fragments (tRFs), and showed that their rapidly declined control over cholinergic transcripts may lead to the fast cognitive deterioration of women living with AD; that they are prominently altered in PD patients' biofluids and that their levels are sex-relatedly modified in the blood of newborn babies, dependent on pre-delivery stress. Her multi-leveled interests in the stress and sex-related cholinergic aspects of AD, PD, adult, and pre-delivery trauma further reflect the impact on acute stress responses as the kernel of the neuroscience research in the current Israeli landscape and has further enabled her a wide-angle view of diverse cholinergic-regulated states and diseases. We are delighted that Professor Soreq answered the Genomic Press Interview, generously sharing her life's trajectory with our readers.

Part 1: Hermona Soreq – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I grew up in a small town in Israel, and my high school science teacher told me that he was confident that I would become a scientist and sent me to a summer school at The Hebrew University, where I was indeed hooked to the charms of research and to which I returned after my postdoctoral training at the Darnell lab in the Rockefeller University and several years at the Weizmann Institute. I recall with fondness that 29 years ago, I published a paper in the inaugural volume of *Molecular Psychiatry*. At the



Figure 1. Hermona Soreq, PhD, The Hebrew University of Jerusalem, Israel.

time, I was intrigued by Julio Licinio's vision for that journal. It's now exciting to witness that same visionary spirit expand into Genomic Press and its new publication, *Brain Medicine*.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

I was attracted to the cholinergic system early on and got funding to clone the two cholinesterase genes, establish engineered transgenic mice over-expressing them, and test their persistence under anti-cholinesterase poisoning, which was indeed improved—but those mice were also stupid, which seemed a high price to pay for resilience and brought me to study the psychiatric implications of the cholinergic network.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

I liked the story about Otto Loewi and the discovery of acetylcholine. I was then charmed by the concept of microRNAs, which later led me to focus on transfer RNA fragments as regulators of cholinergic functioning.



**What impact do you hope to achieve in your field by focusing on specific research topics?**

Others look up to me in my field of expertise, and I am well cited and frequently invited to lecture about my work. On reflection, I must acknowledge the profound impact of the late Edmond and Lily Safra, who established our Brain Research Center. Their vision and support have been instrumental in advancing our work and creating an environment where groundbreaking research can flourish. Their contribution to the field of neuroscience through their generous support cannot be overstated.

Please tell us more about your current scholarly focal points within your chosen field of science.

I am fascinated by the concept of multi-leveled regulation of molecular brain activities and seek to understand it in terms of mental and neurodegenerative diseases.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I always look for new surprises and believe that Nature makes no mistakes, so anything we discover has a meaning—often of a regulatory nature.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

My late father taught me that everything is linked to everything else and introduced me to mystery books as a child; I guess that ever since then, I have loved mystery stories and sought new links between the mechanisms of action that make our brains work the way they do.

What do you most enjoy in your capacity as an academic or research leader?

Going to work has become a relief from the burdens of everyday stresses, which are genuinely very heavy these days. So, work is my refuge from war.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I love reading and like this activity as my leisure time—it also assists in escaping the harsh reality around us this past year. I also like cooking for my family, which is close to biochemistry in my mind—many years ago, there was a short article in *Science* on the biochemistry of meringue that I will never forget. I also enjoy traveling, and science gives me ample opportunities to do that.

Part 2: Hermona Soreq – Selected questions from the Proust Questionnaire¹**What is your idea of perfect happiness?**

Peace and interaction with other peace-seeking individuals.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your greatest fear?

After October 7th, 2023—that it happens again.

Which living person do you most admire?

Jean Pierre Changeux, who is the man of all virtues and masters both science, arts and humanities.

What is your greatest extravagance?

A little while ago, my 12-year-old granddaughter and several of her girlfriends visited my lab and learned some of what we do—and one of them told me, "You are a truly enchanting woman!" which was really great.

What are you most proud of?

At work- my ex-graduates who succeed in their scientific journeys, current students and postdocs who are the best there are and students who ask smart questions at lectures.

What is your greatest regret?

Failure to transfer the love of research to some of my trainees and students who think that it is too demanding.

What is the quality you most admire in people?

Curiosity and the ability to take it to higher levels of understanding.

What is the trait you most dislike in people?

Dishonesty and disrespect to others.

What do you consider the most overrated virtue?

Success in one's career, which depends on much more than personal merits.

What is your favorite occupation (or activity)?

Reading novels.

Where would you most like to live?

Where I do: a small 3,000-years-old village in the outskirts of Jerusalem.

What is your most treasured possession?

An antique coin from the ancient kingdom of Jerusalem, 2000 years ago.

When and where were you happiest? And why were so happy then?

When my eldest son was born and a new life began.

What is your current state of mind?

Scared of the threats of worldwide war in the air.

What is your most marked characteristic?

My friends say that I am hopelessly optimistic, but I fear that I am losing that virtue.

Among your talents, which one(s) give(s) you a competitive edge?

The capacity to link solutions to emerging research questions and come up with answers.

What do you consider your greatest achievement?

Cloning of the two human cholinesterase genes before the human genome project.

If you could change one thing about yourself, what would it be?

Lose weight.

What do you most value in your friends?

Their friendship and independent personalities.

Who are your favorite writers?

I would have to say Lev (Leo) Tolstoy—his books just have this way of getting under your skin and making you see the world differently, you know? Like in *War and Peace*, he captures these huge historical events but also dives deep into the characters' inner lives.



Who are your heroes of fiction?

Recently, I was captivated by Andrew Bevel from Hernan Diaz's novel *Trust*—or *Spaces* as it is called in the Hebrew translation I read. Have you come across it? Bevel isn't your typical hero, but that is what makes him so fascinating. He is this wealthy financier in 1920s New York, who made his biggest killing by anticipating and "shorting" the financial collapse of 1929. The way Diaz peels back the layers of his character through different perspectives is just... wow! It really makes you question the nature of truth and power.

Who are your heroes in real life?

John Gurdon, Eric Kandel, Jean Pierre Changeux.

What aphorism or motto best encapsulates your life philosophy?

The wheat will grow again...

Hermona Soreq, PhD¹ 

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Károly Mirnics: Many medications and chemicals might not be as safe for the developing brain as we think they are; this will greatly depend on your genotype, habits, and environmental factors

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Károly Mirnics is Director and Hattie B. Munroe Professor of Psychiatry, Biochemistry & Molecular Biology, Pharmacology & Experimental Neuroscience, Munroe-Meyer Institute for Genetics and Rehabilitation at the University of Nebraska Medical Center (UNMC). Dr. Mirnics earned his medical degree from the University of Novi Sad School of Medicine (in the former war-torn country of Yugoslavia that does not exist anymore) and his Ph.D. from Semmelweis University in Budapest, Hungary. He completed his postdoctoral fellowship at the University of Pittsburgh, where he established his laboratory in 2000. In 2006, his laboratory moved to the Department of Psychiatry at Vanderbilt University in Nashville, TN. In 2010, Dr. Mirnics was named James G. Blakemore Professor of Psychiatry and served as the departmental vice chair for research and the associate Director of the Vanderbilt Kennedy Center for Human Development. In 2016, he joined UNMC, becoming the Director of the Munroe-Meyer Institute for Genetics and Rehabilitation (MMI). With over 1,000 employees and trainees and roots tracing back to 1919, MMI is among the world's most extensive clinical, research, education, and outreach institutes for intellectual and developmental disabilities (IDD). Funded by the National Institutes of Health (NIH), Dr. Mirnics's innovative research uses a variety of genetic, molecular, cell biology, and behavioral tools across multiple disease models; he has authored over 150 scientific publications, which have been cited more than 17,000 times. As a passionate advocate for diversity, access, and inclusion of individuals with intellectual and developmental disabilities, he currently serves on the board of directors of Special Olympic International (SOI). He chairs the SOI Global Medical Advisory Committee that develops strategies to address the health challenges of more than six million athletes across over 200 countries. He led UNMC's effort to build a highly advanced, award-winning, 20,000 m² multidisciplinary building that serves individuals with intellectual and developmental disabilities across the lifespan. We are delighted that Dr. Mirnics shares his personal and professional paths with our readers.

Part 1: Károly Mirnics – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I do not know if there was a pivotal moment; I undoubtedly do not recall one. From childhood, I wanted to know how things worked. I think I always wanted (or was on a path) to be a scientist. I had great science teachers from my earliest education. They instilled in me a love for the unknown and curiosity about how biological systems work.



Figure 1. Károly Mirnics, MD, PhD, University of Nebraska Medical Center, USA.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

Under the guidance of Pat Levitt and David A. Lewis at the University of Pittsburgh, I learned to be bold and to ask the right questions as a scientist. These mentors also taught me that being bold and being reckless, while on the same continuum, are two very different things. They taught me not to overinterpret my data but to pay attention to all findings that do not make sense, as those might be the most valuable pieces of the puzzle. At Vanderbilt University, I was given an opportunity to get involved in community engagement work and learn management skills. At UNMC, I honed my changemaker and impactful leadership skills. At Special Olympics International, I learned to admire and respect cultures and design systems across various beliefs and customs. Along the way, I had guidance and mentoring from many amazing people, and I am eternally thankful to them. Still, the most pivotal moment in my career was





meeting and working for Pat Levitt, who remains my idol in multiple ways. His “superpower” is caring – about people, science, and society, which makes him a terrific role model.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

Cholesterol gets a bad rap in the public and, to a certain degree, in the medical community. Sterol biosynthesis in the developing brain is essential, yet still much of an enigma. The brain contains about 25 percent of the cholesterol of humans, and the synthesis of all this cholesterol is entirely independent of the systemic cholesterol of the body. We cannot live without it, and the sterol biosynthesis pathway is essential for virtually all cellular and molecular processes. This almost incomprehensible complexity fascinates me, and the Janus duality of cholesterol reminds me daily of the inevitable yin-yang aspect of my everyday life and work – well beyond the scientific endeavors we pursue.

What impact do you hope to achieve in your field by focusing on specific research topics?

The neuroscience and medical fields need to understand how vital sterol biosynthesis is for the developing brain and that many commonly used medications can interfere with it, potentially with very deleterious consequences. All medications must be evaluated for their potential to inhibit brain cholesterol biosynthesis, especially in development and in the context of the mother's and child's genotype. I also hope to identify chemical compounds that would regulate brain cholesterol biosynthesis (or counteract inhibition of it) in conditions where this homeostasis is disrupted.

Please tell us more about your current scholarly focal points within your chosen field of science.

Our lab's recent primary focus is sterol biosynthesis and homeostasis in the developing brain. We investigate critical time windows, the effects of medications on this process, and how and when genotype worsens sterol biosynthesis inhibition by chemicals, lifestyle, and medications. Our previous work focused on gene expression patterns in postmortem brains of subjects with schizophrenia, the role of interneuronal classes in regulating behaviors, and genotype*maternal immune activation interactions. We also explored molecular mechanisms of neuroprotection by exercise and physical activity.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

Honesty, hard work, being transparent, not mincing words, and having compassion are critical traits that I learned from my mentors – which I will treasure for the rest of my life.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

Our perspective tends to be overly centered on Western civilization. The phrase “Let a hundred flowers blossom,” championed by the Chinese intellectual community in 1957 to improve their nation, strikes a chord with me. Embracing cultural variances is crucial; our collective diversity constitutes our collective strength. Unfortunately, the prevalent view remains skewed toward certain cultures and demographics. I am concerned about the widespread notion that groundbreaking ideas and superior scientific contributions are exclusive to top-tier institutions like the Ivy League and their equivalents, leading to overestimating their research outputs. This bias is evident in the grant review process, the selection of studies for leading journals, and the portrayal of scientists in major media channels. However, this perception does not align with reality. Exceptional scientific work is not confined by geography. Take my journey as an illustration: I originated from a nation that no longer exists and earned



Figure 2. Károly Mirnics with a patient at the Munroe-Meyer Institute playground.

my qualifications from a lesser-known institution. Nevertheless, I currently lead a globally acclaimed institute specializing in developmental disabilities.

What do you most enjoy in your capacity as an academic or research leader?

I love seeing other people reach their potential and be amazing at what they do. I love the smiles on the athletes' faces at Special Olympics International events. I love knowing that I made this world a little bit better place for someone.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I enjoy reading a sci-fi book, traveling to new places, fishing or hiking, playing online chess, and talking on the phone with my family.

Part 2: Károly Mirnics – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Depends on the day, my mood or activities, and the circumstances: at work, getting a perfect score on R01 grant or obtaining an extraordinary result in our research study. At a personal level, being on a small fishing boat in Alaska with a big one on my hook, watching the incredible sunsets over the lake with my family, getting overwhelmed by the sound of amazing music at the symphony are all things that give me joy. I find my happy moments whenever I can. I am not picky, and I learned to enjoy the half-full glass.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003, Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**What is your greatest fear?**

This is a tough one. I do not have many fears. Fear inhibits and makes you vulnerable. Fear is not a strategy; you cannot allow it to have power over you; it paralyzes decision-making. My greatest fears are probably related to the health and well-being of my family members.

Which living person do you most admire?

Many different individuals for their particular traits and skills. I will not name them all, as I will leave out many important people in my life from this list. Pat Levitt for his knowledge, passion, dedication to trainees, brain power, and moral/ethical qualities in the scientific community. In public life, I most admire Tim Shriver for his amazing, tireless work in Special Olympics International and his advocacy for civility and dignity. In daily life, my wife, Zeljka Korade, for her unparalleled human qualities, passion for science, hard work, and personality. I admire everyone who cares about their work or activities. Caring is the secret sauce of life and a precondition for doing things well.

What is your greatest extravagance?

I am not sure. You will have to ask my wife and friends. Wearing colorful ties, buying fishing lures that I will probably never use, and owning various hats are the furthest I go in this arena.

What are you most proud of?

Being myself. Speaking truth to power. Being creative and accomplishing almost impossible things even when they are incredibly challenging. Creating frameworks for other people to succeed. Being honest.

What is your greatest regret?

I do not look back with regrets. It makes no sense for me to play the “*what if*” game. I am happy with my life; I have been fortunate and blessed with a job I love, financial security, health, and an adorable family. I regret gaining too much weight, getting hooked on nicotine, occasionally not being kinder to others, and other similar things.

What is the quality you most admire in people?

Being grounded, honest, and comfortable with who they are. I sincerely believe that only caring, friendly people can be happy.

What is the trait you most dislike in people?

Traits, actually. Greed, self-centeredness, selfishness, rigidity, and forcing our beliefs on others are the banes of our society.

What do you consider the most overrated virtue?

It has to be intelligence. I have met many incredible people with intellectual and developmental disabilities who are remarkable human beings. In contrast, I also met crooks whose intelligence was off the scale. This makes you think about what we value vs. what we should value in society.

What is your favorite occupation (or activity)?

Traveling to new places, fishing, hiking, kayaking, playing chess online, having family get-togethers over videoconferencing, and having a scotch while watching the sunset over the lake.

Where would you most like to live?

Alaska or Iceland in the summer, Sint Maarten/Saint Martin or Dominica in the winter. I am also very content in Nebraska, as I love the Midwest. The people here are lovely and genuine. It is like where I was born – the big sky, incredible sunsets, swaying crops in the wind, big rivers with incredible wildlife: what is not to like?

What is your most treasured possession?

My family, my health, my memories of our family travels.

When and where were you happiest? And why were you so happy then?

I have had many unforgettable moments in life. However, I cannot think of one that would stand out as the “one” happiest moment—my happiest

moments included the ones you would expect – coming to the US, getting married 30 years ago, the birth of our two children, getting a tenure-track job, finishing my first marathon, obtaining my first grant as a PI, signing the purchase documents on our first home. One period may stand out. Zeljka and I were trainees at the University of Pittsburgh, with very meager resources (long story), but we had each other and a city and area full of wonders to explore.

What is your current state of mind?

I am worried. For the state of our country, the poisoned rhetoric, the relativity of truth, and the extreme polarization that has become the norm. I am very much a centrist, and there is no place for people like me in our current political landscape. However, this question has a variety of answers. Depending on my activities, focus, and surroundings, my mind will change in the next five minutes.

What is your most marked characteristic?

Most say speaking my mind (perhaps too much!) and wearing my emotions on my sleeve. On the other hand, vision, fairness, and integrity are my best qualities. One of my directors always describes me as a teddy bear at heart with the appearance and manners of a grizzly bear.

Among your talents, which one(s) give(s) you a competitive edge?

My above-listed characteristics, coupled with hard work.

What do you consider your greatest achievement?

Designing and building the world’s most advanced building for diagnosis and treatment of intellectual and developmental disabilities², changing the culture of MMI to be more collaborative, and changing the hearts and minds of our providers to focus on excellence throughout all our activities – with our patients and their families being the focal point.

If you could change one thing about yourself, what would it be?

I want to become a better listener, less deeply invested in my own ideas, and less impatient. I always favor action over inaction, and it would be nice to have a more balanced mindset. I have come a long way but am still a work in progress.

What do you most value in your friends?

Being genuine. Being who they are and not pretending and posturing.

Who are your favorite writers?

Ray Bradbury, David Niven, Isaac Asimov, Orson Scott Card, James P. Owen, Stanisław Lem, Arthur C. Clarke, Partick Rothfuss, Ursula K. Le Guin, Roger Zelazny, George R. R. Martin, Brandon Sanderson, Aldous Huxley, Neil Gaiman, Dan Simmons and many other sci-fi and fantasy writers.

Who are your heroes of fiction?

They share the common characteristic of not being purely good or purely evil. They are human, complex characters. Examples include, but are not limited to, Takeshi Kovacs (Altered Carbon), Kvothe (Name of the Wind), Martin Silenus (Hyperion), and Louis Gridley Wu (Ringworld).

Who are your heroes in real life?

All people who are not in it for money, fame, or personal gain. The unnamed ones that history books will never remember. Single mothers working three jobs, the late Dr. Gorog Istvan from Orebić, Croatia, who worked 18-hour days as the only physician in the diameter of 60 miles, my science teachers and university professors, daycare workers, people who speak up for justice and humanity regardless of grave personal consequences on their lives and freedom, the ones who feed people experiencing poverty yet they have little to feed themselves, and so on. Forgotten inventors who changed the course of human history with fire, wheel, and metal, astronomers of ancient cultures. The list is endless.

²For further details on the Munroe-Meyer Institute, see <https://vimeo.com/560450619/a1fb34aa0d>.



What aphorism or motto best encapsulates your life philosophy?

Immanuel Kant's quote guided my life since I read *"Critique of Practical Reason"* at age of 17: "... the starry heavens above me and the moral law within me." For me, this always meant that human potential is unlimited and that we must dream big and think the unthinkable. The limit is not what we can achieve. Rather the limits should come from the ethical boundaries of a universal moral code contained within all of us. We have to listen to it and tune out our desires and wants.

My leadership philosophy is best summed up in the book *Cowboy Ethics* by James P. Owen. In particular, the following paragraph strongly resonates with me: *"The fundamental problem is that we have confused rules with principles. Rules can always be bent, but principles cannot. So, while bureaucratic rules may reinforce the ways we ought to behave, they are no substitute for personal principles."*

Károly Mirnics¹ 

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Raül Andero Galí: Bridging animal and human studies to understand stress and memory

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Keywords: Stress, Memory, Translational, Fear, Hormones

From pianist to pioneering neuroscientist, Dr. Raül Andero Galí brings a unique perspective to his role as ICREA (Institut Catalana de Recerca i Estudis Avançats) Research Professor at the Autonomous University of Barcelona (Universitat Autònoma de Barcelona). Following his PhD in Neuroscience, earning the Extraordinary Doctoral Prize, he worked alongside Dr. Kerry Ressler at Emory University's Howard Hughes Medical Institute, pioneering innovative approaches that bridge mouse and human studies in fear research. After a productive tenure as an Instructor in Psychiatry at McLean Hospital-Harvard Medical School, he established his laboratory at UAB in 2016, where he continues to break new ground in understanding how stress shapes fear memory formation. His laboratory uniquely combines sophisticated techniques, from in vivo calcium imaging in mice to human fear response studies, focusing on how sex differences and hormonal cycles influence fear processing. Through this work, his team is uncovering new possibilities for treating anxiety disorders and PTSD, offering hope for more targeted therapeutic approaches. Beyond the bench, Professor Andero has cultivated an intellectually stimulating laboratory environment that reflects his broader vision for advancing neuroscience through comparative studies. We are pleased that he completed the Genomic Press Interview, offering our readers valuable insights into both his scientific journey and personal philosophy that drives his innovative research forward.

Part 1: Raül Andero Galí – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was born and raised in the Barcelona, Catalonia area. As a preteen and teenager, I developed a strong interest in music, particularly piano playing. I have performed classical music and jazz in bands and as a soloist. At some point in my late teenage years, I considered pursuing a career in it. One day, I challenged myself to play piano for 8 hours. It was grueling, and I did not even complete it full-time. That day, I realized that being a professional pianist was not going to work for me. So, I decided to pursue a degree in Psychology at the Autonomous University of Barcelona. Before starting, I had enjoyed reading Sigmund Freud, but from the beginning, I discovered that my favorite subjects were those related to neurobiology. Particularly inspiring were the classes taught by Professor Roser Nadal, which sparked my interest in neuroscience.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

I obtained my PhD in Neuroscience in 2010 at the Autonomous University of Barcelona under the direction of Professor Antonio Armario.



Figure 1. Raül Andero Galí, PhD, ICREA, Autonomous University of Barcelona, Spain.

During that time, I studied the neurobiology of stress and its implications for memory mechanisms. After that, I joined as a Postdoctoral Fellow at the laboratory of Professor Kerry Ressler, who was a Howard Hughes Medical Investigator at Emory University. A defining moment in my career was when we pioneered the integration of mouse and human data with neuroimaging in the field of fear research, published in Science Translational Medicine in 2013. Since then, I have found it fascinating and intellectually very challenging to combine data of different species in fear studies. For instance, in the same study, we showed concordant data with *in vivo* calcium imaging of fear in freely moving mice (Miniscopes, UCLA system) and functional neuroimaging in humans (Florida et al. 2024 Science Advances).

Please share with us what initially piqued your interest in your favorite research or professional focus area.

From the start of my career, I realized that focusing on stress and memory provides valuable insights that can be applied across many areas of neuroscience. All animals face threats throughout their lives, triggering adequate stress responses vital for survival. I am also interested in memory, primarily because of the brain's remarkable ability to store and retrieve information, subtly altering it with each recall. Memories shape our reality, and the fact that these are not fixed truths, but malleable constructs influenced by emotions fascinates me. Finally, an essential thing about the stress and memory field is that it can be studied at





multiple levels, from cell cultures, animal models, healthy volunteers, and patients.

What impact do you hope to achieve in your field by focusing on specific research topics?

I hope that shortly, we will develop better treatments for fear-based disorders like PTSD. Current treatments involve psychotherapy and pharmacology, and while there have been positive advancements in both fields, pharmacology faces the challenge that most drugs target receptors distributed throughout the entire brain. My lab has focused on neuropeptide receptors, which are predominantly expressed in the brain's emotional regions. I believe these could serve as promising new pharmacological targets for treating fear-based disorders.

Please tell us more about your current scholarly focal points within your chosen field of science.

Several fascinating areas are a focal point of my lab at ICREA (Institut Catalana de Recerca i Estudis Avançats or Catalan Institution for Research and Advanced Studies). First, we are strengthening both our human fear laboratory and Miniscope recordings in mice. In the human lab, healthy volunteers participate in fear conditioning experiments, where we collect saliva samples to measure sex hormones using novel and highly sensitive liquid chromatography-mass spectrometry methods. We aim to understand how the menstrual cycle influences fear memory formation by combining fear-potentiated startle and skin conductance responses with sex hormone levels. In mice, Miniscopes allow us to monitor hundreds of neurons in real time during behavior in a specific brain region. This approach helps us explore intriguing questions, such as why male and female mice exhibit equivalent behaviors, yet their neuronal responses in crucial brain areas differ significantly.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

The most important thing for me in my laboratory is that it has a healthy and positive environment in which the different members interact and learn from each other. It must also be an intellectually changing place where individuals can grow toward their future career goals.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I believe we need to transform how neuroscience research is conducted by breaking down the traditional barriers between animal and human studies. Too often, these remain separate domains, limiting our progress. We can create a more comprehensive and translatable understanding of the human brain by advocating for more integrated cross-species approaches. This methodological shift is crucial for advancing neuroscience and developing more effective treatments.

What do you most enjoy in your capacity as an academic or research leader?

What I enjoy most is the opportunity to connect with fascinating people from around the world. These interactions help me remember that our work as neuroscientists should ultimately benefit as many people as possible.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I love spending time in nature with family and friends. The beach is always a good time for me.



Figure 2. Raül Andero Galí at Costa Brava, Catalonia, Spain, following his regular swim in the Mediterranean sea. As a neuroscientist studying stress, he finds that time spent at the seaside is an essential balance between his research pursuits and personal well-being.

Part 2: Raül Andero Galí – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Snorkeling and fish-watching in Costa Brava, Catalonia, Spain (see Figure 2).

What is your greatest fear?

Death of my family members.

Which living person do you most admire?

At a professional level, my postdoctoral mentor Professor Kerry Ressler.

What is your greatest extravagance?

Planning trips around exciting food.

What are you most proud of?

Starting my laboratory studying the neurobiology of fear in mice and humans.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**What is your greatest regret?**

Not using my second surname, Galí, in my scientific publications, where I go by Raul Andero (Andero R on PubMed).

What is the quality you most admire in people?

Connecting with others and sending a good vibe.

What is the trait you most dislike in people?

Manipulation.

What do you consider the most overrated virtue?

Writing grants.

What is your favorite occupation (or activity)?

I appreciate any outdoor activity with my family, such as hiking or bike riding.

Where would you most like to live?

Where I live now: in the north area just outside Barcelona.

What is your most treasured possession?

My books from when I was a child that my kid is already reading.

When and where were you happiest? And why were so happy then?

Seeing my wife and kid healthy after delivery.

What is your current state of mind?

A good balance between age and wisdom.

What is your most marked characteristic?

Curiosity.

Among your talents, which one(s) give(s) you a competitive edge?

Learning from colleagues in very different fields and combining that knowledge.

What do you consider your greatest achievement?

Mentoring brilliant young neuroscientists.

If you could change one thing about yourself, what would it be?

I would be more patient.

What do you most value in your friends?

The fact that they pick up the phone when I call them.

Who is your favorite writer?

Anthony Bourdain.

Who are your heroes of fiction?

The main characters in the "Back to the Future" trilogy.

Who are your heroes in real life?

My mom and dad.

What aphorism or motto best encapsulates your life philosophy?

Fool me once, shame on you. Fool me twice, shame on me.

Raül Andero Galí, PhD¹

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Tatia Lee: Neuropsychology and human neuroscience research insights inform the theoretical and translational framework for fostering brain and psychological health

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Tatia Lee, PhD, is Chair Professor of Psychological Science and Clinical Psychology at The University of Hong Kong, a clinical psychologist, and a board-certified clinical neuropsychologist. Her research focuses on the neuroplastic basis of neurocognitive and affective processes underpinning normal and pathological neurocognitive and psychological functions. She is an elected Fellow of esteemed international societies, including the World Academy of Sciences, Academy of Social Sciences (UK), American College of Professional Neuropsychology, Association for Psychological Science, and American Psychological Association. She is the Founding Chair of the Clinical Neuropsychological Society under the Chinese Cognitive Science Society of China. She has received numerous awards and recognition, including The University of Alberta Alumni Horizon Award, the Fulbright Hong Kong Scholar, the State Scientific and Technological Progress Award, and the Humanities and Social Sciences Panel Prestigious Fellowship Award. Acknowledging her substantial contributions and academic achievements in advancing neuropsychological sciences, The University of Hong Kong bestowed her the “May Endowed Professorship in Neuropsychology.” Professor Lee is happy to provide our readers with reflections on her life and career.

Part 1: Tatia M.C. Lee – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

From a young age, I was an inquisitive child, eager to explore the world around me and understand the intricacies of how it operates. My curiosity extended beyond the physical world to encompass human behaviours. I wanted to learn why people act the way they do and what drives their decisions—the pivotal moment that ignited my passion for science occurred during my school years. My science teacher had an uncanny ability to transform complex concepts into relatable stories, sparking my desire to dig deeper into the mysteries of the human world. I was captivated by the idea of using scientific principles to uncover the hidden mechanisms that govern our behaviours.

As I continued my education, my interest in health promotion began to develop. I was inspired by the potential of science to improve the quality of life. I realized that understanding the brain and mind relationships could lead to more effective strategies for disease prevention and overall well-being. I became particularly drawn to neuropsychology, fascinated by the intricate relationships between the brain and human behaviours. I began to see the immense potential for health promotion through understanding the underlying neuropsychological causes of normal and abnormal brain and psychological functioning. This realization solidified my resolve to dedicate my career to unravelling these complex relationships and using my findings to improve the lives of others.



Figure 1. Tatia M.C. Lee, PhD, The University of Hong Kong, Hong Kong SAR.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My career trajectory began with a clinical psychology internship at the Department of Clinical Health Psychology of the University of Manitoba. This invaluable experience exposed me to the practical applications of psychological theories and allowed me to work directly with patients, deepening my understanding of the human mind. Upon completing my internship, I graduated at a time when neuropsychology and neuroscience were vibrant and rapidly evolving fields. The confluence of these disciplines presented a unique opportunity for me to combine my interests in psychology and brain research. I was excited to be part of this interdisciplinary movement that pushed the boundaries of our understanding of the relationships between the brain, mind, and behaviours.

A defining moment in my career trajectory came with the realisation that in-vivo exploration of brain activity is feasible through functional neuroimaging methodologies. This breakthrough opened an avenue for exciting brain research, allowing scientists to visualise the workings of the human brain in real time.

My dedication and achievements in the field have led to my appointment as the Director of the State Key Laboratory of Brain and Cognitive Sciences at The University of Hong Kong. In this position, I have the privilege of working with talented researchers to uncover the neural underpinnings of cognitive and emotional processes. I embraced the challenge and channelled my passion for neuropsychology and neuroscience into leading my team to explore new frontiers in brain research.





Please share with us what initially piqued your interest in your favorite research or professional focus area.

Reading, for example, Oliver Sacks' books about exciting medical discoveries ignited my interest in my current research and professional foci. These captivating narratives brought the complexities of neuropathology, psychology, and neuroscience to life, and they had a profound impact on the development of my current research career.

My exceptional neuroscience and neuropsychology teachers and clinical mentors, whose passion for their respective fields, further inspired and encouraged my commitment to my favourite research and professional focus areas. Their engaging lectures and dedication to advancing our understanding of the brain, mind, and their interactions further solidified my desire to delve deeper into this fascinating area of study.

What impact do you hope to achieve in your field by focusing on specific research topics?

I hope to significantly impact several key areas, ultimately contributing to the promotion of brain and psychological health. Firstly, through my research, I aim to prevent or slow down the development of neurocognitive and affective dysfunction by identifying preventable risk factors early and developing targeted interventions to mitigate these issues before they develop into more severe conditions. Secondly, I strive to minimise the disease's impact on those already affected by cognitive or emotional disorders. By advancing our understanding of the neural underpinnings of these conditions, my research will contribute to developing novel treatment approaches that can more effectively address the unique challenges faced by individuals with these disorders. Lastly, I am committed to developing cost-effective and broadly accessible screening methodologies and intervention strategies for neurodegenerative diseases and mood disorders. By making these tools widely available, I hope individuals from diverse backgrounds and resource-limited settings can benefit from early detection and appropriate interventions, leading to better health outcomes and improved quality of life.

Please tell us more about your current scholarly focal points within your chosen field of science.

My current scholarly focal points within my chosen field of science encompass several key areas: (1) Investigating the role of the PONS in affective processing and regulation through observing social and affective behaviours in individuals with pathological mood problems. My research provides critical insights into how the PONS interacts with various brain regions to process and regulate emotions, contributing significantly to our understanding of the neuropathology of anxiety and depression. (2) Developing prediction models for social behaviours and stress response, which offer valuable insights into mental health research and sciences in developing countries where access to professional facilities is limited and facilitates timely interventions for neurodegenerative and affective disorders. (3) Developing online neuropsychological assessment platforms and comprehensive sets of normative data on neuropsychological measures to facilitate brain-behaviour research and clinical development.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I have developed crucial habits and values shaping my scientific inquiry approach. Perseverance, resilience to failure, adherence to ethical principles, and patience are all integral aspects of my work ethic. I have learned to face challenges and setbacks, bounce back from failures, and maintain the highest ethical standards in my research.

Additionally, I continuously strive to broaden my perspective by engaging with diverse ideas, disciplines, and collaborators, recognising that innovation often emerges from synthesising different viewpoints and approaches. I strongly emphasise innovation in my research, developing novel methodologies, insights, and solutions that challenge existing paradigms and push the boundaries of our understanding. By embracing these habits and values, I have cultivated a research environment that fosters curiosity, rigour, and collaboration, enabling me and my students

to make meaningful contributions to advance the frontiers of scientific knowledge.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

One such issue that comes to mind is the under-representation of women scientists, although it is worth noting that the situation has been gradually improving. Additionally, we must exercise caution regarding the representation of scientists from different geographical regions and ethnic origins. Their inclusion and participation are vital to ensuring a comprehensive and global perspective in scientific research. Ensuring these potential balances and fostering a diverse and inclusive environment within the scientific community is a crucial and ongoing endeavour.

What do you most enjoy in your capacity as an academic or research leader?

As an academic and research leader, I most enjoy witnessing the development and success of students and young talents, as well as my colleagues. Seeing them grow, thrive, and contribute to our field is incredibly rewarding. Furthermore, I am very satisfied to know that my research has positively impacted human health and quality of life, contributing to a lasting, beneficial effect on society.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Personal development and growth are essential, even during leisure time. I enjoy delving into various books, exploring new subjects, and expanding my horizons. Travelling also plays a significant role, providing opportunities to immerse myself in diverse cultures and experiences. Above all, spending quality time with family and friends is paramount and contributes to a balanced and fulfilling life.

Part 2: Tatia M.C. Lee – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Perfect happiness is achieved when experiencing a state of inner peace and tranquillity.

What is your greatest fear?

The greatest fear is fear itself.

Which living person do you most admire?

The volunteers of the Médecins Sans Frontières and other charitable organizations.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**What is your greatest extravagance?**

Travelling; professional/personal development.

What are you most proud of?

My students' achievements.

What is your greatest regret?

I do not have this feeling because I see experiences as learning opportunities rather than moments of regret.

What is the quality you most admire in people?

Kindness.

What is the trait you most dislike in people?

Arrogance and hypocrisy.

What do you consider the most overrated virtue?

Righteousness can be an overrated virtue. We all want to be "right." However, if you constantly assert your correctness, it comes off as self-righteous or gloating. Nonetheless, the opinion on overrated virtue varies depending on individual perspectives, personal beliefs, and cultural values.

What is your favorite occupation (or activity)?

Interacting with people.

Where would you most like to live?

Where my social connections are.

What is your most treasured possession?

Memories of my loved ones.

When and where were you happiest? And why were so happy then?

The moments when my children were born. Witnessing the miraculous arrival of new lives was joyful.

What is your current state of mind?

Peaceful.

What is your most marked characteristic?

Loyalty, Perseverance, and Resilience

Among your talents, which one(s) give(s) you a competitive edge?

Multicultural experiences and people skills are talents that offer me a competitive edge.

What do you consider your greatest achievement?

The happiness and achievements of the two children I brought up and the professional and/or research psychologists I trained.

If you could change one thing about yourself, what would it be?

Be more daring and outspoken.

What do you most value in your friends?

Sharing and support.

Who are your favorite writers?

George Orwell, Oliver Sacks, and Yuval Noah Harari.

Who are your heroes of fiction?

The Swallow and the Happy Prince.

Who are your heroes in real life?

My mother.

What aphorism or motto best encapsulates your life philosophy?

"Knowledge is serene and indestructible wealth."

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Etienne Sibille: Investigating the cellular and molecular bases of depression and aging for innovative therapeutics

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Keywords: Neuropsychiatry, depression, aging, Alzheimer's, molecular mechanisms, therapeutics

Etienne Sibille, a pioneering figure in neuropsychiatric research, has yet to follow conventional paths. From his early days as a photojournalist editor in New York to becoming one of neuroscience's most innovative voices, his journey reflects the same creative thinking that drives his groundbreaking research at the University of Toronto. As a Professor of Psychiatry, Pharmacology & Toxicology, he brings a fresh perspective to understanding how our brains age and why we get depressed. At the Center for Addiction and Mental Health (CAMH), where he directs the Neurobiology of Depression and Aging research program, his team is turning fascinating discoveries about brain chemistry into potential new treatments. Building on his influential work at Columbia University and the University of Pittsburgh, Sibille has challenged traditional views of brain disorders, particularly through his insights into the GABAergic system and aging. While serving as CAMH's Campbell Chair (2014–2024) and Deputy Director of the Campbell Institute (2017–2020), he has pushed the boundaries between basic research and real-world treatments, recently diving into biopharma development to help bridge this gap. In this Genomic Press Interview, he shares the winding road that led him from behind a camera lens to the forefront of psychiatric research, offering a candid look at what drives his passion for unraveling the brain's mysteries.

Part 1: Etienne Sibille – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I grew up in France and attended medical school, but it was not for me. I was too restless and moved to New York to pursue a career in photography and journalism. The biotech boom in the 1990s created a lot of hope and enthusiasm that the biological sciences could finally tackle some of the problematic brain-related challenges with a huge potential impact on individuals' quality of life and society at large. Since I have always had affinities and capabilities for the life sciences, I jumped when an opportunity to go back to science presented itself. I did a PhD in Pharmacology at Cornell with Miklos Toth, a postdoc at Columbia with René Hen, and then trained in human postmortem studies with Victoria Arango before setting up my lab at Columbia, then at the University of Pittsburgh. My career changes and moves have never been planned and have resulted from opportunities that presented themselves through scientific networks. In 2014, I moved to CAMH and the University of Toronto to set up a program on the molecular bases of depression and aging, with a strong focus on translation and drug development for brain disorders.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My more relevant leadership roles involve guiding multidisciplinary research groups and focusing them on a particular research question. I have



Figure 1. Etienne Sibille, PhD, University of Toronto and The Centre for Addiction and Mental Health, Canada

some aptitude for seeing big pictures, but I also realize that it takes a village to bring them to fruition. These goals and visions drove me to leadership roles as necessary means but hopefully also as key stimulating factors in generating group enthusiasm towards a shared goal.

Please share with us what initially piqued your interest in your favorite research or professional focus area

I have always been fascinated by the fact that small molecules can profoundly affect brain functions, including aspects that make us who we are (e.g., emotions, creativity, drive). Rather quickly, it became apparent to me that I would dedicate my time and energy to understanding underlying mechanisms and harness them toward the goal of reducing the burden of mental health conditions. However, after training in rodent genetics, I grew frustrated by the need for new ideas and directions for novel neuropsychiatric interventions. So, when the opportunity presented itself, I moved to human postmortem studies to generate new leads and ideas based on the primary pathologies of brain disorders. Results from early omics studies we performed in the human brain were so stunning (e.g., effects of age and sex, reduced neurotrophic effects, altered GABAergic





function) in both control and affected individuals that they have led my research program for the following (now) decades.

What impact do you hope to achieve in your field by focusing on specific research topics?

My hope for impact—in other words, what wakes me up early every morning and gets me going—is that I will have enough time for our understanding of novel pathophysiological mechanisms to translate into tangible changes in someone's life. The next question addresses my hope for specific research topics.

Please tell us more about your current scholarly focal points within your chosen field of science

Two main themes emerged from our early human postmortem studies: disturbances in aspects of the GABAergic system and the interaction of age and brain disorders. These two themes have largely dominated my research program since. For the GABAergic system, we have now gone from correlational studies in human brains in depression and aging to causal links in rodent systems, identification of novel targets (subunit-specific GABA-A receptors), and development of novel therapeutics to address the unmet clinical needs of cognitive deficits in depression and age-related disorders. The fact that we will soon have the opportunity to test it in clinical trials is a dream for a basic scientist. For the second theme of age-by-disease interaction, I hope that some of the weak biological links we have identified in postmortem studies will similarly translate into testable hypotheses in clinical trials to support brain health and delay/prevent aspects of age-related disorders.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

I often tell trainees that science is exciting but tedious, requiring tenacity and a high tolerance for failure. So early on, I developed robust work scheduling ethics: I never stopped. This avoids overcoming the high energy barrier to get started (on grants, papers, analyses, etc). I still take time off, but my mind never gets off projects. It works for me, and I enjoy it, but it may only work for some.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

A single culture can have dominant and restricting effects. So, I have strived over the years to create a research environment that is multicultural, rich in various perspectives, and not dominated by a single culture. I believe this supports better mental health and creates a more fertile ground for creativity.

What do you most enjoy in your capacity as an academic or research leader?

I love to see the trajectories of trainees at all levels. It is a real pleasure for me to see people develop their sense of self and grow into their careers over time.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Outside of work, I spend a lot of time outside, working on projects on my property, and taking care of animals (dogs, horses). Reading is also important. My reading list is quite eclectic, including fiction, mystery, historical novels and science, either in English or French.



Figure 2. “Rock the World.” Professor Etienne Sibille demonstrates his enthusiasm for science and music against a tie-dye backdrop. While his childhood dream of playing guitar like *The Who*'s Pete Townshend may have evolved into air guitar performances, Dr. Sibille channels that same rock star energy into his groundbreaking neuroscience research. The playful image captures his philosophy that revolutionary scientific discoveries, like great music, can genuinely “rock the world.”

Part 2: Etienne Sibille – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

I am at home in the country with my family (and my dogs and horses) and traveling to new places regularly.

What is your greatest fear?

None that I can think of. I prefer to focus on the present.

Which living person do you most admire?

I do not think in these terms, but I have had various mentors who have significantly shaped my scientific thinking over the years, including Miklos Toth, René Hen, Catherine Belzung, David Lewis, Victoria Arango, and Ron Duman. From my previous career in photography, I also have great respect

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



and appreciation for the works of socially aware photographers, such as Sebastião Salgado and the Magnum Photos team.

What is your greatest extravagance?

I am not sure. I would probably try to forget about it.

What are you most proud of?

I am not sure either. I am proud of the team's many accomplishments and the fact that we are in the process of translating basic findings into potential clinical reality. This is being accomplished through [Damona](#), a biopharma company I have co-founded with CAMH.

What is your greatest regret?

The same here. I do not really think in terms of personal life goals to achieve, and I tend to focus on the present. There were some childhood dreams. As a kid, I wanted to play guitar like Pete Townsend from The Who. But I have no sense of music, and all I can do is play air guitar on beach toys (see Figure 2).

What is the quality you most admire in people?

Integrity, vision, and persistence.

What is the trait you most dislike in people?

Arrogance and blind ambition.

What do you consider the most overrated virtue?

Modesty. In science, it is hard to be too modest and succeed.

What is your favorite occupation (or activity)?

Being in the present, doing what I am doing.

Where would you most like to live?

After living in Europe and the US, I am delighted to have landed in Canada. Frequent trips to Paris and Europe provide the perfect balance.

What is your most treasured possession?

I enjoy possessions but do not treasure them.

When and where were you happiest? And why were so happy then?

At work, I tend to have data-dependent mood states, so they vary from day to day (and over grant cycles...). In my career, I have truly enjoyed all the places I have been fortunate to work at (Cornell, Columbia, Pittsburgh, and now Toronto).

What is your current state of mind?

I am hopeful for the future of neuropsychiatry, merging with neuroscience and evolving into precision medicine.

What is your most marked characteristic?

I easily see the big picture and quickly analyze it. I believe that I have also been a good mentor over the years.

Among your talents, which one(s) give(s) you a competitive edge?

Seeing what other people do not see.

What do you consider your greatest achievement?

Having sustained a rich scientific and mostly stable scientific team and environment over the years.

If you could change one thing about yourself, what would it be?

Not sure. I do not spend too much time thinking about how to change myself.

What do you most value in your friends?

The safe space they can provide

Who are your favorite writers?

It varies. Recently, I have tremendously enjoyed reading the Louise Penny series on Inspecteur-chef Armand Gamache.

Who are your heroes of fiction?

I am still trying to decide.

Who are your heroes in real life?

I do not think along these lines, but I have greatly admired greater-than-life personalities like Nelson Mandela.

What aphorism or motto best encapsulates your life philosophy?

Work on topics that excite you, balance your private life, eliminate useless activities, and empower people around you in their private and professional lives.

Etienne Sibille¹

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Helen Lavretsky: Translational neuroscience of integrative medicine

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Professor Helen Lavretsky, a pioneering force in geriatric psychiatry and integrative medicine at the University of California, Los Angeles (UCLA)'s Departments of Psychiatry and Biobehavioral Sciences, has fundamentally reshaped our understanding of brain health and aging. Her groundbreaking research connecting mind-body interventions with neurobiological mechanisms has transformed skepticism into scientific acceptance, establishing new paradigms in mental health care. As director of research for the UCLA's Integrative Medicine Collaborative and Late-life Mood, Stress and Wellness Research Program, she has led seminal studies on novel therapeutic combinations for treatment-resistant depression and cognitive disorders. Her work, recognized by "triple crown" honors from major psychiatric associations in 2020, spans from innovative psychopharmacology to pioneering investigations in yoga and Tai Chi for mental health. A dedicated mentor who has championed women and underrepresented minorities in science for over 25 years, Professor Lavretsky currently serves as President of the American Association for Geriatric Psychiatry (2022–25), and she is on the Advisory Research Council to the National Center of Complementary and Integrative Medicine. In her engaging Genomic Press Interview, Professor Lavretsky shares insights from her remarkable journey from a young medical student to becoming a leading voice in integrative psychiatry, offering a compelling glimpse into the future of personalized mental health care.

Part 1: Helen Lavretsky – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I grew up in Ukraine and Russia in a family of academic physicians, my mother was and still is a psychiatrist and a psychopharmacologist at the age of 89, and my father was a neurologist and a clinical pharmacologist. My great-aunt and great-uncle were prominent psychiatrists in Moscow, Russia. From an early age, I was obsessed with understanding brain-behavior relationships and started working in a psychiatric hospital at 15 years of age. I started medical school at 17 and immediately joined a medical students' research interest group for psychiatry. By the 4th year, I conducted my first study of psychiatric symptoms in women with gynecological cancers that won a prize at the Medical Student Research Conference and was published. This started my research career, which was initially focused on the neurobiology of late-life mood and cognitive disorders of aging. Once I moved to the USA in 1989, I pursued training in geriatric psychiatry and neuroscience with the help of the National VA Neuroscience Fellowship, which helped me gain all the necessary skills in neuroimaging. The next step was to learn skills in conducting pharmacological trials of depression and cognitive disorders in older adults. The early grants from the Brain and Behavior Foundation (then known as the



Figure 1. Helen Lavretsky, MD, MS, University of California, Los Angeles, USA.

NARSAD) and a Mentored K23 award from the National Institute of Mental Health (NIMH) afforded me protected time to learn the next level of research skills to launch my independent career in developing novel clinical interventions for treatment-resistant depression and cognitive impairment in older adults and stressed caregiver with the use of cutting edge biomarkers to characterize neurobiological mechanisms of response to these interventions using neuroimaging, genetic, and immune biomarkers. I conducted some of the seminal trials of the methylphenidate and memantine combinations with antidepressants that uncovered neuroplastic and anti-inflammatory mechanisms of drug response. My efforts at the time were recognized with early career awards from the American Association for Geriatric Psychiatry, and recognition of my research was placed in the top 10 in psychiatry by the *New England Journal of Medicine* in 2015. I also loved mentoring junior researchers and students and spent the next nearly 20 years in mentoring with the support of sequential



K24 Research Career Development awards from the National Institute of Mental Health (NIMH) and the National Center for Complementary and Integrative Health (NCCIH).

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

The professional organization that became my professional home is the American Association for Geriatric Psychiatry. I am grateful to the numerous teachers and mentors whom I met through that organization, who have promoted my career and contributed to my success. I am a graduate of its research mentoring network that was funded by the NIMH—the Summer Research Institute (PI-Dilip Jeste) and the Advanced Research Institute (PI-Martha Bruce). Later, I became one of the devoted mentors for these networks for the next 20 years and wanted to contribute to the AAGP via my service as a Chair of the Research Committee, a Board member, and finally, as President-elect, President, and immediate past President (2022–25). I was grateful for the opportunity to provide my vision for the field of geriatric mental health and contribute to many successes of the organization, including the Brain Health Summit that was held in 2023. The AAGP treated me well and recognized my contributions by awarding me with the Member-in-Training (1997), Junior Investigator award (2002), and Senior Investigator award (2020). To date, I am the only one to receive this honor and recognition, but I am sure that our talented young researchers will catch up soon. There are a few other organizations that I consider “home” that contributed to my career trajectory and success, like the American College of Neuropsychopharmacology and the American Psychiatric Association, American College of Psychiatrist that elected me as a Distinguished Fellow (APA, AAGP) and a Fellow (ACNP and ACP). In 2020 – I received “a triple crown” of awards for my contributions to the understanding of the mechanisms of resilience in older adults from the APA (Jack Weinberg Award in Geriatric Psychiatry), ACP (Research in Geriatric Psychiatry), and AAGP (Senior Scientist Award) – all Awards for Research and Career in Geriatric Psychiatry. The same year, I received the Best Research Mentor award from my own Department of Psychiatry at the University of California, Los Angeles (UCLA). It felt good to have been recognized for the intense, focused climb up the academic ladder during a very scary time of the world closing under the pandemic threat. I even wrote “A Scientific Biography of the Spiritual Seeker in the Year of Hindsight 20/20” to commemorate the confluence of events and this abundance of recognition that was published in the American Journal of Geriatric Psychiatry. Another professional family is the Editorial Board of “Psychiatric Times” on which I have served for nearly 20 years and contributed many publications on my favorite topics of geriatric psychopharmacology, integrative medicine, Long-COVID and many others that trained many junior colleagues to write educational papers.

Please share with us what initially piqued your interest in your favorite area of research or professional focus

Twenty years ago, through my practice of yoga as a stress reduction tool that improved my health, I put my attention on designing research studies of mind-body interactions and applied everything I learned before investigating the mechanisms of response to the mind-body and lifestyle interventions. Some of the studies of yoga and Tai Chi became groundbreaking and set a new trend in research and clinical practice that emphasized whole person health and prevention potential of using integrative medicine. I became one of the leading voices promoting lifestyle and integrative psychiatry and promoting translational neuroscience of integrative medicine in psychiatry, which is finally getting traction with mainstream psychiatry. I served as a Co-Chair of the International Congress of Integrative Medicine in 2018 and currently serve on the Advisory Research Council of the National Center of Complementary and Integrative Medicine. I have contributed as an editor of the issues of the Psychiatric Times devoted to Complementary and Integrative Psychiatry and developed annual programs for the Caucus on Complementary and Integrative Psychiatry for the American Psychiatric Association. I worked

across organizations supporting lifestyle medicine and brain health— such as AARP, the American Heart Association, and the American College of Neuropsychopharmacology. I have published the book *Resilience and Aging: Research and Practice*, edited *Complementary and Integrative Therapies for Mental Health and Aging*, and co-edited *Convergence Mental Health: A Transdisciplinary Approach to Innovation* and have contributed to numerous textbooks and reviews of the field of integrative medicine relevant to psychiatry and geriatrics.

What kind of impact do you hope to achieve in your field through your focus on your specific research topics?

I hope that the field of psychiatry and mental health will open from a strict disease and acute-care-oriented field of medicine to embrace brain health-oriented prevention for neuropsychiatric disorders. As a geriatric psychiatrist, I know well that aging starts at conception when social determinants of health and other risk factors start dictating the future trajectories of health that eventually lead to late-life neuropsychiatric disorders, but public awareness does not rise to recognize this until it is too late. Nobody thinks about aging or dying in their youth. Nothing happens to the brain or the body on the 65th birthday of an older adult. All the effects are cumulative and stem from poor lifestyle habits, head injuries in childhood and young adulthood, environmental toxic exposures, and prolonged stress and trauma exposures starting in utero and throughout childhood and young adulthood that are left untreated for too long. What is needed is a broad public educational campaign about preventive strategies and the importance of lifestyle factors (physical and mental activities, sleep, stress reduction, social connections; healthy diet and adequate nutrition, environmental safety) and attention to prevention of head traumas and depression, cardiovascular risk factor reduction (blood pressure, cholesterol, obesity, blood glucose control). If we all do all of those things, as a society, we will be healthier and live longer and with healthier brains. As psychiatrists, we are more likely to spend time in prevention and stress reduction than in an acute hospital setting.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your own research environment?

I learned that everyone deserves a chance to try to succeed, but only some will. Perseverance and belief in yourself are essential to your success. Others may tell you that you do not deserve success, and they may deny your originality and inner quest for truth. But there are others who will support and promote you who need to find. Knowing the rules of engagement in academic and research environments is essential, but following your dreams and convictions is also important in your path to success. Opening the door to students, trainees, and other colleagues will greatly enrich your journey. My work has become very collaborative across departments, institutions, and fields. I enjoy working with many colleagues and trainees from diverse backgrounds.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I have chosen to mentor women and underrepresented minorities during the past 25 years because I perceived the great need. Over time, I have witnessed a significant increase in women entering biomedical research who no longer feel excluded. We are still struggling with identifying talented physician-scientists from underrepresented backgrounds and fostering their leadership roles to create role models for all.

What do you most enjoy in your capacity as an academic or research leader?

I have witnessed the broadening and deepening of public and academic interest in integrative medicine and health. I was present at the



Figure 2. A tranquil autumn scene in Northern Idaho, where Professor Lavretsky finds respite and spiritual renewal. The image captures a rocky mountain stream bed with large volcanic boulders reflecting in still pools, framed by golden aspens and evergreen conifers against a backdrop of forested mountains and clear blue sky. This natural setting serves as a meditation and retreat space where she connects with nature between academic deadlines.

beginning of this movement when yoga or meditation was laughed at and frowned upon. I was told that I am interested in “weird things,” and my yoga studies were rejected by the Institutional Review Board (IRB) review. My research has been important in changing this perception and providing evidence for the broad use of mind-body interventions for neuropsychiatric disorders of aging and understanding the neurobiology of response. I am happy that this field is becoming more nuanced and complex. I also enjoy mentoring young scientists and trainees, some transitioning into leadership roles over time. I feel responsible for ensuring their success.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I have a peaceful cabin in Northern Idaho, a retreat to de-stress and find my center after stressful grant deadlines (see [Figure 2](#)). I like meditating, hiking, communing with nature, birds and animals, and swimming in lakes. I have two granddaughters and love to travel and spend time with them. I enjoy writing, playing piano, painting, and dancing; otherwise, I find joy through my work. Keeping our balance supports our bodies and minds. As I get older, I am also aware of the fleeting time and the need to enjoy all I can before it is all over.

Part 2: Helen Lavretsky – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Me, granddaughters, beach, swimming, dancing, sunset, great family dinners, the smell of tropical flowers, dolphins. Pure Joy. And peace.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**Which living person do you most admire?**

I have great admiration for President Jimmy Carter, who lived a long life with a great sense of purpose and integrity. Rosalynn Carter was his much admirable partner.

What is your greatest extravagance?

Massage and bodyworks- keeps me going.

What are you most proud of?

My vision for geriatric mental health and integrative psychiatry has come true through my efforts and ability to inspire others.

What is the quality you most admire in people?

Open-mindedness and open-heartedness.

What is the trait you most dislike in people?

Superficiality.

What do you consider the most overrated virtue?

Being a "team player." It does not guarantee anything.

What is your favorite intellectual activity?

Writing—grants, scientific papers, books, memoirs, and blogs. That is how I create my reality: first putting it on paper, then manifesting it into the "physical." I feel the rhythm of the words, and they flow through me; it becomes more like creating music.

Where would you most like to live?

My tastes have changed throughout my life. I was a "city girl" who needed yoga studios, Starbucks, shoe stores, and Opera. Now, I just crave peace and quiet in nature.

What is your most treasured possession?

My collection of rocks and crystals- I am very much into gemology and the spiritual nature of things.

When and where were you happiest? And why were so happy then?

I wanted to freeze time when my son was young, but I was too stressed out by my career/family imbalance and felt guilty all the time because my career demanded a lot of my time and attention away from raising my son. I am the happiest now when I do not have to struggle or climb that academic ladder with a vengeance. I still long for more balance in life and work, but my life is still defined by deadlines.

What is your current state of mind?

Calm, smiling at the chaos, curious about what the future will bring, hopeful for joy.

What is your most marked characteristic?

My self-determination, resilience, and persistence have been keys to my success.

Among your talents, which one gives you a competitive edge?

My intuition about selected research direction, my originality, and my ability to convince others to collaborate have given me a competitive edge in business.

What do you consider your greatest achievement?

Succeeding in the business of neuroscience of integrative medicine, when it was viewed as "fringe," and seeing it move to the popular topic in medical education and healthcare while feeling pride for participating in this shift.

If you could change one thing about yourself, what would it be?

The need to take care of others.

What do you most value in your friends?

Inspiration.

Who are your favorite writers?

Margaret Atwood and Agatha Christie both had an incredible literary longevity that kept everybody guessing.

Who is your hero of fiction?

Alice Kingsleigh (Alice in Wonderland) who kept following her heart, inquisitive mind, and the white rabbit.

Who are your heroes in real life?

Those who sacrifice their lives for the idea of freedom.

What aphorism or motto best encapsulates your life philosophy?

Shakespeare wrote: "To thine own self be true" (Hamlet, Act 1, Scene 3). My personal version is "Stay true to yourself and do what brings you joy." This has worked for me in my life, work, and mentoring others.

Los Angeles, California, USA

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INNOVATORS & IDEAS: RESEARCH LEADER

Carlos A. Zarate, Jr.: Using clinical translational neuroscience to develop the next generation of antidepressant treatments that act more rapidly and effectively

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Carlos A. Zarate, Jr., MD, spearheads transformative research in psychiatry and neuroscience. As a National Institutes of Health (NIH) Distinguished Investigator, he leads the Experimental Therapeutics and Pathophysiology Branch and the Section on the Neurobiology and Treatment of Mood Disorders at the National Institute of Mental Health (NIMH). His additional role as Clinical Professor of Psychiatry and Behavioral Sciences at George Washington University underscores his commitment to research and education. Dr. Zarate's pioneering work focuses on decoding the pathophysiology of treatment-resistant mood disorders and suicide while developing novel therapeutics that are reshaping approaches to patient care. His research integrates cutting-edge techniques from neuropsychopharmacology, electrophysiology, neuropsychology, neuroimaging, and genomics to forge new pathways in treating mood disorders. Perhaps most notably, Dr. Zarate's team has been instrumental in demonstrating that ketamine, an NMDA receptor antagonist, can produce rapid and long-lasting antidepressant and anti-suicidal effects. This discovery has catalyzed a paradigm shift in psychiatry, proving that antidepressant response within hours, not weeks, is achievable. Dr. Zarate's innovative approach extends beyond the lab. He employs a bi-directional translational strategy, seamlessly integrating clinical, behavioral, and imaging technologies with basic science collaborations. This holistic method has led to numerous breakthroughs in mood disorders research, addressing critical issues such as the speed and efficacy of current treatments. His exceptional contributions to the field have earned him numerous accolades, including election to the National Academy of Medicine in 2020. These honors recognize his research excellence, his innovative spirit, and his dedication to mentoring the next generation of scientists. We are privileged to feature Dr. Zarate in this Genomic Press interview. His insights promise to offer our readers a glimpse into the cutting edge of psychiatry and the tangible hope his work brings to millions suffering from mood disorders.

Part 1: Carlos A. Zarate, Jr. – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

Oddly enough, my professional journey began with tennis. During high school in Cordoba, Argentina, I gave tennis lessons to the chief of cardiovascular surgery at a private hospital. In return, he allowed me to observe cardiac surgeries and neurosurgeries. I spent all my summers in high school doing that and fell in love with neurosurgery, which led me to get interested in the brain. I went to medical school at the Catholic University of Cordoba, and after moving to the USA and completing the clinical part of my foreign medical exam, I was fortunate enough to be offered a psychiatry residency at the Massachusetts Mental Health Center/Brockton Veterans Administration Medical Center. There, I was inspired by some of



Figure 1. Carlos A. Zarate Jr, MD, National Institute of Mental Health, National Institutes of Health, USA.

the “legends of neurobiology and psychopharmacology” at the time, including Drs. Ming Tsuang, Robert McCarley, Alan Schatzberg, Alan Green, Carl Salzman, and Joe Schildkraut. I later solidified my interest in clinical psychopharmacology research under the influence and mentorship of Drs. Mauricio Tohen, Anthony Rothschild, Bruce Cohen, Jonathan Cole, and Ross Baldessarini at McLean Hospital.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

At McLean Hospital, I was allowed to create and develop the Experimental Psychopharmacology Clinic with Dr. Mauricio Tohen. During my fellowship, it became clear that despite the effective medications and psychotherapies at the time, many patients were unable to achieve complete





Figure 2. Dr. Carlos Zarate catching up on work while soaking in the views of the Sierras de Córdoba, Argentina. From his terrace vantage point, he overlooks Lake San Roque, its waters stretching out amidst the rolling hills. The Sierras, with their mix of lush and rugged terrain, offer a striking change of scenery from the clinical environment of NIH. This quiet corner of central Argentina, dotted with small towns and resorts, gives Dr. Zarate a moment of respite. Here, surrounded by nature, he finds space for reflection – a valuable asset for his innovative work in psychiatric research.

remission or recovery. For that reason, Dr. Tohen and I decided to pursue novel therapies with the goal of obtaining treatments that were significantly more efficacious than existing ones at the time. However, I could see that we were only making minor incremental progress with some of the new medicines we were testing in the clinic. I realized that I needed to pursue more rigorous neurobiology and neuropsychopharmacology training and research to approach the problem from that perspective. I was recruited to the National Institute of Mental Health (NIMH) in 2001, where I developed a neurobiology and experimental therapeutics program focused on tackling the challenge of developing novel and improved treatments for mood disorders, a program I continue to lead.

Please share with us what initially piqued your interest in your favorite research or professional focus area

From the beginning, the driving force underlying all my research efforts has been that most currently available antidepressant treatments require weeks to months to achieve their full effects, and many patients do not respond to them at all. When I began my clinical career, it was immediately apparent that this lack of rapid-acting, safe, and effective therapeutics was a major public health concern that prolonged suffering and led to adverse outcomes for our patients. During my fellowship at McLean Hospital, I was seeing literally hundreds of people with severe bipolar disorder, psychosis, schizophrenia, and schizoaffective disorder. While we could help patients with standard therapeutics, their quality of life and function was not excellent. The realization that we needed to come up with better treatments laid the groundwork for one of my most significant accomplishments: changing the way we study patients with severe mental disorders (both those with treatment-resistant depression and suicide ideation). Prior to the creation of our Branch at the NIMH in mid-2000, very little research had been conducted into experimental therapeutics and neurobiology for the seriously mentally ill for several reasons. These include the ethics of studying patients with severe depression in a drug-free state, the feasibility of studying biomarkers in a drug-free state (in order to better understand the neurobiology of disease and effects of the medicine under investigation), and the logistics of conducting proof-of-concept studies with experimental drugs in such patients. Envisioning, developing, instituting, and successfully and safely conducting such research has been the driving force of my career.

What impact do you hope to achieve in your field by focusing on specific research topics?

The ultimate goal of all my research efforts is to develop better and safer treatments for our patients and alleviate the suffering of millions of individuals worldwide with mood disorders. Globally, my work with ketamine has already had a clear, transformative impact on mental health, and I anticipate that my continued research into the mechanisms of ketamine and its metabolites will significantly increase our knowledge of the neurobiological targets involved in rapid antidepressant effects, the biomarkers that predict clinical improvement, and the neurobiology underlying the therapeutic response. To date, my paradigm-shifting research—especially with regard to the rapid antidepressant effects of ketamine—has already raised the bar for developing the next generation of faster-acting and more effective antidepressants.

Please tell us more about your current scholarly focal points within your chosen field of science

My lab conducts cutting-edge, high-risk, high-impact research in mood disorders and suicidal behaviors. Our proof-of-concept studies use novel compounds and neuroimaging, electrophysiology, and other central and peripheral biomarkers, and we collaborate across many disciplines to identify potentially relevant drug targets, biosignatures of treatment response, and treatments for mood disorders (major depressive disorder and bipolar disorder) and suicidal behavior. In the short term, we have recently begun a Phase 2 trial of the ketamine metabolite (2R,6R)-HNK, which is not an anesthetic agent, has no dissociative side effects, and no misuse potential.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

First, service. Those who know me know that service has always been an essential part of my personal and professional life, and I often think of my work to develop novel treatments for mood disorders as a public service. Second, gratitude. It is impossible not to reflect on my career without gratitude for the many opportunities I have been granted. Third, diversity. My overarching philosophy is that diversity is good for science. The term “diversity” is often used or misused, but I consider it to mean diversity of thought, scientific background, or opinion. We have made progress in this area, but more progress is needed.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers’ personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

It has become increasingly clear that collaboration is the secret to transformational science. As an example, the past few decades have seen concerted efforts by “Team Science”—universities, Government, private foundations, industry, and advocacy groups—to find and develop better treatments for patients with mood disorders. Multiple technologies, including genetics, proteomics, transcriptomics, optical genetics, induced pluripotent stem cells, and neuroimaging (to name a few), have been used to explore the pathophysiology of these disorders. I believe that in our interconnected world, cross-disciplinary and cross-organizational collaborations will be needed to advance the field significantly.

What do you most enjoy in your capacity as an academic or research leader?

The work is essential, but it is also fun to mentor trainees. I really enjoy seeing them progress through their careers from training to independence. The NIMH intramural research program allows for high-risk, innovative research that would be very hard to do outside of the intramural research program. It is both unique and rewarding and permits us to train and develop the next generation of investigators. Ultimately, they are the ones who will pave the way to full recovery or “cures” for our patients.



Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I am a big fan of sci-fi films, love to read, and enjoy spending time with my family.

Part 2: Carlos A. Zarate, Jr. – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Conceptually, I do not pursue perfect happiness. Instead, I view myself as continuously blessed with all the opportunities that have come my way. This allows me to continue to serve and enjoy what I have.

What is your greatest fear?

Not being able to serve or contribute in a meaningful way, not being able to help those who suffer.

Which living person do you most admire?

My wife, Silvina. She has an immensely rich life of faith, spirituality, and service. She keeps me grounded and helps me become a better person.

What is your greatest extravagance?

Everything that I do not need is an extravagance. I do not need material things; rather, I focus on the pleasure I get from seeing people smile, laugh, and do well.

What are you most proud of?

This question is difficult to answer. I tend not to feel pride, preferring to focus on my enormous sense of gratitude.

What is your greatest regret?

Not being able to do more for others.

What is the quality you most admire in people?

The quality I enjoy most in people is their uniqueness. Everyone has their own lives, career goals, passions, and ways of thinking—their creativity. I enjoy getting to know people and working together to tackle important problems.

What is the trait you most dislike in people?

I honestly try not to say or think that “I don’t like” or “hate” something. Instead, I like to think that there is something worth liking in everyone.

What do you consider the most overrated virtue?

Our virtues are special graces given to us; they are present in each of us to different degrees and make us unique individuals.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust’s answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust’s handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual’s inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your favorite occupation (or activity)?

There are many: reading, having conversations with and interacting with others, spending time with my family, eating asados, enjoying the beautiful views in las Sierras de Cordoba, Argentina (Figure 2), etc.

Where would you most like to live?

Exactly where I live now.

What is your most treasured possession?

I do not have a “treasured possession.” My family—including my wife and children—and my faith are the most important things in my life. They are not my possessions but what is most meaningful to me.

When and where were you happiest? And why were so happy then?

In general, I always feel content and at peace.

What is your current state of mind?

Calm and at peace.

What is your most marked characteristic?

I usually leave it to others to describe what they see. Perhaps it is my ability to stay calm and always make it clear to others that I am available to help.

Among your talents, which one(s) give(s) you a competitive edge?

Being able to see solutions to problems that others may not see and setting up systems to get the job done

What do you consider your greatest achievement?

Setting up the necessary systems and infrastructure (e.g., research methods and next-generation researchers) to investigate current and future problems in psychiatric research.

If you could change one thing about yourself, what would it be?

This is a work in progress. I like to think we continue to grow and change over time for the better.

What do you most value in your friends?

Loyalty, as well as being open to letting me know when they need help.

Who are your favorite writers?

The Bible. Edgar Allen Poe, Robert Frost, and many others.

Who are your heroes of fiction?

I enjoy fiction but do not consider those characters my heroes. Rather, I am interested in each character’s makeup and how they interact with each other to advance the story, deal with villains, and help those in need.

Who are your heroes in real life?

My wife Silvina and children Carolina, Diego, and Sofia – in other words, my family.

What aphorism or motto best encapsulates your life philosophy?

“I’m gonna have to science the shit out of this.”

Mark Watney (played by Matt Damon in *The Martian*).

Carlos A. Zarate, Jr.

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Raz Yirmiya: The inflammatory underpinning of depression

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Keywords: Depression, inflammation, microglia, cytokines, neurogenesis, antidepressants

Professor Raz Yirmiya stands at the forefront of research exploring how the immune system shapes mental health, leading the Laboratory for Psychoneuroimmunology at the Hebrew University of Jerusalem. His seminal discoveries transformed our understanding of depression's biological roots when he became the first scientist to demonstrate experimentally that inflammation triggers depressive symptoms. By developing sophisticated animal models and conducting careful human studies, he revealed how inflammatory challenges affect mood and cognition, illuminating entirely new perspectives on depression's underlying mechanisms. His research unveiled the essential role of brain inflammation and microglia cells in stress-induced depression, particularly documenting how interleukin-1 β and microglial dynamics influence both depressive symptoms and neurogenesis. This foundational work has become an extensive exploration of novel treatments, as Professor Yirmiya leads efforts to develop innovative antidepressants that target microglial function. Beyond his research breakthroughs, he has shaped the field through leadership roles, including serving as President of the Psychoneuroimmunology Research Society and associate editor of *Brain, Behavior, and Immunity*. In this Genomic Press Interview, Professor Yirmiya reflects on his scientific journey and shares insights illuminating the personal and professional dimensions of his quest to understand depression's biological foundations.

Part 1: Raz Yirmiya – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was dedicated to playing the piano in my youth and envisioned a future as a professional musician. After high school, I joined a military entertainment band and was fully immersed in music. However, tensions within the group led us to a week of intensive psychological group dynamics. Observing the profound impact of the psychologists leading our sessions, I was captivated by their work and decided to pursue a career in psychology. I began my undergraduate studies in Psychology and joined a special honors program, which paired each student with a personal mentor and immediate lab experience. My mentor was a psychobiologist, and soon after joining his lab, I experienced the thrill of seeing our hypotheses supported by experimental results. This hands-on experience sparked my passion for science, especially Psychobiology, and set me on an entirely new path. After graduation, I decided to deepen my understanding of biology, undertaking many basic courses in math, physics, chemistry, and biology before pursuing an MSc in Physiology. During this period, I worked with diverse animal models, from cockroaches to monkeys, studying the brain-behavior relationship in each. My admiration for the brain grew with every experiment, and I knew that neuroscience was my true calling. My graduate studies in the Neuroscience program at UCLA allowed me to learn from some of the leading scholars in the field, solidifying my fascination with



Figure 1. Raz Yirmiya, PhD, The Hebrew University of Jerusalem, Israel.

the brain and its connection to behavior and the multiple bi-directional interactions between the brain, behavior, and the body's physiological systems.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

After completing my PhD, I remained at UCLA as a Postdoctoral fellow for an additional two years, working in the laboratory of Professor John Liebeskind, an esteemed pain researcher who developed a profound interest in the new field of psychoneuroimmunology. During that period,





Prof. Libeskind, together with prominent psychiatry researchers at UCLA, including Prof. George Solomon and Prof. Herbert Weiner, and under the guidance of the journalist and scholar Mr. Norman Cousins, established the Cousins Center for Psychoneuroimmunology. I was honored to be among the first postdoctoral fellows at the Center, in which I began to identify myself as a “psychoneuroimmunologist” – a designation that has defined my career to this day. Following the postdoctoral training, I accepted an academic position in the Department of Psychology at the Hebrew University of Jerusalem. In the early 1990s, I attended the inaugural meeting of the Psychoneuroimmunology Research Society (PNIRS). That experience solidified my commitment to this field, and PNIRS has been my primary scientific community ever since. Over the years, I attended almost all of the society’s yearly meetings. I contributed to its success in many ways, including serving as its president and associate editor of *Brain, Behavior, and Immunity* journal. Within my university, I have held various administrative roles. However, I am incredibly proud that more than two decades ago, I had a leading role in establishing and directing the Inter-departmental Psychobiology Program—the first of its kind in Israel—which attracts some of the best students in psychology and life sciences each year.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

In 1990, when I established my laboratory as a beginning faculty member at the Hebrew University, my research interest, similarly to the entire field of psychoneuroimmunology at that time, was focused on the influence of brain and behavior on immune functioning and resistance to cancer. However, given that my position and laboratory were in the Department of Psychology, which in my university is located on a different campus than the Life and Medical Sciences faculties, I was unsure whether I could maintain a state-of-the-art immunology and experimental oncology laboratory. Just a year later, I participated in a scientific meeting in Jerusalem and was introduced to Prof. Robert Dantzer, who shared a preprint of a review paper in which he and his colleagues coined the term “sickness behavior” – referring to the nonspecific behavioral symptoms that accompany the immune response to infection. Immediately after reading this paper, I knew this was my most enjoyable and suitable research topic. I began by characterizing the components of sickness behavior following the administration of LPS (as a model for bacterial infection) or specific cytokines, particularly interleukin-1. While conducting these experiments, I realized that the symptoms of sickness behavior bear a resemblance to the diagnostic criteria of major depression, so I began to experimentally explore whether this similarity reflects a shared mechanism. In 1996, I published the first experimental evidence linking inflammation and depression, showing that LPS produces anhedonia in rats, reflected by significant suppression of the preference for a palatable saccharin solution, as well as reduced sexual, social, and exploratory activities, which are naturally rewarding for rodents. Further reinforcing the putative mechanistic link between sickness behavior and depression, I found that chronic (but not acute) prophylactic treatment with antidepressant drugs prevented LPS-induced anhedonia and related depressive-like symptoms. Soon after this publication, I initiated studies to extrapolate and validate these findings in humans by investigating the effects of inflammatory challenges, such as vaccination or LPS administration, on mood and cognitive functioning in healthy human volunteers. For example, in a randomized, double-blind, cross-over study, we found that following LPS administration, subjects experienced a transient pronounced increase in symptoms of depressed mood and anxiety, as well as impairments in memory function. Crucially, these affective and cognitive disruptions were significantly correlated with the LPS-induced elevations in inflammatory cytokine levels. These experiments piqued my interest in the inflammation-depression nexus, which remains my favorite research focus area three decades later.

Please tell us more about your current scholarly focal points within your chosen field of science.

Most depressed patients do not have any overt inflammatory disease. However, we and others found that exposure to stress, which is the most

significant trigger of depression in humans and animals, also activates inflammatory processes, particularly in the brain. Specifically, we discovered that unpredictable chronic stress elevates the levels of the cytokine interleukin-1 (IL-1) in the brain of rodents, and this elevation plays a causal role in the development of depressive-like symptoms. The finding that brain IL-1-associated depression was accompanied by activation of microglia cells, the brain’s resident immune cells, led us to hypothesize that microglial activation may be the source of stress-induced IL-1 production and, therefore, the mechanism underlying depressive symptomatology in this model. Surprisingly, our early experiments revealed that prolonged chronic stress led to reduced density and degeneration of microglia instead of the expected activation. In subsequent experiments, we discovered that the effects of repeated stress exposure are dynamic, including an initial IL-1-mediated activation phase of these cells, followed by a period of apoptosis and decline. Our studies revealed that early intervention with anti-inflammatory treatments can prevent these changes and the onset of depressive-like behaviors. However, these treatments are less effective once microglia degeneration has set in. This insight has shifted my focus towards understanding how compounds that stimulate microglial activation following prolonged stress might have antidepressant effects, potentially through enhancing hippocampal neurogenesis—a key action mechanism of many antidepressants. We are particularly interested in modulating immune/microglial checkpoint mechanisms in depression. Specifically, our findings indicate that chronic stress induces the expression of several microglia checkpoint receptors, including lymphocyte-activation gene-3 (LAG3), which may be involved in the microglia decline and associated depressive-like symptoms. Indeed, blocking LAG3, whether by electroconvulsive therapy (ECT) or specific antibodies, shows significant antidepressant effects. Similarly, we are examining the role of CX3CR1, another checkpoint receptor expressed exclusively by microglia, in stress resilience and depression. In another project, we use a chemogenetic approach to identify the specific neurons in various brain regions that generate inflammation-induced depressive-like symptoms and to examine the interactions between the neurons and microglia in their vicinity.

What impact do you hope to achieve in your field by focusing on specific research topics?

My overarching aim is to harness the extensive knowledge from my research and others to accelerate the development of novel antidepressant therapeutics targeting inflammatory processes. Recognizing that both the activation and suppression of the immune system, particularly microglia, can precipitate depressive symptoms, it is clear that a universal treatment approach is insufficient. Therefore, I advocate for a shift towards personalized medicine in treating depression. This tailored approach would commence with a thorough diagnostic assessment of a patient’s inflammatory profile, followed by individualized treatment plans designed to modulate the immune and microglial responses through targeted therapies. Recently, we have identified and patented several innovative microglial modulators. For conditions characterized by microglia suppression and degeneration, we are developing therapeutic strategies involving microglia stimulants, such as M-CSF and GM-CSF, and exploring the potential of microglial checkpoint inhibitors, including anti-LAG-3 and anti-CX3CR1 antibodies, as antidepressants. Additionally, we developed several formulations of cannabinoids, flavonoids, and NSAIDs aimed at treating depression linked to microglial activation. By focusing on these specific areas, I hope to pioneer advancements that improve the treatment of specific symptoms and pave the way for more precise and effective management of depression, shifting the clinical paradigm towards customized therapeutic interventions.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

A fundamental habit I developed during my academic and postdoctoral training and steadfastly maintained in my research environment is the meticulous effort to prevent my initial hypotheses from biasing the experimental design, data analyses, or interpretation of results. The risk



of unconscious bias is significant and can divert research into unproductive directions. Some of my key discoveries have emerged from results that contradicted my original hypotheses. For instance, it was unexpected to find that prolonged stress exposure can lead to exhaustion and degeneration of microglia rather than their activation. Another core value I uphold is the openness to alternative interpretations of data, actively seeking out evidence that might contradict my initial assumptions. The following is a pertinent example of this value's benefit. After finding that prolonged chronic stress leads to microglial degeneration, I told my student, Tirzah Kreisel, that maybe we should try to treat the "depressive-like" mice with a microglial stimulator, such as LPS. Tirzah paused momentarily and said, "But we already did such an experiment." She went to her office and fetched the results of an experiment we ran more than a year earlier, hypothesizing that the depressive-like responsiveness to LPS will be greater in stress-exposed animals. However, we abandoned this research project because the results contradicted our hypothesis. Following the new insight from the microglia study, we replicated this experiment, finding that LPS produces opposite effects: In normal, non-stressed animals, it produces a depressive-like condition accompanied by microglia activation and neurogenesis suppression, whereas, in chronically stressed animals (with suppressed microglia activation status), LPS paradoxically produces antidepressant and neurogenesis-promoting effects. This example emphasizes the importance of diligently revisiting and reconsidering data, especially when it challenges our expectations. Embracing this approach has not only prevented potential misdirection in my research but has also led to groundbreaking discoveries that could redefine therapeutic strategies

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

Depression is a universal condition affecting diverse populations across all cultures and regions. However, cultural, gender, socioeconomic, and other demographic factors significantly influence both the prevalence and severity of depression. These factors can also shape how inflammatory processes contribute to the development and maintenance of this condition. For example, in one of our early studies, we discovered that active vaccination led to depressive symptoms predominantly among participants from lower socioeconomic backgrounds. Despite this diversity in susceptibility, the majority of research in this area predominantly involves participants from the Western world, typically with an overrepresentation of males, individuals of white ethnicity, and those with good access to medical services.

Additionally, experimental studies in animal models of depression often utilize only male subjects. Future studies should broaden their demographic scope to include more women and participants from varied cultural and socioeconomic backgrounds to ensure that findings are truly representative and applicable universally. Addressing these disparities will not only enrich the scientific understanding of depression but also enhance the development of targeted, effective interventions. I hope to see this transformative scrutiny in the scientific community, ensuring that research endeavors are as diverse as the populations they aim to serve.

What do you most enjoy in your capacity as an academic or research leader?

In my role as an academic leader, two aspects are gratifying. First is the exhilarating moment of analyzing new experimental data and realizing that it reveals a genuinely novel and fundamental scientific truth – one that, at that moment, is known only to me. Such moments have been rare throughout my career, but the euphoria and excitement they bring are profound and enduring. They fuel my enthusiasm and motivation, sustaining my dedication to research. The second aspect I cherish is witnessing the academic growth of my students. The journey is deeply fulfilling, from their early days as research assistants to their evolution into independent

researchers with impressive academic careers. I have been privileged to mentor many outstanding students, and it brings me immense joy and pride to know that the foundational skills and knowledge they acquired in my laboratory have empowered them to excel in the academic world. This ongoing legacy of learning and discovery is what I value most as a mentor and leader.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Outside of my professional life, I cherish the time spent with my family. My wife, Nurit, and I enjoy frequent gatherings with our wonderful four children, their spouses, and our three adorable granddaughters. It is fulfilling to follow and support my children's stellar career trajectories, offering advice and resources that help them professionally and personally flourish. Nurit and I are fortunate to be part of a close-knit group of friends we consider our 'family by choice.' Over three decades, we have met at least weekly, celebrating holidays and special occasions together, embarking on domestic and international travels, and facing life challenges and sorrows. These enduring friendships are a cornerstone of our social life, offering immense joy and support. My passion for music remains a significant part of who I am. As a pretty good amateur pianist who once played semi-professionally, I cherish this form of expression, although I hardly found time to practice in the past few decades. I am excited about dedicating more time to my musical pursuits, exploring new compositions, and collaborating with other musicians.

Part 2: Raz Yirmiya – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

For me, perfect happiness is the profound sense of fulfillment that comes from knowing my actions have positively impacted my life and those of my family, friends, and the broader society. This kind of happiness often requires substantial time and effort, but precisely, this investment brings deep meaning, contentment, and satisfaction to my existence. The interconnectedness of my efforts with my well-being and the welfare of others is what truly defines perfect happiness for me.

What is your greatest fear?

My greatest fear is the prospect of becoming incapacitated, disabled, and dependent on others. Throughout my life, I have always strived to excel in almost everything I undertake, sometimes even avoiding activities where I felt less adept. This drive stems from a deep-seated aversion to feeling helpless or pitiable. As I contemplate the aging process, the idea of losing my independence and becoming reliant on others is particularly daunting. However, this fear also serves a constructive purpose—it motivates me to maintain excellent physical fitness and to lead a well-balanced life that integrates work and leisure. This proactive approach alleviates my fears and enhances my overall well-being, ensuring I can live fully for as long as possible.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



Figure 2. Raz and Nurit Yirmiia explore Antarctica's stunning seascape aboard an expedition boat, with sea ice and their cruise ship visible in the misty background. The image captures a moment from their unforgettable polar expedition, which they shared with a group of good friends, set against the pristine backdrop of floating ice sheets and clear blue Antarctic skies.

Which living person do you most admire?

One living person I greatly admire is Richard Dawkins, a distinguished evolutionary biologist and author. His seminal scientific works profoundly contributed to the theory of genetic evolution via natural selection, a cornerstone of biology and our understanding of life. Beyond his scientific contributions, Dawkins is a vocal advocate for science and reason, consistently challenging religious dogma and fanaticism. His ability to articulate complex ideas with clarity has not only popularized scientific thought but also fostered broader public engagement and critical discourse on the essential role of science in society.

What is your greatest extravagance?

My greatest extravagance is my love for travel. Over the years, I've had the privilege of visiting nearly half of the world's countries, exploring every continent, including unique and exotic locales such as Lapland, Patagonia,

French Polynesia, and Antarctica, as well as countless islands across the Oceans and the Mediterranean Sea. This passion for exploration has been a perfect leisure activity, but it also serves as a profound source of inspiration and learning that enriches my understanding of the world.

What are you most proud of?

I am most proud of my four children, who have grown into kind, responsible, and conscientious individuals. They are incredibly bright and highly successful in their respective endeavors, embodying qualities that any parent would be proud of. I also take great pride in the achievements of the students who have graduated from my laboratory, most of whom have become leading scientists at respected academic and medical institutions. Beyond my family and mentees, my professional contribution to understanding the biological basis of depression is a source of great pride. It is immensely gratifying to know that my work has been



instrumental in paving the way for developing novel and effective antidepressants based on immune-modulating compounds, particularly for those who do not benefit from current therapeutics.

What is your greatest regret?

My greatest regrets were the periods during my career when I diverged from my primary research focus on the inflammation-depression nexus to explore other interesting but unrelated topics. These explorations included studies on the effects of alcohol, cannabis, and cannabinoids on brain-behavior-immune interactions and the role of inflammatory processes in Alzheimer's disease. While these diversions were intellectually fulfilling and broadened my understanding of related fields, I sometimes reflect that maintaining a more singular focus on depression and inflammation could have accelerated my progress toward developing much-needed therapeutic solutions for depressed patients.

What is the quality you most admire in people?

Generosity and kindness.

What is the trait you most dislike in people?

Violence and cruelty.

What do you consider the most overrated virtue?

While industriousness is often celebrated as a key driver of success and productivity, it can sometimes be overrated, especially when it leads to work overshadowing other essential aspects of life. In academic life, the emphasis on being perpetually active can discourage creativity and strategic thinking, which require time for reflection and rest. Therefore, while industriousness is valuable, it is crucial to balance it with periods of rest and rejuvenation to maintain long-term productivity and well-being.

What are your favorite activities?

Playing the piano and cycling.

Where would you most like to live?

I love my home. I would not like to live anywhere else.

What is your most treasured possession?

My most treasured possessions are not material but define my deep connections with my family and friends. My loving relationships with my wife, children, and granddaughters are irreplaceable and provide me with immense joy and support. Similarly, my decades-long comradeship, characterized by deep bonds with a close group of friends, is something I hold very dear. These relationships enrich my life far beyond what any physical object could, underscoring the belief that loving and supportive connections are the most valuable possessions one can have.

When and where were you happiest? And why were so happy then?

Reflecting on my life, I realize I have been the happiest since the beginning of my sixth decade. After navigating numerous challenges in my childhood, adolescence, and early adulthood—each challenging for different reasons—it was during these later years that all aspects of my life began to stabilize and flourish. Personally, professionally, financially, and socially, I found a harmonious balance that has progressively increased my happiness. This period of stability and contentment continues to deepen with time, so I am at the peak of my well-being.

What is your current state of mind?

Currently, I am in a state of mixed emotions. I am content and fulfilled, grateful for the happiness and joy in my life. However, deep concerns about my country's ongoing political and social challenges overshadow my sense of peace. The threat of moving towards an autocratic system with fascist and ultra-religious characteristics is particularly alarming. Despite these troubles, I remain hopeful that reason and moderation will prevail and that we will return to a more balanced and democratic governance.

What is your most marked characteristic?

My most marked characteristic is commitment. This dedication permeates all aspects of my life—from my family and friends to my students and scientific work. I am deeply committed to the welfare and success of those around me, as well as to advancing our understanding and application of science for the betterment of society. This steadfast commitment drives me to consistently strive for excellence and support others in achieving their goals.

Among your talents, which one(s) give(s) you a competitive edge?

My competitive edge in my field stems primarily from my ability to synthesize diverse knowledge—facts and concepts—into a cohesive and comprehensive understanding of the subjects I explore. This capability allows me to develop a panoramic view of complex scientific landscapes, enabling breakthrough insights and innovations. My willingness to embrace data contradicting prevailing dogmas and even my initial hypotheses is also crucial. This openness fuels my scientific creativity and fosters significant advancements in my research.

What do you consider your greatest achievement?

My most outstanding achievement is undoubtedly my groundbreaking work demonstrating the causal role of inflammation in depression through a series of pivotal studies. My initial research, published in *Brain Research* in 1996, was the first to show that an inflammatory challenge, namely lipopolysaccharide (LPS), could induce a depressive-like episode in rats. This study laid the foundation for the LPS model of depression, which has significantly influenced the field by providing a reliable method to investigate the pathophysiology of depression related to immune system dysfunction. Furthering this line of inquiry, my team and I published the first study on LPS-induced cytokine-dependent depressed mood in humans in the *Archives of General Psychiatry* in 2001. These foundational studies have since inspired over 700 subsequent research papers utilizing the LPS model of depression, significantly advancing our understanding of the biology of this disease. My subsequent research, including pivotal publications in *Molecular Psychiatry* in 2008, 2014, and 2022, pioneered exploring and establishing the critical roles of interleukin-1 in the brain and dynamic microglial alterations in chronic stress-induced depressive-like states. These contributions have not only enriched our understanding of depression but have also opened new avenues for the development of novel antidepressant therapeutic interventions based on the modulation of inflammation processes.

If you could change one thing about yourself, what would it be?

If I could change one aspect of myself, it would be my tendency toward perfectionism. While striving to excel in every activity I undertake has its merits, it often comes with relentless pressure that can be exhausting. I wish to cultivate a more lenient and forgiving attitude towards myself, balancing pursuing excellence with a healthier acceptance of imperfection.

What do you most value in your friends?

Loyalty, integrity, trustworthiness, supportive, and unjudgmental attitude.

Who are your favorite writers?

Mario Vargas Llosa, José Saramago, David Grossman, and A. B. Yehoshua.

Who are your heroes of fiction?

One of my fiction heroes is Henri Charrière's character Papillon from the autobiographical novel *Papillon*. This character embodies resilience, resourcefulness, and an indomitable will to regain his freedom against overwhelming odds. Papillon's journey is a tale of physical survival and a profound narrative of the quest for justice and the refusal to be broken by unjust circumstances. His story inspires hope and a steadfast belief in the strength of the human spirit and one's ability to overcome adversity.

**Who are your heroes in real life?**

My real-life heroes are the leaders and activists who courageously oppose tyranny and autocracy globally and within my country.

What aphorism or motto best encapsulates your life philosophy?

You will never be sorry for investing too much time and effort in your family, friends, and your own body

*Jerusalem, Israel
12 December 2024*

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Neural mechanisms of cognitive generalization across species: From hippocampus to cortex

Zhenzhen Quan¹, Da Song¹, and Hong Qing^{1,2}

How do brains take what they have learned and apply it to new situations? This fundamental question sits at the core of cognitive generalization—a crucial ability that allows organisms to adapt to novel circumstances by drawing on prior experiences. While this mental flexibility enhances survival across species, the underlying neural mechanisms connecting different brain regions in rodents, primates, and humans remain poorly understood. Our review maps these neural pathways of generalization from hippocampus to cortex across the evolutionary spectrum. We show how hippocampal remapping and replay processes create abstract rules during generalization, with different hippocampal subregions handling distinct memory types. The prefrontal cortex emerges as essential for rule-based categorization across all species studied, while the orbitofrontal cortex drives value-based decision-making, and the posterior parietal cortex guides generalization through perceptual processing of past experiences. We explore the neural circuitry connecting these regions and examine how similar these brain structures and their associated behaviors are across species. Additionally, we discuss how disruptions to cognitive generalization manifest in various neurological conditions and their corresponding brain regions. This comprehensive analysis not only clarifies the neural foundations of cognitive generalization but also suggests promising directions for interventions targeting related neurological disorders.

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Introduction

Experience is the best teacher of life. The ability of fast adapting from past experiences to novel circumstances is required for survival and better living in animals and humans. Generalization is the presentation of adaptive performance which requires the abstraction of common rules or concept or pattern features from learned tasks of specific behaviors and then that be transferred and applied to similar but novel circumstances. The process of generalization can be basically divided into three steps: firstly, individual experience of an event, situation or a task is obtained; secondly, the event, situation or task should be abstracted as a concept or a rule; thirdly, the abstracted concept or rule is employed into subsequent similar events or tasks. Taking a simple example, once a man has learned a skill from a specific sport game badminton, he could quickly get the skills of how to play a similar sport game tennis. During this process, the memory information of playing badminton has been abstracted as a common feature or rule that can be generalized to the learning process of playing tennis. Generalization enables the identification of commonalities and relationships among diverse events, objects, and actions via semantic learning, concept learning, category abstraction, structure learning, and etc., thus being applicable in diverse high intelligent behaviors, such as, perception, learning and decision-making, and future planning (1).

Identification of common features or rules is the most prominent step for generalization. This is based on the comparison and interactions among memories from different tasks, which is also supported by the geometry of abstraction (2). Abstract rule is different from concrete rules; concrete rule is based on simple spatiotemporal links between objects, events, and actions, while abstract rules are complicated, applied to multiple circumstances, and generalized from past to novel circumstances (1, 2). For a particular abstract rule, the core of the rule is rigid and does not change with environmental factors.

Transfer is another key step of generalization that the abstracted rules or structural knowledge between elements are transferred rather than knowledge of the individual elements themselves. This is thought to be critically dependent on the instability of memory, which is helpful for transferring (3). Transfer of structural knowledge in spatial and nonspatial tasks both can improve efficiency. Memories, or the neurons that carry them, show variability in response to changes in the environment under the guidance of abstract rules. This shows the mutual unity of the transferred structure and the abstract structure in representing generalized behavior. One situation can be abstracted into a structure, which maps to a new and similar situation with different sensory input. The solution is inferred with a shorten process. This phenomenon can be explained by psychology as “the formation of learning sets” (4).

According to these two important properties of generalization, there are two types of neural populations with opposite characteristics that cooperate to support generalization. A single neuron showing stable firing pattern or neural ensembles converging onto a low-dimensional feature for representing the common structure that supports generalized cognitive operation. On the other hand, there also exists neurons with flexible property, which would change their activity pattern to cope with variable external factors. This change is directional, not random, which is followed by the main process for characterizing common features of tasks.

Regarding the limited study of generalization but its importance for adaption and survival, in this review, we focus on reviewing the neural mechanism of generalization of spatial and nonspatial representations in different cortical and subcortical brain regions, including hippocampus, prefrontal cortex (PFC), orbitofrontal cortex (OFC), and posterior parietal cortex (PPC) from rodents to primates and humans, which will explicit a brief frame for the neural manipulation of generalization from hippocampus to cortex and provide cues for revealing the circuitry connections among these brain regions in modulation of the cognitive generalization.

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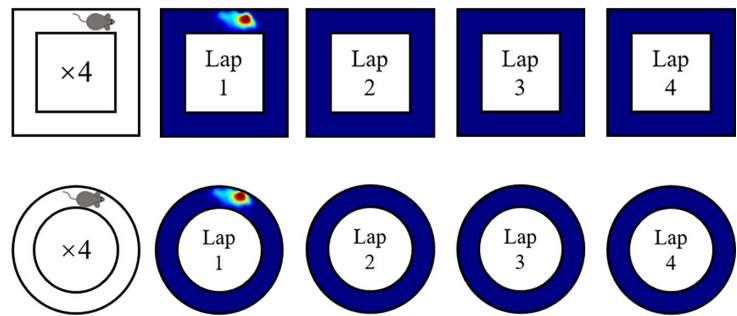
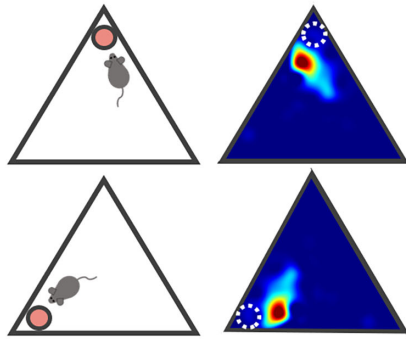
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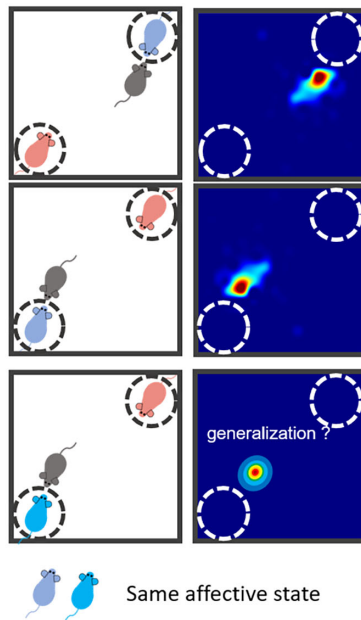




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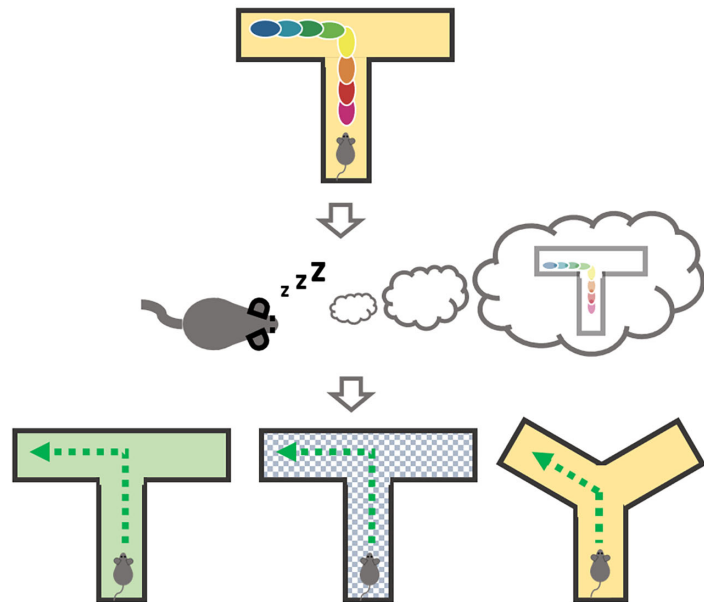


Figure 1. Hippocampal remapping and replay in cognitive generalization. (A) Left: Hippocampal neurons show remapping activities to represent the altered spatial stimulus; Right: In this article (70), the event-specific rate remapping neurons support transfer learning on two geometrically distinct mazes, from square maze to circular maze. (B) In this article (60), hippocampal CA2 neurons show remapping activity to same mice with changed locations. While it needs to be further explored whether CA2 cells also remap to another mouse with same state compared with the previous one. C, Hippocampal neural replay guides mice to accomplish the similar tasks with different contexts. The replay activity occurs during sleep and awake state.

Hippocampal Replay and Remapping Underlie Generalization

Hippocampus encodes spatial information, which links sensory features to context. It is well established that hippocampus contains place cells which store memories of specific locations. Hippocampal place cells exhibit maximal firing especially when a specific spatial place field is occupied, which is not responding to simple sensory stimulus or specific motor behaviors (5, 6). Each place cell is considered to possess individual place fields and correspondingly each location is encoded by a particular cluster of place cells, thus leading to a comprehensive mapping of an environment in hippocampus (7). Hippocampus not only encodes spatial information, but also maps nonspatial dimension. It is shown that hippocampus supports general cognitive processes (8) and bilateral hippocampus support generalization of gradual internal learning (9). Hippocampus has been found to selectively fire or cease to fire when mouse perceives nests or beds, suggests that hippocampal neurons have the ability to extract fundamental features and commonalities from various episodic experiences and to then generalize them into abstract concepts and knowledge from behavioral experiences (10). Hippocampal neurons have also been reported to response to visual (11), auditory (12), and olfactory cues (13, 14) or combinations of those. When hippocampus encodes both nonspatial

and spatial features of an experience, a complex and highly organized ensemble is introduced to build a schematic framework for multiple related memory elements (15). During mapping the environment through spatial and nonspatial information, the neurons in hippocampus that encode spatial and sensory representations show characteristics of replay and remapping, which may play crucial roles in generalization (Figure 1).

Hippocampal Replay During Sharp-wave Ripples Retrieves Experience to Future Decisions

Replay is the sequential reactivation of hippocampal place cells that represent previously experienced behavioral trajectories, which is considered as a crucial characteristic of hippocampus processing, storing, and updating of event memories. Early in 1989, Pavlides and Winson firstly reported the replay phenomenon and observed that place cells elicit higher firing rates and increased bursting during non-rapid eye movement and rapid eye movement (REM) sleep, which is considered as an important form of memory processing (16). Later study found pairs of cells whose place fields overlapped during behavior tended to fire together during subsequent sleep, which is defined based on the presence of hippocampal sharp-wave ripples (SWRs) (17). The sequential firing patterns of



hippocampal place cells for cognitive representation in spatial navigation that encodes previously experienced behavioral trajectories can be replayed in a temporally time-compressed format of either forward or reverse sequence during non-REM sleep state and during awake state, especially in a transient halt period (16–18). Hippocampal circuit could also replay random trajectories of former cognitive map, which has potential to generate future behavioral outcome, especially generalization (19). It has supposed that generalization and structural learning may partially depends on hippocampal replay, which is crucial for extracting task rule from awake experience during replay initiation (20, 21).

It is widely accepted that sleep replay is linked to memory consolidation (17, 22). Learned memory reactivation during sleep could be integrated into former cognitive schema (23). Daytime naps facilitate generalization of concept learning both in infants and adults in human studies (24–26). Neural recording experiments suggest hippocampal replay during SWRs may act roles in past experience consolidation and future plan (27, 28). Especially, replay during sleep SWRs show potential to reorganize the spatial representations and iconic events of previous memory, which suggests that multiple experiences are integrated during sleep SWRs to support the form of generalization (29, 30). Through downsampling and compression, the hippocampal replay representation is effective in integrating knowledge, helping to generalize to a level similar to the exact veridical replay of experience that improves generalization performance. Therefore, it represents a feasible and efficient memory consolidation solution without compromising effectiveness (31). Feedback blockade of SWRs during a learning process prevents integration spatial path optimization, demonstrating the necessity of replay for generalization (32).

Awake replay during immobility might represent neuronal trajectories of either current environment or previously experienced environment and is associated with the processes with ongoing memory-guided preparatory behavior, such as foraging, exploratory, goal-directed or planning behaviors (18, 33, 34). Studies have suggested awake replay is important for memory-guided behavior and cognition (33, 34). Different from replay in sharp waves during SWS, replay in awake state occurs immediately after spatial experiences in a temporally reversed order, that allows immediate evaluation of the preceding events in precise temporal association with a current event, which maybe considered as an integral mechanism for learning from recent experiences (35). It is recently reported that awake replay is mainly dominated in past experiences of locations with a reliably delivered reward and those not recently been visited, suggesting the contribution of memory-related processes by awake replay is due to its role in memory storage rather than in directly guiding subsequent behaviors (36).

Awake SWRs occurred in hippocampal replay of past experiences, which are able to predict choice of correct trials than error trials in memory-guided decision-making (37). Hippocampal replay in awake state contributes to decision-making especially during spatial navigation (37, 38). Awake SWRs are suggested to support rearrangement of stored information with novel combinations, in order to reactivate new firing pattern for future decision-making. The replay in SWRs can preferentially occurs in rarely experienced trajectories, to maintain integrity of cognitive map or as a prereplay for prospective events (39). While the contrary finding indicates that hippocampal replay shows specific past experiences, not a plan of future choice (36). And it is reported that there were no trial-by-trial relationships between replay content and subsequent behavioral trajectory (32, 40), suggesting that replay would not affect subsequent behavior. The controversial conclusion may be caused by different memory types of tasks. Trajectory replay of hippocampal CA1 in reference memory tasks is proposed to predict future decision goals. On the contrary, the trajectory replay in working memory only exhibits previous goal arms (41). Nevertheless, replay could still facilitate the long-term consolidation, integration, and maintenance of particular experiences as a storage role, preparing for future tasks served in generalization.

Moreover, in human study with functional MRI (fMRI), hippocampal replay reflects the order of previous task-state sequences, building representations of complex and abstract tasks (42). And replay in human hippocampus prefers weakly learned information and predicts subse-

quent memory performance (38). Through magnetoencephalography to measure fast spontaneous sequences of representations, Liu *et.al.* proposed that an abstract replay is a mechanism for generalizing structural knowledge to new experiences. Through replay, not only are the experienced subtrajectories connected, but also the sequence in the new order by abstract structural knowledge can be rebuilt (21). Recent researches have shown that SWRs in hippocampus act as potential functional biomarkers of memory impairment in neurodegenerative diseases, especially in Alzheimer's disease (AD) (43–46). It is reasonable to assume that the replay ability might be decreased in AD mice that could not be applied to represent replay information to guide subsequent tasks for generalization.

Hippocampal Subregional Remapping in Spatial and Nonspatial Aspects Adapts to New Environment

In reality, it is comprised of multiple modalities of sensory features that special spatial information is encoded by each modality for navigation, thus leading a combination of sensory and abstract reference frames in brain maps (47). Under multisensory environments, hippocampal place cells can reorganize their population representations in response to the changing factors of environmental geometric (48) or nongeometric cues (odor, color, and etc.) (47, 49), the process of which is well known as “place field remapping” or simply “remapping” (50). Remapping often occurs by changes of sensory inputs (51), motivational state (52), and other inputs from outside environments. Intensive studies have classified remapping into several types, including “global remapping,” “null remapping,” “partial remapping,” “rate remapping,” and even “graded remapping” in an attempt to distinguish different mnemonic conditions (7, 53–55). The remapping of hippocampal cognitive map driven by experience encodes location through spatial and nonspatial dimensions to predict and estimate new environment (56). The working pattern of hippocampal remapping makes it with great potential to abstract events into putative concepts or rules, promoting transfer learning.

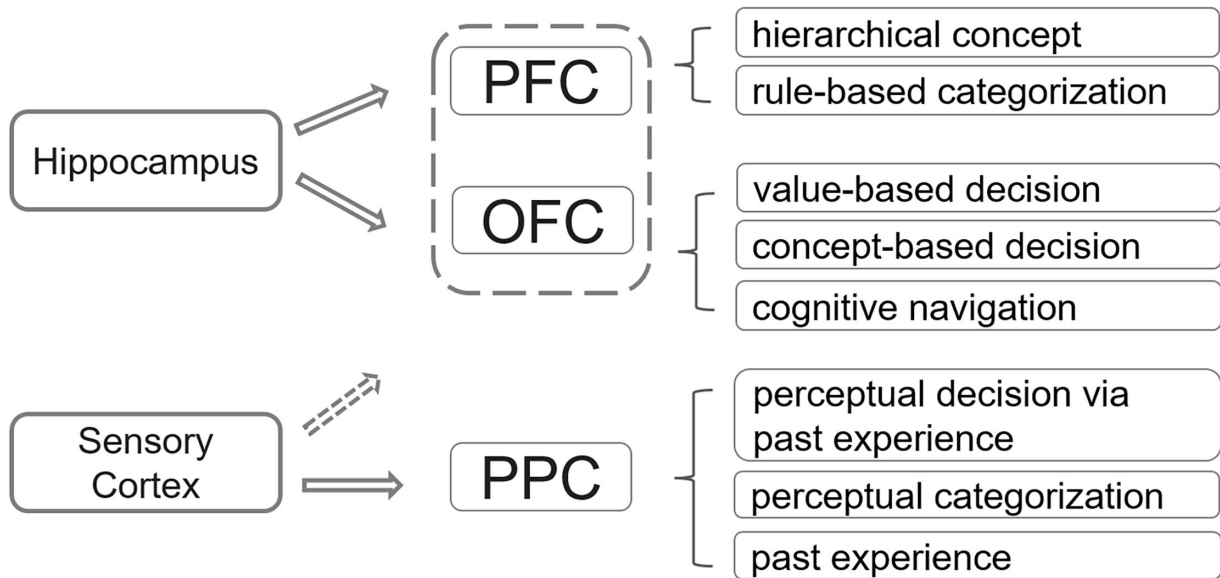
Numerous studies have reported all the hippocampal subregions, including CA1, CA2, CA3 and dentate gyrus, possess place cells that encode place fields in navigation. When encoding experiences in new environments, hippocampal neurons show heterogeneity that CA1 place cells fire faster than CA3, while CA1 place cells gradually shift backward with experience and remap when under re-expose to the environment one day later. Oppositely, CA3 place cells fire gradually but display less backward and more reliable trial-to-trial and day to day dynamics (57). CA3/DG remapping show stronger episodic associative information, which reflects the sight effects of episodic learning (58). CA2 place cells exhibit different activity patterns from those of CA1 and CA3 that their firing rates change over time even in the same environment and do not persistently code for space or contexts (59). CA2 neurons remap to social stimulus, termed social-remapping cells, indicating the preferential reactivation of CA2 neurons encodes social representations following social experience and may act a role in social memory generalization (60). It is interesting but unknown whether CA2 neurons have potential in remapping to abstract emotional states for reorganizing social subjects (61, 62).

Under different circumstances, hippocampal firing has been verified to contain both stable encoding (63) and transient programming (64). For hippocampus and its related circuits, upstream brain regions (like CA1-projecting CA3 neuronal ensembles or CA1-projecting MEC neuronal ensembles) tend to show reproducible firing patterns and structural representations, which lead downstream CA1 neurons remapping in a directional manner to support the generalization of transitive structure (65, 66). This indicates that remapping of hippocampal place cells is thought to play a crucial role in learning generalization. Therefore, this combined stability and flexibility leads hippocampal circuits to encode both external fixed circumstance and draw cognitive maps with change environment of related experiences. Firing fields of hippocampus could be generalized with progress through behavior, which could be useful for linking events in episodic memory and for planning future actions (67).

Hippocampal CA1 neurons exhibited nonspatial event-specific elevated firing activities by transient theta sequence, which can be flexibly



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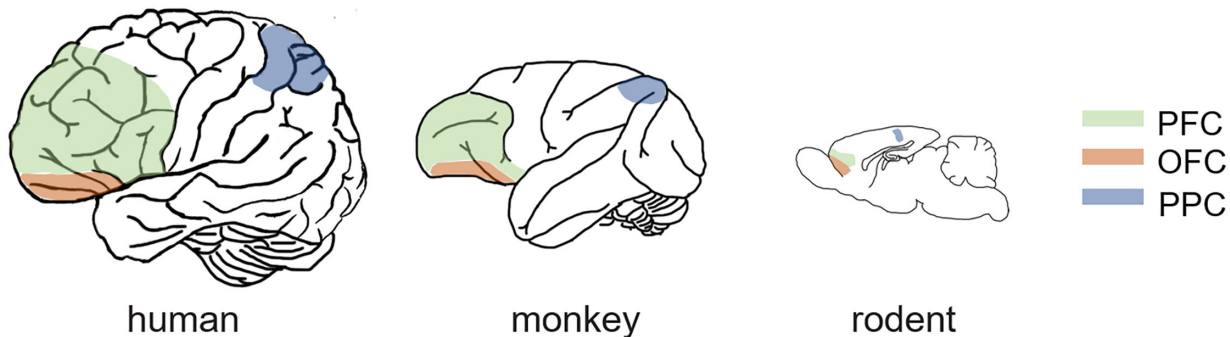


Figure 2. Neural circuits associated with three cortical regions in cognitive generalization with different manifestations from different species. (A) Emotion-related brain regions mainly project to PFC and OFC; Sensory-related brain regions mainly project to PPC. (B) PFC, OFC, and PPC show similar brain area distributions from humans, monkeys to rodents.

reorganized (68). Through a tilted and rotated rectangular track experiment, CA1 place cells are shown to be sensitive to three-dimensional orientations that a majority of place cells change their place fields unpredictably, leading a partial remapping; while a minority kept the same field in x-y coordinates of the track, neglecting z-axis. Reorganization and reactivation of hippocampal assemblies with SWRs represent the formation and expression of new spatial memory traces, suggesting the generalization potential (69). Sun *et al.* found a specific kind of neurons in hippocampal CA1 that encode generalized information from a designed task instead of precise sensory information. The neurons, called event-specific rate remapping cells, show lap-specific activity in a square maze composed of four indistinguishable lap events with a reward only on lap 1. This kind of activity can transfer from square maze to rectangle, circular and even nonspatial factor changed maze, which suggests the hippocampal CA1 activity pattern not only reflect events but also generalize these events as rule experiences (70). A certain population of hippocampal CA1 place cells has also been reported to present environment orientation and topology. The orientation selectivity is contributed by a redistribution of place cells remapping, which indicates that the prior experience generalization improves predictability of future environmental representations (71).

Hippocampal neurons in primate study encode position within an abstract value space and construct a map for an abstract cognitive variable through place like representations (72). In human study through fMRI, hippocampal remapping and entorhinal grid realignment predict spatial representation, which show ability to distinguish among different

navigational experiences (73). Hippocampus is also involved in reasoning over social hierarchies (74). Whittington *et al.* proposed the Tolman-Eichenbaum Machine (TEM), which introduces that hippocampal place cells remapping between environments represent generalization (66). The TEM is capable of learning the abstract set of relationships that govern social hierarchies (66). Furthermore, fMRI studies in humans have shown that hippocampus can encode more cognitive variables, such as the sequential nature of a nonspatial tasks (42) and social interactions (75, 76). The human studies integrated with rodent and primate researches together to reveal the crucial role of hippocampal remapping in spatial and nonspatial related memory generalization.

The Prefrontal Cortex Required for Abstraction and Categorization is Essential for Generalization

Generalization requires the abstraction of pattern features or principles that are commonly occurred across experiences, which is in certain degree dependent on the ability of PFC neurons (3, 77). Initially, it was considered that the PFC supports abstract, or verbally-mediated, semantic knowledge rather than sensory-based properties (78). While, it is now widely accepted that PFC neurons are capable of encoding a diversity of information by stimulation of different sensory modalities and controlling "high order" behaviors, which include category abstraction, rule learning, etc. (79–82). Regarding to category abstraction, it can be divided into the specific and generalized representations that are organized and determined by different subregions of PFC (83) (Figure 2). In a dot-pattern categorization task performed by monkeys, the ventral PFC is shown to be



responsible for processing more low-level abstractions via bottom up dynamics of stimulus-locked gamma power and spiking, while the dorsal PFC (dLPFC) is capable of processing more high-level abstractions via top-down dynamics of beta power and beta spike-local field potential (LFP) coherence (84). In humans under a reinforcement learning paradigm, it was demonstrated the rostrocaudal architecture of the frontal cortex is responsible for rapid rule learning at multiple levels of abstraction, especially under novel behavioral context (85), indicating its capacity of generalizing past learning to new problems. Patients with PFC lesions exhibited impaired acquisition of second-order in abstract rule learning when performing a hierarchical reinforcement learning task (86). In monkeys performing a rapidly learned task based on the formation of abstract concept, bilateral lesion of lateral PFC significantly impairs rule reversal rather than acquiring roles, while would not affect either rule tasks without concept-based role. These implicate that lateral prefrontal cortex (LPFC) is responsible for modifying abstract rule after establishment, which might not be renewed in the absence of PFC (87). Considering the importance of PFC in categorization and abstraction, we will illustrate the role of PFC in generalization in terms of both individual neural activity and neural ensembles representation.

In rodent experiments, mice learn rule-based categorization and generalize to novel stimuli during the entire learning process. During learning, neurons in the PFC display different dynamics in obtaining category selectivity and different engagement in subsequent rule-switching tasks, which is the key to rule-based categorization (88, 89). When rats perform a medial prefrontal cortex (mPFC)-dependent rule-switching task on a plus maze, the principal neuron in mPFC primarily represent a generalized form of space via encoding the relative position between the start and the goal. And independent of hippocampus, mPFC can imitate entire spatial trajectories via replaying ordered activity patterns in generalized positions, indicating its role in flexible behavior (90). In mouse, through repeatedly imaging individual cells in mPFC during a "Go"/"No Go" rule-based categorization learning paradigm, Reinert *et al.* reported that a subpopulation of neurons is selectively and uniquely responsible for categories and reflect generalization behavior. Therefore, the categorical neuronal representation is acquired gradually rather than temporarily recruited, indicating that neurons in the mPFC are part of the specific semantic memory of the learning category (91). Neuron ensembles in mPFC of rats are responsible for applying abstract structure to a new situation based on their selective firing patterns, which become less selective for perceptual features but more selective for common rational features and immediately generalize to the new situation (92), suggesting mPFC has the ability of developing a knowledge structure and adapting it to new experiences.

In monkeys performing "match/nonmatch rule" experiment, which requires rule-based comparisons of similarities or differences between stimuli that generalize to multiple examples, single neuron recording demonstrates that some prevalent neuronal activity observed in both dorsolateral PFC and ventrolateral PFC reflects the coding of abstract rules (93, 94). When performing visual symbol response in a repeat-stay strategy, neurons in mPFC of monkeys display selective activity in choosing which is not only based on fixed mapping, but also based on abstract strategies during trial-and-error learning (95). In a series of studies of number rules, a high proportion of recorded cells in the PFC encodes information about the number, generalized across changes in the physical appearance changes (96, 97). In rule switching tasks, monkeys are capable of switching between rules and generalizing the rules to new examples. The substantial proportions of neurons in mPFC show constantly changing neural activity to adapt switching rules (98, 99). In monkeys performing a cognitive-set-shifting task, a cluster of neurons in the inferior arcuate region of PFC were identified to be selective for shifting cognitive set. While, pharmacological inactivation impairs the performance of behavioral shifting, further suggesting this region supports cognitive shifting between rules (100). The dorsal anterior cingulate cortex and putamen of monkeys exhibit different representations during new rule learning that neurons in the cingulate cortex mainly rotate toward the role for a policy searching while neurons in the putamen exhibit a magnitude increase following the rotation of cortical neurons for enhancing the con-

fidence of the newly acquired role-based policy (101). Neurons could rotate to decrease the angle to rule in order to change strategy of learning. For single neural activity, the readout of a neural ensemble can improve performance because of a change in individual neuron properties or because of a change in weights given to each neuron by a readout node.

Neural populations in response to structure in PFC show representative features of generalization in the neural geometry level that are not apparent at the level of individual neurons. Through a linear classifier to decode a large number of different variables, when monkeys perform serial-reversal learning tasks with different hidden and explicit variables, it was observed that neural ensembles in PFC represent multiple variables in a geometry to reflect abstraction and support generalization in novel situations (2). The mPFC stores representations of the common spatial structure, termed schema, across environments. While, through high-resolution fMRI approach determining the roles of PFC and hippocampus in human participants during spatial environments retrieval, pattern separation and repulsion have been found in different subregions of hippocampus (102). Similar to hippocampus, neural activities in mPFC holds similar firing patterns between places with similar task contexts. What's more, the mPFC replays organized sequences of positions indicating generalized behavioral trajectories. The mPFC trajectory replay performs both in the forward and the reverse sequences, indicating that it is not a mere rehearsal but an abstraction of the original experience. Through regulation of hippocampal activity, neural representation of a subset of PFC ensembles generalizes across different paths, which provides a potential mechanism for generalization across individual experiences (103).

Memory processing through mPFC has been involved using prior experience to improve learning of new tasks (104). Activity in PFC is associated with representing the structure of ongoing tasks (105). Neural computational model of PFC underlies the framework of hierarchical predictive coding, which indicates individual neurons in mPFC encode multiple task variables with a more abstract stimulus value code. fMRI experiments in human study reported that the ventral medial PFC (vmPFC) and its functional connection with visual cortex, as top-down control of sensory cortices, construct abstract representations through a goal-dependent valuation process (106). Through novel tree-like categorization task performed by human participants and analyzed via computational model comparisons, it is shown that mPFC traces accumulated hierarchical conceptual knowledge along time, and mPFC and hippocampus both update trial-to-trail information, indicating mPFC and hippocampus are required for the integration of accumulated evidence and instantaneous updates into hierarchical concept representations as time goes by (107). In a compositional representation task, fMRI and multivariate pattern analysis demonstrated that LPFC can transfer practiced rule presentations into novel contexts, guiding cognitive performance in novel circumstances (108).

The OFC with Value-guided Characteristic Reestablishes Cognitive Map with New Information

The role of OFC in generalization depends on its pivotal function in decision-making, which is associated with the heterogeneity of OFC neurons. OFC shows different responses to sensory inputs during decision-making, such as relative and economic values (109, 110), reward- and value-based behaviors (109, 111–115), expected or predicted outcomes (116, 117), confidence estimates (118), cognitive map of task space (119, 120), regret (121), and credit assignment (122). Wilson *et al.* proposed a theory that OFC may encode the current abstract state of a task for reinforcement learning. They hypothesized that OFC can distinguish tasks with similar sensory inputs but different kernels, indicating that OFC can categorize events, based on different concepts (120). OFC encodes task structure representation as a more general role, which can also include value representation derived from the task structure.

Single neuron responses are essential for understanding representation in nature, for individual neuron contributes in a different way to the ensemble encoding of stimuli and performs a different profile of tuning a subset of the stimuli to provide high capacity and generalization. OFC



neural activity correlates with economic value, representations are usually much more specific to elements of task structure, indicating that OFC contains an abstract representation of decision confidence (123). OFC does not show specific activity in simple or even some complicated learning tasks. While, tasks that force animals to adjust their behaviors in light of new learning are generally dependent on OFC function. Outcome devaluation depends on OFC activity, which encodes specific sensory features of outcomes (111, 124, 125).

OFC has been reported to support abstract representation of multi-sensory decision-making (126). A statistical confidence computation and predicted behavioral reports of confidence can be underlined through OFC activity. Masset *et al.* found that single neuron in OFC of rats can generalize statistical decision confidence information regardless of sensory modalities to predict multiple confidence-guided behavior during decision-making (127). Researchers have found that OFC neurons respond transiently to the rule switching during reversal learning tasks. Through a reversal learning task for head-fixed mice, a subpopulation of OFC neurons was found to display remapping activity in order to respond to updated sensory inputs, and particularly, that dynamically interact with sensory cortex to implement computation and form plasticity for flexible sensory processing and adaptive decision-making (116). Zhou *et al.* reported that neural ensembles of OFC in rats can converge low-dimensional neural code across both problems and subjects to generalize common structure of the problems and its evolution, thus forming a schema for supporting a complex cognitive operation (128).

Primate studies show that OFC lesion significantly impairs the ability of acquiring and reversing the concept-based rule (87). OFC is essential to distinguish different concepts and classify similar rules. Through performing a Wisconsin Card Sorting Task by macaques, the neural firing rates in OFC change reliably for rule identity and rule category (129). The same group further found that the OFC neurons are also activated in relation to rule shifting during cognitive set reconfiguration (130). Social characteristics can also be encoded by OFC, which represents facial categories related to social and emotional behaviors. Neurons, called face cells, encode the intrinsic properties conveyed by the face and its expressions, suggesting that this cluster of neurons in OFC abstract social information through faces and generalize to other facial expressions with similar physical properties (131). Lesion studies suggest that the OFC involves the evaluation of decision outcomes and effectiveness of updating rules (132, 133).

In human studies with fMRI, OFC has also been proposed to act as a cognitive map of spatial task and provides strong support for the state representation theory of OFC (134). This experiment requires participants to conjecture the trial type, which is a hidden state that needs to be learned from previous trials. OFC is found to represent task states, rather than explicit values. Other human researches also proved that OFC represents hidden states (75, 135). OFC activity is also required for the distant and unseen future consequences of goal-directed actions (136). A theory model recently argues that representation of value in OFC is relevant to its more general role in representations of task structure (137). Together, neural recordings in rodents, primates, human imaging, and neural stimulation studies have highlighted the essential role of OFC in performing higher-order representations related to abstract information.

OFC is also involved in emotional processing. The dysfunction of the OFC may cause symptoms of affective disorders, such as anxiety, depression and impulsivity. It is reported that emotion-related diseases are also associated with cognitive dysfunction. Early life stress-mediated mice model shows impairment of rule-reversal learning, indicating deficit of generalization-related process might function as a potential indicator of OFC impairment-related diseases (138).

PPC with Perceptual Stimulus of Historical Experience Guides Generalization

PPC also contributes to generalization. This is not surprising since PPC plays an essential role in sensory-mediated decision-making and categorization behaviors that supports generalization to varying degrees. PPC contains two encoding patterns: heterogeneous encoding for specific representation and comprehensive encoding for globe representation, which

together shows potential advantage to generalization. For instance, neurons in the inferior parietal lobule in primates encode different types of movements, respectively, in a structured sequence (139), similar to rodents research in hippocampus, which represents lap numbers in round track (70). PPC has been shown to encode a large variety of sensory-, cognitive-, and motor-related signals during a wide range of behavioral contexts and tasks (140), including working memory (141, 142), spatial navigation (143, 144), especially in encoding for locations in egocentric space, decision-making (145), top-down and bottom-up attention (146, 147) and episodic memory (148). PPC seems to encode information in a low dimension, which can represent different aspects of physical feature, such as shape classification (149), movement direction, and counting number (150).

Recent findings indicated that the PPC plays an important role in memory updating (151). Using a goal-reaching task in mouse, it was shown that PPC implements and updates to forecasts, when prediction uncertainty decreases because of new sensory inputs (152). The PPC has been proposed to act as a sensory history buffer for use in a future relevant experience (153). PPC ensembles are required for both encoding and the recall of associated memory. Retrieval suppression of the corresponding PPC cell population dissociates experience from pre-exposed context and leave individual memories intact, which suggests that PPC ensembles can flexibly bind or unbind to different information. This process underlies that PPC abstract experience from events, leading to the formation of generalization. PPC is highly related to the processing of previous experience information, which represents previously learned sensorimotor associations to guide decision-making in seeking reward on new sensory stimuli. Inhibition of PPC decreases performance of reward based categorical decision-making on new sensory stimuli, which indicates that PPC is crucial for abstracting task rule from previous experience and applying that in similar tasks with new cues. PPC could encode previous category knowledge to counterbalance the uninformative influences.

It also suggests that PPC may act an important role in reward based generalization (154). For different task diagrams in working memory, PPC neurons carried far more information about the sensory stimuli of previous trials. Inactivation of PPC improves working memory performance and results in less interference with experienced stimuli (155). Although silencing PPC neural activities leads to opposite task performance in different task paradigms, this is consistent with the function of PPC in previous stimulus process, which is related to memory generalization. In addition, through long-term neural recording of PPC, the neural firing pattern of PPC has been found to be reorganized across days about task features. There exists a neural ensemble that represents a new activity pattern when mice learn a new associative task, indicating this neural ensemble possess malleable activity patterns that might be required for abstracting learned representations (156). The generalized categorical encoding in PPC suggests it is involved in a wide variety of abstract cognitive functions beyond categorization. PPC is most likely a node in the network mediating abstract cognitive computations.

Quite a few primate studies also show the function from categorization to generalization in PPC (also known as LIP in primates). In working memory based visual motion categorization task, categorization training influences cognitive encoding in PPC, suggesting task-specific mnemonic encoding in PPC. While PPC displays strong activity in both discrimination and categorization tasks. PPC is selectively engaged in cognitive abstraction (157). Parietal cortex is found to encode shape selective information of visual stimulus to present generic categorical outcomes. PPC neurons also form associations between different features. A same population of neurons can encode learned associations in separate task, which implicates a foundation of learning generalization (149). In number rule task, there is a substantial proportion of neurons in PPC cortex encoding numerical information, which is conveyed by auditory and visual stimuli, indicating PPC acting its role in multimodal representations of abstract numerical information (158–160). In addition, single neural activity in PPC can also represent rule shift in rule switching tasks.

In human study through fMRI, visual processing is divided between a ventral and dorsal stream specializing in object recognition and vision for



action. Dorsal stream has been reported to enhance action and identity information, leading to an abstract representation in PPC (161). PPC and primary motor cortex show a connection between motor memory formation and neural representation. This connection supports intrinsic (body based)-extrinsic (world based) space for generalization pattern, which indicates that representation of learning is based on a combination of local representations in intrinsic and extrinsic coordinates (162). PPC is more active during the execution of novel than that of practiced instructions but show similar activities between the execution phase and the instruction phase. This pattern implies that the PPC support cognitive processes in both the encoding and the execution of novel instructions (163).

Hippocampal-cortical Connections in Generalization

Cortex and hippocampus are strongly interacted by direct and indirect pathways. Many studies have highlighted interactions between the hippocampus and the PFC that acts an essential role in episodic memory. While we know little about the function of hippocampal-cortical interactions in generalization, there are three main pathways existing between the PFC and the hippocampus: Firstly, a monosynaptic projection is from ventral hippocampus to mPFC, as well as OFC. The complementary learning systems theory is proposed to discuss the generalization of hippocampus-dependent memories (164, 165). In this theory, the hippocampus represents individual memories, and the common features are abstracted by cortex. In the process of memory consolidation, the memory generalization emerges through information transformed from hippocampus to cortex. Secondly, the mPFC bidirectionally communicate with hippocampus through intermediate medium: thalamic nucleus reuniens (NRe). A model is reported to underlie the mechanism of the NRe's control of memory generalization (166), in which NRe regulates hippocampal excitability persistently, thereby controlling memory generalization (167). mPFC-NRe-hippocampus circuit may regulate memory generalization by actively controlling hippocampal remapping. Thirdly, the mPFC connects to medial and lateral entorhinal cortex, which produces strong projection to hippocampus. This pathway is required for processing object and event representations (168, 169). Hippocampal-cortical representations corresponding to multiple-to-one associations reflect the ability of neural connection in abstracting similar and repeated features of ongoing tasks.

Researches show that hippocampal-cortical communications connect specific-to-general links (90, 103). In a mouse study of reversal learning problems with same structure but different physical implementations, the PFC showed similar representations across problems, suggesting its role in abstracting common structure for generalization, while hippocampus is more highly influenced by specific problems, indicating it takes charge of the specific structure of the current situation (170). In addition, Zhou *et al.* reported that hippocampus and the OFC of rodents function complementarily in familiar environments, that the OFC encode current situation while hippocampus ensembles support prospective memory for future performance in a cognitive map (171). Through concept-learning tasks in humans with model-based fMRI, Bowman *et al.* found that anterior hippocampus and the vmPFC work together to modulate the abstraction of concept during generalization via abstracting information integrated from multiple events, particularly, hippocampus integrates and forms generalized memory representations, while the vmPFC contributes by representing these abstract categories and aiding their applications to new situations (172). In human-related study, Mizrak *et al.* demonstrated through fMRI studies that hippocampus and OFC highly correlated to differentiate between context-determined and context invariant task structures after learning, suggesting their cooperation in guiding selections of future decision strategies (173). Though there are few studies displaying the hippocampal-cortical neural connections for common structure/role abstraction in different tasks, which are the basis for cognitive generalization, thus further studies revealing the neural networks among hippocampus and cortex that influences cognitive generalization should be considered.

Discussion and Prospect

The ability of generalization, which reflects the ability of learning and memory, is crucially required for adaption of novel circumstances both

animals and humans. In this study, we mainly focus on reviewing the neural mechanism on the generalization from hippocampus and cortex in rodents, primates, and humans. We summarized that hippocampus show characteristics of remapping and replay activities, which represents changed states in new but similar task contexts applied to abstract rules. The activation of PFC, PPC, and OFC is necessary for decision-making and goal achievement through context dependent abstract rules. Single neural activity and neural geometry both display heterogeneity and generality of PFC when abstract rules are formed and used for guiding behaviors to assessment of decisions. PPC, by virtue of its vast connectivity, participates in multiple cognitive processes, especially in decision-making, planning and categorization. It also mediates some abstract and symbolic cognitive capacities. PPC neurons represent previous sensory experience to guide decision-making on new sensory stimuli. OFC is a key brain region in reward evaluation. Its feature of updating value judgments supports abstract representation of decision-making. All these studies through rodents, primates, and humans have implicated the potential neural mechanisms of generalization, laying a solid foundation for understanding the neural basis of cognitive function.

Remapping, a hallmark of cognitive flexibility, occurs when encountering a new situation, based on the fact that the new situations share similar feature with previous experiences. However, it is counterintuitive that remapping may indicate generalization. Because remapping means variations in different forms of neural activities to deal with changes of sensory or cognitive inputs, while generalization suggests that neurons show common activity patterns to respond similar but slightly different environments or perceptual inputs. Interestingly, it was shown that single neurons in primate hippocampus exhibit similar functions as rodent's place cells to encode space information through value place fields, which can be remapped to adapt changed but gradually correlated environments, leading to generalization of maps (72). This contradiction could be explained due to different reference coordinate system. The positional changes of external sensory inputs result in neural remapping, while when treating sensory inputs as reference coordinate system, the similar neural patterns occur in response to different environments. Taking an example of goal-vector cells, which are active at certain distances and directions from goals to permit rapid generalization to novel goals in novel environments (72, 174), based on the fact that the new situations share similar feature with previous experiences. Therefore, we may propose a hypothesis that neuronal ensembles carrying generalization properties could remap in a direction-guided manner according to changes in different environments.

Hippocampal neurons change dynamically to realize cognitive generalization. Most studies focused on the populational ensembles of place cells and their functional connection of remapping and replay with cognitive generalization. However, hippocampal place cells are only accounted for half of the recorded population. It was recently reported that, there is a distinct subset of neurons in hippocampal CA1 exhibits weak spatial selectivity but gradually develops correlated activity with place cells, thus effectively links discrete place fields of place cells into map-like structure after latent learning and during sleep (175). Through large-scale longitudinal two-photo calcium imaging of hippocampal CA1 neurons, it was found that hippocampal neural activity progressed along with improved animal behavioral efficiency and showed similar patterns within and across tasks, but undergoes a series of decorrelation steps and finally resulted in orthogonalized task-specific representations, indicating the dynamic changes of hippocampal population plays crucial role in generalizing learned states into novel situations (176). Contrasted to the place cells with consistent and temporally adjacent spiking in spatial place fields, isolated spikes in hippocampal CA1 were found to preferentially occurs during hippocampal theta oscillations and transiently encodes nonlocal spatial situation, indicating its association with the evaluation of distant physical locations. Furthermore, these events are coordinated with ongoing activity of PFC, evidencing the interactions across brain regions, especially hippocampal-prefrontal cortical networks (177). These studies suggest the heterogeneity of hippocampal neurons and their coordination with multiple brain networks should be considered for their possible neural representations in cognitive generalization.



In this manuscript, we reviewed different brain regions of cortex, especially the PFC, OFC, and PPC, in cognitive generalization across different species. It is known that PFC functions as a critical hub in the brain to manipulate many high ordered cognitive behaviors, such as future planning, problem solving, new environments adapting, and so on. Due to ethical issue, many related studies are based on single neuron recordings or neural circuit regulation in nonhuman (rodents and primates) models. However, the connectivity patterns, parcellation, and layered structure of PFC in humans are different from rodents, but to a lesser extent in primates (178). In anatomical view, rodents have a putative homolog of the agranular medial frontal cortex and OFC of primates; while, the granular frontal cortex (dlPFC) lacking in rodents is composed of the largest part of PFC in most primate species (179, 180). Evolutionally, basal primates possess a small granular PFC, while more advanced simian species, like humans own an increasingly larger granular PFC (178, 181). In functional view, the PFC across species exhibits a high degree of functional homology, particularly when considering its involvement in complex cognitive functions like decision-making, memory, and abstract rule learning (178). For instance, the mPFC in rodents mediates similar cognitive functions like decision-making and attention as that in primates and dlPFC in humans, although they are not anatomically equivalent (182). OFC is phylogenetically originated from PFC in humans, that has essential role in value-based decision-making. Ongur and Price have demonstrated that the laminar organization and cellular distribution in the OFC of humans and monkeys share similar features (183). Comparative neuroanatomical studies also made clear that, central OFC and vmPFC in monkeys are homologous to that in humans separately and belong to distinct networks (184). Lesions with OFC in different species all exhibited similar features that impairments occurs in reversed contingencies, but not in learning (111, 185–187), suggesting the OFC composes a common framework for processing generalization across species. However, when issuing these cortical regions in cognitive-related functions, there are still discrepancies existing since there are differences in multiple aspects, including anatomical differences across species, different behavioral tasks applied as well as different neural recording methodologies for evaluation of the connectivity between neural activity and behaviors. Therefore, future research should bridge methodological and task-based differences to explore the role of hippocampal-cortical networks in cognitive generalization across different species.

Cognitive generalization requires concept/rule/structure abstraction and the formation of higher-order representations. This process necessitates capturing precise neural dynamic to represent abstract rules, concepts and decision-making, as well as measuring large-scale network activity to unveil functional connections among brain regions, including hippocampus, and PFC and associative cortical areas. As evidenced in many studies, single-unit or populational (LFP) recordings are basically applied in studies of rodents/primates, which exhibit high spatial and temporal resolutions and provide direct insight into how individual neurons encode specific roles versus specific experiences, or how neural populations represent hippocampal replay to link memory retrieval to memory generalization. But it only limited its use in animals or neurosurgical patients and also fail to displaying broader network interactions. For human studies, fMRI is a powerful tool that owns high spatial resolution for identifying localization of brain regions (e.g., vmPFC, hippocampus) involved in rule abstraction and can also track cross-brain network interactions in generalization. However, fMRI has poor temporal resolution and only measures indirect neural activity. Therefore, a multimodal, integrative approach combining high temporal and spatial resolution techniques will provide the most comprehensive insights into how the brain generalizes knowledge across different contexts.

Studies have shown impairment of cognitive generalization is tightly related to neurological diseases. In preclinical, autosomal dominant AD mutation carriers exhibit significant memory generalization impairment, which is associated with the left hippocampal volume (188). In a recognition and categorization of visual dot pattern tasks, impaired ability of recognition was shown in patients with both mild AD and moderate AD and impaired categorization found in patients with moderate AD (189). In a study of AD, it was reported that the remapping activity of hippocam-

pal CA1 neurons is severely disrupted and the grid cells in MEC impaired in model mice of AD, indicating that memory generalization deficits in AD might be associated with hippocampal remapping dysfunction and disrupted hippocampal-MEC circuits (190), which could be further studied. In addition, dysfunction of the mPFC has been found in various neurological and psychiatric disorders, such as depression, anxiety disorders, schizophrenia, autism spectrum disorders (ASD) (191). Patients with schizophrenia display deficits in abstracting perceptual categorization and are strongly drawn attention from task-irrelevant conflicting abstract rules (192). Their memory deficits are associated with hypoactivation in caudal LPFC regions and hyperactivation in rostral LPFC regions (193). Young kids with ASD have difficulties of learning abstract rules, while adults with ASD struggle to categorize atypical exemplars and form prototypical presentation (194, 195). These neurological diseases further reflect the functional integrity of PFC is necessary for generalization. This will further provide clues (which might be potential biomarkers or preclinical diagnosis) for generalization dysfunction-related neurological diseases and shed light on the intervention and treatment of these diseases.

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Author Contributions

Z.Q. and H.Q. conducted and designed the studies; Z.Q. and D.S. wrote the manuscript and D.S. plotted the figures. The manuscript has been read and approved by all authors. All authors take full responsibility for all figures and text and approve the content and submission of the study. No related work is under consideration elsewhere.

Corresponding authors: Professor Z.Q. for any aspect of the work except for figures and Professor H.Q. for whole manuscript. These corresponding authors take full responsibility for the submission process.

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Competing Interests

The authors have confirmed that no conflict of interest exists.

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Dynamic memory engrams: Unveiling the cellular mechanisms of memory encoding, consolidation, generalization, and updating in the brain

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One of the fundamental questions of neuroscience is how the brain can store, generalize, and update memories. Memories are believed to be stored through biophysical and molecular changes in neuronal ensembles called engrams, which are distributed across different brain regions. The dynamic changes that occur in engram cells during the encoding, consolidation, generalization, and updating of memory are still not fully understood. However, recent advancements in techniques for labeling and manipulating neural activity have allowed for investigation of the dynamic changes of memory engrams across different memory processes. Understanding engram dynamics may inform interventions for posttraumatic stress disorder and memory disorders. In this review, we summarize the recent progress in dynamic memory engrams across memory encoding, consolidation, generalization, and updating, shedding new light on the mechanisms underlying engram formation and maturation.

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Introduction

One of the fundamental questions of neuroscience is how the brain can store, generalize, and update memories. The search for the mechanistic substrates of memory, what Richard Semon called the “engram” has continued into the present day. Hebb pioneered the idea of neuronal ensembles, which is small populations of sparsely distributed neurons, are active in response to a specific salient stimulus and the synaptic connections between them are strengthened. The explosion of research that is beginning to uncover the dynamic cellular and molecular mechanisms by which memories are encoded, consolidated, and updated. Recent advancements in techniques for labeling and manipulating neural activity have facilitated the study of engram cells throughout memory acquisition, retrieval, generalization, and updating.

Engram Storage of Memory

Memory is a vital cognitive function, allowing organisms to encode, store, and retrieve information. The concept of memory engrams, discrete physical traces that represent stored memories in the brain, dates back to early theoretical models but has recently gained empirical traction with modern neurobiological techniques. Recent advances in memory engram technology, combining immediate early gene (IEG)-based tagging and optogenetic manipulation, have enabled the identification and control of neuronal ensembles encoding specific memories. Studies by Mayford and Tonegawa demonstrated that reactivating tagged engram cells can induce memory retrieval, even in novel contexts, while inhibiting these cells impairs recall. These findings confirm that engrams are sparsely distributed, functionally linked neuronal populations that undergo enduring changes during learning and reactivate during retrieval. Engram formation is driven by intrinsic excitability and CREB-mediated transcriptional regulation, with hyperexcitable neurons preferentially recruited into memory-encoding ensembles. During consolidation, synaptic stabilization and systems-level reorganization transition memories from hip-

pocampal to cortical storage, enabling long-term persistence. Retrieval involves the reactivation of original encoding ensembles, with artificial stimulation of engram cells bypassing natural cues to induce memory recall. Collectively, these insights reveal engrams as dynamic, distributed networks that encode, consolidate, and retrieve memories through coordinated neural activity. This framework not only advances our understanding of memory mechanisms but also holds promise for addressing memory-related disorders.

Defining the Engram: From Theoretical Abstraction to Biological Reality

The term engram raised by Richard Semon in 1904 as the “mnemonic trace” encoding memory which has evolved from a philosophical construct into a cornerstone of modern neuroscience (1, 2). Despite its conceptual simplicity, defining the engram with biological precision remains a challenge, requiring integration across molecular, cellular, and systems-level perspectives. Semon’s original formulation posited the engram as a latent neural modification persisting after learning, capable of being reactivated to reproduce conscious memory. However, early 20th-century neuroscience lacked tools to empirically validate this idea. Karl Lashley, a geneticist turned psychologist tried to find an engram but failed. In his experiments, he trained the rat to learned maze memory task by giving the reward. However, the size, but not the location, of lesion in cortex correlated with the memory deficits (3). After more than 30 years of searching, Lashley concluded that memory is not localized to a particular brain area (4).

As the next leap of engram, Hebb raised a concept that “neurons that fire together, wire together” (5, 6). It was hypothesized by Hebb that a cell assembly is formed through reciprocal connections between cells that are simultaneously active during an experience. Furthermore, reactivation of a subset of these assembly cells was proposed to trigger the reactivation of the entire assembly.

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Despite these scientists have defined and described the engram, there remains a paucity of studies investigating its biological basis. The growing interest in engram research has been significantly driven by innovations in memory engram technology, which facilitates the identification and controlled modulation of neuronal ensembles encoding specific memories. This methodology integrates IEG-based cellular identification with optogenetic control mechanisms. Neuronal activation during memory retrieval is visualized through IEG immunohistochemical markers, while cells engaged during initial encoding are selectively tagged via temporally regulated IEG promoters that induce stable fluorescent reporter expression. A brain region (or global network) is considered to harbor an engram when the overlap between training-activated (tagged) and retrieval-activated (IEG-expressing) neurons exceeds stochastic expectations. Mayford and colleagues targeted amygdala neurons activated during auditory fear conditioning—a behavioral paradigm where a neutral auditory cue (conditioned stimulus, CS) becomes associated with an aversive footshock (unconditioned stimulus, US) (7). Posttraining re-exposure to either the CS or context elicits freezing behavior in rodents, reflecting robust associative memory. Their experimental design involved reintroducing mice to the conditioning context 3 days posttraining, with zif268 immunohistochemistry identifying retrieval-activated neurons. Strikingly, the observed overlap between tagged (training-active) and zif268+ (retrieval-active) neuronal populations in the amygdala nucleus surpassed chance levels, with ~11% of sampled neurons exhibiting dual activation—a finding consistent with the existence of an engram supporting this conditioned fear memory. Comparable findings have been replicated across diverse neuroanatomical regions—such as the dorsal hippocampus (8–12), amygdala (7, 9, 11, 13–15), and cortical areas (9, 14, 16, 17)—using varied activity-dependent labeling techniques in multiple memory paradigms. Collectively, these investigations corroborate the widespread existence of engram-associated neuronal ensembles. Nevertheless, functional validation remains critical to confirm whether reactivated candidate engram cells genuinely constitute the neural substrate of experiential memory.

Tonegawa and colleagues provide the first causal evidence through a gain-of-function approach, tagging dentate gyrus (DG) neurons activated during contextual fear conditioning (pairing a specific environment with footshock) to express the light-sensitive cation channel channelrhodopsin-2 (ChR2) via activity-dependent promoters (7, 18). In a novel, nonconditioned context where mice exhibited no spontaneous freezing, optogenetic stimulation of these labeled DG neurons elicited robust freezing behavior—the learned adaptive response (10)—despite the absence of prior aversive experiences in this setting. Crucially, this effect was memory-specific: photoactivation failed to induce freezing when downstream CA1 neurons were silenced during initial training, thereby blocking memory formation (19). Subsequent studies employing optogenetic or chemogenetic activation protocols demonstrated that in the absence of natural sensory cues, targeted reactivation of engram cells in various brain regions reliably evokes memory-associated behaviors across multiple tasks (20–25). These findings align with Semon's concept of *ecphory*—the process by which latent engrams transition to active memory states. Complementing these gain-of-function results, loss-of-function experiments reveal that subsequent ablation or inhibition of engram neurons consistently impairs memory retrieval, further solidifying their necessity in mnemonic processes.

Together, engrams are sparsely distributed populations of neurons that undergo enduring physical or chemical changes during learning from different levels, thereby storing specific memory information (Figure 1). Following memory consolidation, these cells are functionally linked through strengthened synaptic connections and reactivate during memory retrieval. Critically, engram cells are not confined to a single brain region but form interconnected engram complexes across the hippocampus, amygdala, prefrontal cortex, and other circuits, depending on memory type (e.g., episodic, emotional, or procedural).

Engram in Memory Encoding

The engram represents enduring neurobiological modifications induced by learning experiences, which subsequently enable the retrieval of corresponding memories. Engram neurons are operationally defined as cel-

lular subpopulations selectively engaged in the encoding, consolidation, and retrieval of specific mnemonic information.

A central question in memory research concerns the mechanisms underlying selective neuronal recruitment during encoding. Emerging evidence implicates cell-autonomous properties, particularly intrinsic excitability (the propensity of neurons to generate action potentials in response to synaptic input), as a critical determinant of engram allocation. Neurons with elevated baseline excitability exhibit preferential activation during learning and are disproportionately incorporated into memory-encoding ensembles (26–28). This excitability bias aligns with observations that neurons overexpressing CREB—a transcriptional regulator known to enhance both intrinsic excitability (29–31) and dendritic spine density (30, 32)—are selectively recruited into engrams, whereas CREB-deficient neurons are excluded from encoding processes (33–35). Notably, transient CREB upregulation immediately prior to learning enhances memory formation, demonstrating its capacity to regulate mnemonic allocation on behaviorally relevant timescales (35).

The prevailing model posits that CREB-driven engram recruitment operates via excitability modulation. Empirical support for this mechanism includes: **Excitability Suppression:** Pharmacogenetic inhibition of CREB-overexpressing neurons abolishes their preferential engram integration. **Excitability Enhancement:** Artificially increasing neuronal excitability (independent of CREB manipulation) promotes engram membership. These findings establish a direct causal link between cellular excitability states and competitive engram allocation during memory encoding. While traditional models posit memory storage at the level of individual neurons, contemporary frameworks emphasize encoding through neuronal ensembles—functionally coordinated cell assemblies that exhibit stimulus-, task-, or state-dependent synchronous activity. A critical unresolved question centers on whether these ensembles merely aggregate independent neurons or emerge from specialized intercellular relationships. Holographic optogenetic techniques, particularly two-photon precision stimulation, have provided mechanistic insights into this issue (36, 37). Repeated photostimulation of defined neuronal groups enhances their spontaneous coactivation probability, even in the absence of external cues—a hallmark of ensemble formation (37). Strikingly, such assemblies self-organize through cell-autonomous mechanisms: unexpected strong and persistent increased intrinsic excitability within stimulated neurons showing their correlated activity, with an initial depression followed by a potentiation after a recovery period in presynaptic plasticity (38). These observations align with theoretical models proposing that memory encoding involves the preferential recruitment of hyperexcitable neurons into temporally coordinated activity patterns (39). Collectively, these findings challenge synaptic plasticity-centric paradigms, suggesting intrinsic excitability states—rather than synaptic rewiring—serve as primary drivers of ensemble-level memory representation.

Engram in Memory Consolidation

Newly acquired memories are initially sustained by transient, experience-dependent neuronal activation (26, 38, 40–43). However, such memories remain labile and prone to rapid decay unless stabilized through subsequent molecular processes. The conversion of transient memory traces into enduring forms necessitates transcriptional activation and *de novo* protein synthesis. These molecular cascades drive synaptic stabilization, characterized by strengthened connectivity among coactivated neuronal ensembles engaged during encoding (44, 45). Crucially, interventions disrupting these molecular pathways—termed synaptic consolidation—abrogate long-term memory persistence. Pharmacological or genetic disruption of these pathways blocks the transition to long-term memory storage (29, 46). For instance, inhibition of CREB-mediated transcriptional activation—a key regulator of synaptic plasticity—impairs mnemonic persistence (30, 45). Similarly, postlearning administration of protein synthesis antagonists abolishes long-term memory formation (44, 45). Thus, synaptic stabilization constitutes a pivotal bottleneck: memories undergoing this process attain persistence and future retrievability, whereas unstabilized traces are subject to decay.

Long-term hippocampal memory formation is enhanced through repeated behavioral or internal reactivation of the learning event.

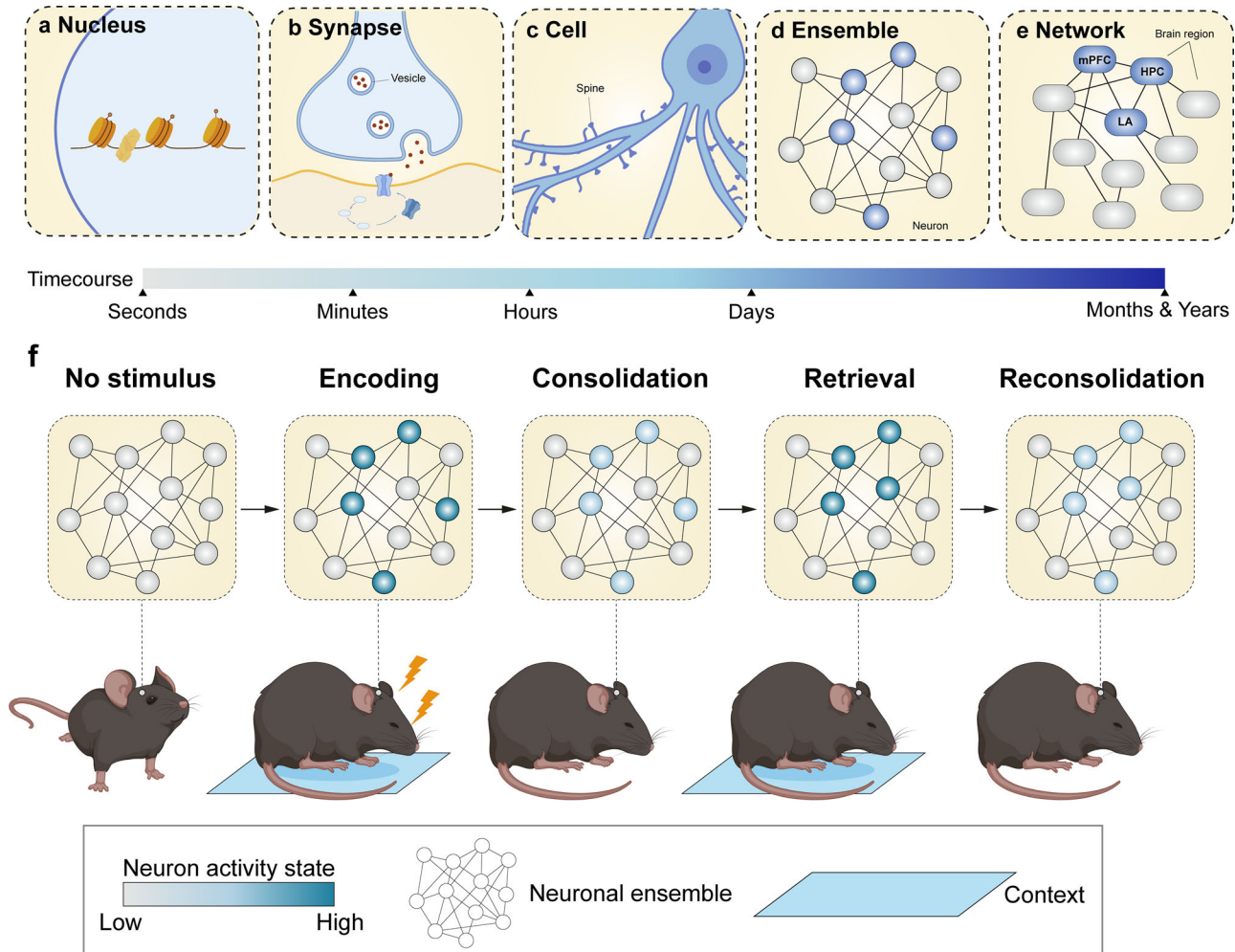


Figure 1. Hierarchical organization and dynamic states of fear engrams. (A–E) Multiscale engram representations: (A) Nuclear level of epigenetic/transcriptional remodeling; (B) Synaptic level change of neurotransmitter release; (C) Cell level of neuronal connectivity reconfiguration and plasticity change; (D) Regional ensemble coactivation; (E) Network-level engagement (blue = learning activation); (F) Mnemonic state transitions: Engrams (highlighted in dark blue) emerge through activity-dependent synchronization of neuronal ensembles during contextual fear memory acquisition (encoding). During subsequent consolidation processes, these engrams undergo gradual transition into a dormant state characterized by stabilized synaptic connectivity. Notably, memory retrieval triggers transient reactivation of consolidated engrams, temporarily destabilizing their established neural activity patterns while simultaneously manifesting as context-specific freezing behavior. Crucially, this reactivation phase initiates reconsolidation mechanisms that restabilize modified engram configurations, ultimately restoring them to a quiescent storage state with updated mnemonic information. HPC, hippocampus; LA, lateral amygdala; mPFC, medial prefrontal cortex.

Notably, such reactivation occurs not only during active engagement but also during offline states (e.g., sleep or quiet wakefulness), where spontaneous replay of activity patterns emerges among recently activated hippocampal neurons. These replay events are temporally coupled to sharp-wave ripples (SWRs)—high-frequency network oscillations—and critically facilitate memory stabilization. Experimental interventions demonstrate that optogenetic reactivation of lateral amygdala engram cells during fear conditioning consolidation enhances subsequent memory robustness (24), with analogous findings observed in the retrosplenial cortex (47). Furthermore, fear memory engram neurons exhibit sleep-preferential reactivation, and suppressing their activity during sleep (but not wakefulness) abolishes consolidation (48–50), underscoring the role of endogenous replay in memory reinforcement.

Following initial synaptic stabilization, memories undergo system consolidation, transitioning from hippocampal dependence to medial prefrontal cortex (mPFC)-dependent storage over days to years. This process, termed systems consolidation, allows coexistence of hippocampal and mPFC engrams representing the same experience (51, 52). However, memory phenomenology diverges based on activated ensembles:

hippocampal engrams retain episodic, context-specific details, whereas mPFC ensembles encode schematic, generalized representations post-consolidation (52–56). Mechanistically, mPFC-dependent consolidation unfolds over weeks, marked by delayed structural plasticity: dendritic spine density increases and strengthened engram-to-ensemble connectivity emerge weeks postencoding (11, 57). A prevailing model posits that hippocampal indexing—where hippocampal SWRs reactivate neocortical activity patterns from initial encoding—drives mPFC maturation (36, 58). According to this framework, repeated hippocampal-mPFC replay during sleep promotes neocortical stabilization, ultimately enabling hippocampus-independent recall. Disrupting hippocampal engram activity during this critical window prevents mPFC plasticity (e.g., spine remodeling, synaptic strengthening) and retrieval-related reactivation (11, 57, 59, 60), validating the hippocampus’s instructive role in systems consolidation.

Engram in Memory Retrieval

Once an engram has been consolidated and stored, it can be activated to induce memory retrieval. Consolidated engrams mediate memory



retrieval, a process governed by the similarity between retrieval cues and the original encoding context. Successful retrieval recapitulates neural activity patterns present during encoding. Seminal studies employing Arc RNA catFISH revealed that contextual memory retrieval preferentially reactivates hippocampal CA1 neurons active during initial encoding (61). Subsequent work in TetTag mice demonstrated that fear memory retrieval reactivates basolateral amygdala (BLA) engram cells, with reactivation rates predicting memory strength (7). These findings established that retrieval engages original encoding ensembles—a principle replicated across diverse paradigms and brain regions (12, 57, 62).

Crucially, engram neurons are necessary for retrieval. Pretraining amplification of excitability in select lateral amygdala or hippocampal neurons enables memory allocation to these cells. Their targeted ablation (34) or inhibition (63–65) disrupts specific memory retrieval without impairing new learning, a phenomenon generalizable across DG, CA1, insular cortex, nucleus accumbens, and mPFC (8, 11, 16, 33, 66). Artificial engram reactivation bypasses natural cues to induce memory retrieval (10, 19, 67–69). Multiregional co-activation enhances retrieval efficacy compared to single-region stimulation (69), replicating across fear conditioning, place preference, and social memory tasks (6, 22, 36, 70, 71). Retrieval itself transiently boosts engram excitability via Kir2.1 channel modulation, improving behavioral discrimination and pattern separation (72). Notably, minimal stimulation suffices: activating two visual cortex engram neurons drives ensemble-wide pattern completion and memory retrieval (37). Hippocampal engram stimulation further recruits downstream amygdala and cortical ensembles (59, 73), illustrating system-level coordination. This capacity for activity pattern completion from sparse inputs underlies artificial engram-driven retrieval.

Engram and Memory Generalization

Fear overgeneralization represents a maladaptive behavioral response to nonthreatening stimuli or neutral environments. This phenomenon, a hallmark feature of anxiety spectrum disorders such as generalized anxiety disorder, panic disorder, and posttraumatic stress disorder (PTSD) (74, 75), demonstrates significant clinical relevance. This section synthesizes current understanding of hippocampal and extrahippocampal engram contributions to fear generalization, with particular emphasis on neural circuit mechanisms driving this pathological memory process.

Hippocampal Engrams and Fear Generalization

Engram cells within the dorsal dentate gyrus (dDG) critically support memory precision through pattern separation—a computational process essential for discriminative memory retrieval (76, 77). The temporal degradation of memory specificity correlates with dynamic hippocampal-cortical network reorganization during systems consolidation (78). Hippocampus plays an important role in maintaining the specificity of memories over time through the hippocampal-cortical interactions that underlie memory consolidation (79, 80). Recent mechanistic studies reveal DG circuit regulation of memory precision: (1) DG-CA3 connectivity via stratum lucidum inhibitory interneurons (SLINs) modulates recent memory specificity (81); (2) Mossy fiber terminal filopodia contacting SLINs mediate feedforward CA3 inhibition (82, 83); (3) DG-driven inhibitory control shapes CA3 activation patterns and memory precision (81, 84). Notably, the actin-binding protein ABLIM3 emerges as a learning-sensitive regulator of DG-SLIN connectivity. ABLIM3 downregulation enhances context-specific engram reactivation in hippocampal-cortical networks while reducing remote fear generalization (85), positioning it as a molecular brake on memory specificity.

Neuronal competition analyses demonstrate that generalized fear expression in novel contexts arises from fear engram dominance over non-engram dDG populations. Complementary findings reveal ventral DG mossy cell (vMC) suppression correlates with context-generalized fear, while vMC-dDG pathway activation selectively attenuates generalized fear responses without affecting conditioned fear (86).

Stress constitutes a homeostatic challenge critically involved in PTSD pathogenesis and fear memory generalization (87). Stress exposure during memory encoding/processing induces maladaptive fear generalization characterized by context-inappropriate memory expression (88). Stressors activate the hypothalamic-pituitary-adrenal axis, triggering

adrenal glucocorticoid release that potentiates memory generalization (89, 90). Engram formation follows sparse encoding principles, preferentially recruiting hyperexcitable principal neurons while suppressing incorporation of less responsive cells (65, 91). Through activity-dependent TetTag labeling of footshock-activated ventral CA1 neurons, researchers demonstrated that chronic aversive engram activation drives fear generalization, directly linking stress exposure to maladaptive memory expression (92). Postconditioning glucocorticoid elevation induces contextual fear generalization, correlating with enhanced excitability and expansion of DG engram populations. Notably, chemogenetic silencing of these activated DG engrams blocks stress hormone-mediated generalization (93). Engram expansion occurs through training-phase disruption of inhibitory networks, particularly parvalbumin-positive (PV⁺) interneurons (94). Targeted PV⁺ interneuron suppression in dorsal CA1 during threat conditioning produces hyperdense engrams and generalized fear memories (95). These findings support a mechanistic framework where stress-induced PV⁺ dysregulation alters engram/non-engram competitive dynamics, potentially enabling context-independent fear retrieval.

Engrams in Other Brain Areas and Memory Generalization

Emerging evidence suggests that stress-mediated corticosterone signaling enhances fear engram ensemble density within the lateral amygdala, thereby promoting fear generalization (96). Mechanistic investigations revealed that pharmacological interventions targeting glucocorticoid receptors (antagonists) and endocannabinoid systems (synthesis inhibitors), combined with neuromodulatory approaches enhancing PV⁺ neuronal activity or suppressing cannabinoid receptor expression in lateral amygdala PV⁺ neurons, effectively restored threat memory specificity and normalized engram sparsity in stressed mice. These findings establish a critical retrograde signaling mechanism through which endocannabinoids modulate PV⁺ interneuron activity to mediate stress-induced memory generalization (96).

Current theoretical frameworks propose three potential mechanisms for memory generalization: (1) encoding-phase modifications, (2) retrieval-phase manifestations, and (3) temporally dynamic recruitment of distinct neural networks (97, 98). Recent advances in neuronal tagging technology, particularly the scFLARE2 system (single-chain fast light- and activity-regulated expression 2), have enabled precise temporal tracking of amygdala neuronal ensembles during threat conditioning. These studies demonstrate that temporally proximate threat experiences become neurobiologically linked through collocation to overlapping engram ensembles, establishing this as a fundamental mechanism of memory generalization (99).

The neural substrates of memory generalization extend beyond canonical hippocampal-amygdala circuits. The retrosplenial cortex (RSC) demonstrates multimodal involvement in cognitive processes ranging from spatial navigation (58) to prospective cognition (100) and contextual memory retrieval (101). Postacquisition reactivation of memory engrams facilitates neocortical ensemble maturation through activity-dependent synaptic plasticity, a critical process in systems consolidation (11). Notably, high-frequency stimulation of RSC engrams 24 hours postlearning induces fear generalization and shifts recent memory retrieval dominance to the anterior cingulate cortex (ACC), bypassing hippocampal involvement (47). This neural reorganization exhibits state-dependent specificity, occurring exclusively during offline brain states (sleep/anesthesia) rather than active wakefulness (47). Complementary findings reveal regulatory mechanisms in prefrontal circuitry. Chemogenetic silencing of infralimbic (IL) cortical ensembles established during learning exacerbates generalization, whereas their activation enhances memory specificity, indicating IL-mediated inhibitory control over fear generalization (102). Furthermore, molecular investigations identify insulin-like growth factor 2 receptors (IGF-2R) in auditory cortex layer 2/3 as critical modulators of engram precision. Reduced IGF-2R expression correlates with fear generalization, while exogenous IGF-2 administration directly into auditory cortex preserves remote fear memory specificity, suggesting IGF-2 signaling maintains engram fidelity over time (103).

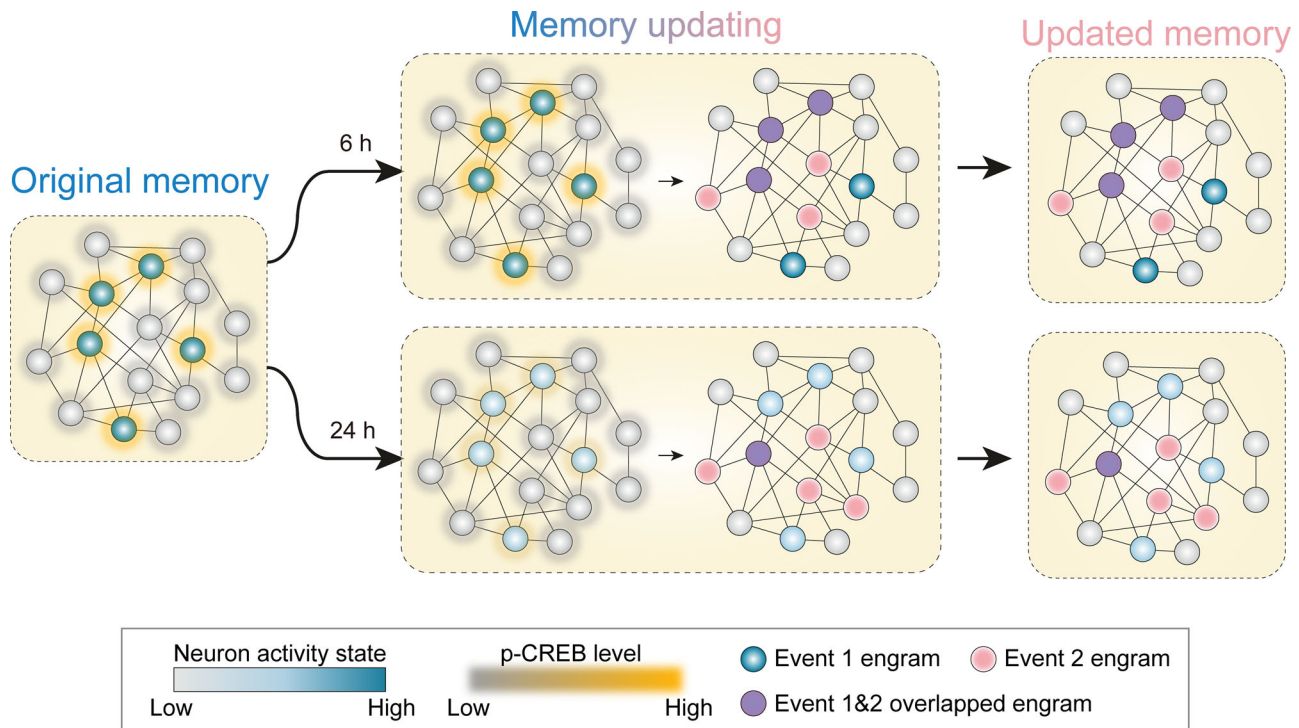


Figure 2. Engram competition in memory updating. During memory consolidation processes, engrams initially encoded by event 1 (blue) maintain a state of heightened excitability and p-CREB level relative to adjacent neuronal populations for ~6 h postencoding. When a similar event 2 (pink) occurs within this temporal window, the hyperexcitable event 1 engram neurons demonstrate preferential recruitment during event 2 encoding, resulting in overlapping engram (purple) formation and subsequent memory trace updating from event 1 to event 2. Following extended temporal intervals (24 h), event 1 engrams undergo intrinsic excitability reduction. Subsequent event 2 encoding under these conditions engages a novel population of hyperexcitable neurons achieve preferential recruitment for event 2 engram formation. This temporal-dependent segregation of memory traces enables memory updating.

Engram and Memory Updating

Memory updating is a fundamental process that allows organisms to adapt to new information, modify existing knowledge, and integrate novel experiences with pre-existing memories. Memory linking is one of the most extensively studied examples of memory updating in current research. The neural representation of memories, or engrams, is central to this process. Recent advances in neuroscience have shown that memory engrams are not static but are instead malleable, subject to modification or updating through mechanisms such as reconsolidation, synaptic plasticity, and cellular reorganization. In this section, we summarize the dynamic engram overlap in memory updating and how to switch the valence of engrams.

Engram Overlap in Memory Updating

The hypothesis that overlapping neuronal ensembles mediate memory traces originated from Pavlovian conditioning paradigms, wherein animals learn to link a CS (e.g., tone/light) with an US (e.g., shock/food) to elicit conditioned responses (e.g., freezing) (104). While not strictly reflecting memory linkage, this process necessitates stimulus association (Figure 2).

Early work visualized CS-US convergence using Arc—an IEG dynamically redistributed between nucleus (0–5 min postactivation) and cytoplasm (5–30 min) (61). By temporally separating CS/US presentations by ~25 min, amygdalar neurons coactivated during associative learning were identified (105–107), with their convergence proving essential for taste memory formation (108). However, these static snapshots lacked temporal resolution to resolve ensemble dynamics during association. To address this, subsequent studies employed *in vivo* real-time calcium imaging in freely behaving mice to record ensemble activity during the presentation of the CS and US, as well as during the following periods. One study demonstrated that the neuronal ensemble in the amygdala re-

sponding to the CS changed to resemble that of the US after successful association, suggesting cross-talk between subensembles of the same memory (109). A second study revealed another form of neuronal cross-talk in the hippocampal area CA1 (110). During the presentation of the CS and US, their respective ensembles responded independently to each input. However, after the presentation of both stimuli, a phase of network reverberation occurred, during which the two ensembles exhibited synchronized activity, facilitating the successful CS-US association. This finding indicates that, in addition to cellular overlap, a temporal overlap in the activity of distinct ensembles may also link different aspects of a memory.

Signals related to the CS and US converge on the same neurons within seconds or minutes to generate associations within a single episodic memory. Similarly, studies have demonstrated that different memories, encoded hours apart, may (under specific conditions) be stored within the same neuronal population, facilitating memory linking. One study illustrated how neuronal collocation, defined as overlap between neuronal ensembles, can naturally link contextual memories encoded in close temporal proximity within the hippocampus (111). In this study, mice exposed to two different contexts within a short temporal window (5 h) showed that the memories of these contexts were linked. Specifically, a foot shock in one chamber caused the mice to freeze significantly in the other chamber. This response was not merely due to generalization, as the mice were able to distinguish between the two linked contexts and a neutral context that had never been associated with the prior two, demonstrating that the memory linkage was specific and the identity of each memory was preserved. Calcium imaging and engram labeling, using genetic and immunohistochemical techniques, revealed a higher degree of overlap between the active ensembles encoding each context when the memories were linked, as compared to when they were separated by a longer temporal window, in which case no linkage occurred. A similar study, using

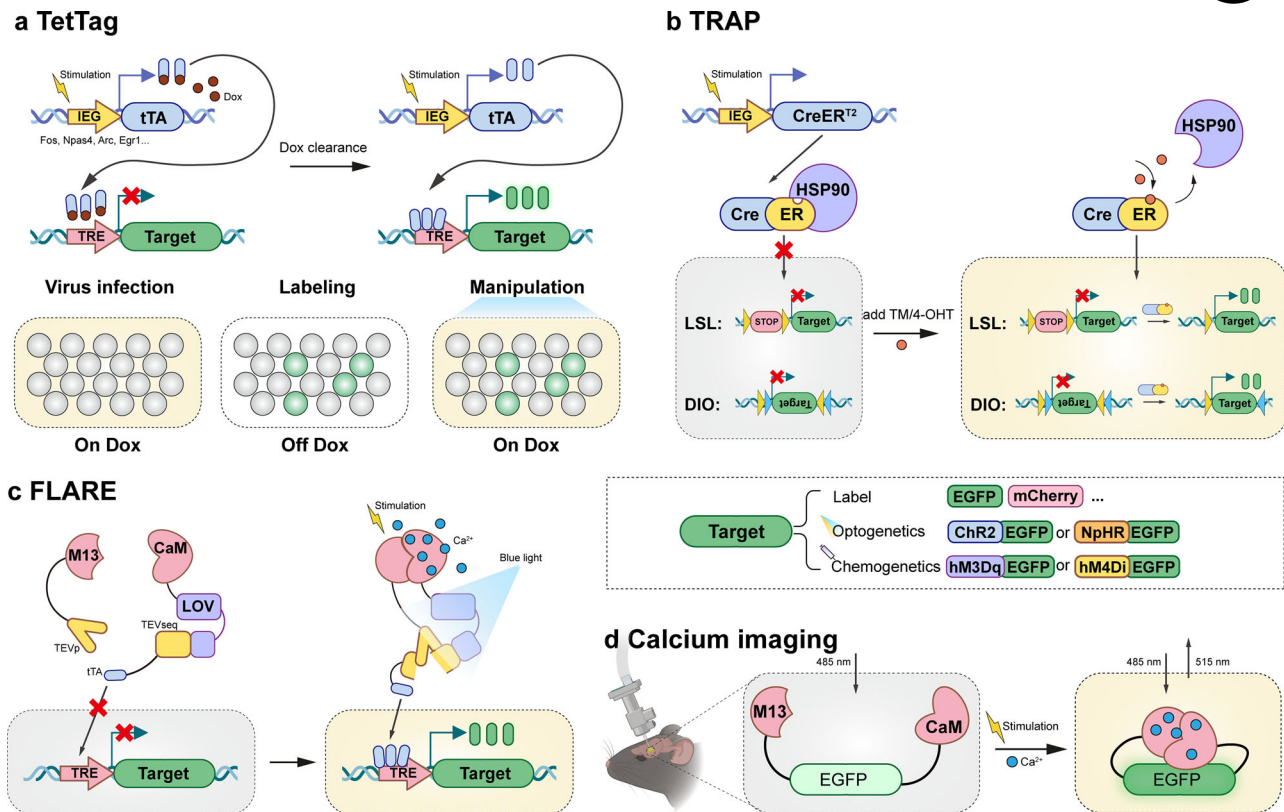


Figure 3. Neuronal activity-dependent tools for labeling, manipulating, and recording neurons. (A–D) Diagram of activity-dependent tools for neuronal labeling and manipulating, TetTag (A); TRAP (targeted recombination in active populations) (B); FLARE (Fast Light and Activity-Regulated Expression system) (C); (D) Diagram of GCaMP-based calcium imaging technology.

auditory fear conditioning (AFC) with two separate tones, showed comparable collocation and memory linking in the mouse amygdala when the tones were presented in close temporal proximity (65). This research further demonstrated that engram overlap and memory linking can also be induced by the mere recall (rather than initial learning) of an event shortly before the encoding of a second memory. In addition to linking memories of the same type, there are also reports of linking between different types of memories. It has been reported that two amygdala-dependent emotional memories—conditioned taste aversion (CTA) and AFC—were linked through repeated coretrieval sessions (112). This linkage was demonstrated by the observation that mice froze (the behavioral response to AFC) upon receiving saccharin, the conditioned taste aversion stimulus. Labeling and optogenetically inhibiting the overlapping ensemble shared between both paradigms preserved both memories but disrupted the link between them. This finding illustrates that memories can be specifically linked without altering the individual memories, providing valuable insights into the content encoded within the overlapping engrams. Memories to be linked across long periods such as days are poorly understood. A recent study found that two memory ensembles separated two days apart is overlapped during the offline period after learning (113), which suggested that offline periods after learning may be important for memory integration as well. In addition, ensembles coreactivation occurs more during wake than during sleep.

Above researches have primarily focused on memory linking through engram manipulation without altering the original memory engrams. While this approach constitutes a form of memory updating, real-world memory updating often involves modifications to memory content—such as the transformation of a positive memory into a negative one. A critical unanswered question remains: does engram overlap occur during such content-modifying memory updating processes? A previous study reported that the original memory engram of fear contributes to re-

mote fear attenuation via high overlap with extinction ensembles which have been reported distinct with fear ensembles in the fear extinction paradigm (114). However, these prior investigations relied on IEG-dependent tagging approaches, which lack the temporal resolution to resolve dynamic engram interactions during active behavioral states. The development and application of genetically encoded calcium indicators (GECIs) have established the monitoring of cytosolic calcium ion concentration dynamics as a prominent methodology for real-time detection of neuronal activity (Figure 3) (115). In addition to monitoring neuronal activity, FLARE, developed from GECI, enables high temporal resolution labeling and manipulation of neurons by using 10 min of blue light stimulation to drive the specific expression of any target protein (116). Nonetheless, due to the inherent limitations of optogenetics, the potential for artificial effects remains an inherent drawback of both optogenetic and chemogenetic approaches. Furthermore, while hippocampal engram overlap has been characterized, the existence and mechanisms of engram overlap in prefrontal circuits remained unexplored. Our lab was the first to identify a high overlap between fear and extinction engrams during a postretrieval paradigm, using *in vivo* calcium imaging at the single-cell level in the prefrontal cortex (PrL) (23). Fear extinction memory has been previously reported as a newly formed reward memory (23). These findings support the concept of engram overlap in memory updating, suggesting that memory updating is mediated by the rewriting of the original memory trace through significant engram overlap.

Switch of Valence Associated with Engram

Engram overlap has been observed in various memory updating scenarios, and experiments manipulating engrams have shown that the information encoded in the original engram can be either enhanced or attenuated. However, it remains unclear whether the value encoded by the original engram can undergo a revise. The reactivation of engram cells



by natural cue, or optogenetic manipulation could be a prerequisite for memory malleability to integrate the new information outside the original memory trace and orchestrated to constitute an updated memory. It has been reported that the valence associated with the hippocampal DG memory engram could be bidirectionally reversed (22); however, the BLA engrams were not able to reverse the valence of the memory. Consistent with this report, our previous study found that the reactivation of BLA engram cells is not sufficient for the memory valence updating; however, US stimulus, which triggers a more generalized BLA activation, could induce the BLA engram encoding updating (23). While we demonstrated that memory updating is specific to learning-associated memory encoding as the valence of innate fear engrams (shock labeled) was unchanged. In addition, the valence associated with engram in PrL could also be revised by increased overlap with another engram which encode opposite valence (23). Only a part of original engram showed increased activity during memory updating, suggesting that a part of cell activation pattern alteration might be sufficient for switching the function of original engram.

What is the underlying mechanism through which engrams contribute to memory updating? As proposed by Morris and colleagues (117), the modification of synaptic connection patterns, mediated by synaptic plasticity, is the fundamental mechanism by which the brain stores memory. Using synaptic optoprobe techniques, Kasai and colleagues demonstrated that acquired motor learning was disrupted by optical shrinkage of potentiated spines, but this manipulation had no effect on spines activated by a distinct motor task in the same cortical region (118). This suggests that acquired motor memory depends on the formation of a task-specific, dense synaptic ensemble. Furthermore, optogenetic manipulation of synaptic plasticity specific to one memory was shown to affect the recall of only that memory, without altering a linked fear memory encoded in the shared ensemble (25), indicating that synapse-specific connectivity of engram cells preserves the identity and storage of individual memories. Additionally, using the dual-eGRASP (GFP reconstitution across synaptic partners) technique, it was reported that fear conditioning enhanced connectivity and increased spine morphology between engram cells, while extinction weakened the connectivity between these cells. We hypothesize that memory information is stored in the specific pattern of connections among engram cells, and that memory updating may alter the original engram encoding by modifying its connections with other engrams.

Dynamic of Engram Cells Maturation

Memory formation involves experience-responsive neuronal ensembles that constitute both the necessary and sufficient substrate for recall. A fundamental question in neurobiology concerns the temporal progression of engram states following initial encoding. Current models propose that engrams undergo molecular and circuit-level refinement during consolidation, with encoding-activated cells playing essential roles in successful retrieval (6). Notably, prefrontal circuitry demonstrates time-dependent functional specialization in memory processing. Chemogenetic silencing experiments reveal that mPFC engram cells activated during acquisition become indispensable for remote memory recall (typically 2–4 weeks postencoding), yet remain nonessential for recent memory retrieval. Intriguingly, these mPFC ensembles exhibit natural cue-induced reactivation specifically during remote timepoints, suggesting their progressive integration into cortical memory networks (11). Conversely, hippocampal engram cells display inverse temporal dynamics. Calcium imaging studies demonstrate complete absence of natural cue reactivation in CA1 engram populations 15 days postconditioned fear consolidation (CFC) (11, 119). Longitudinal monitoring of synaptic reorganization in hippocampal pyramidal neurons revealed rapid turnover of basal dendritic spines, with learning-associated connectivity patterns dissipating within 15 days postacquisition (11, 119). This synaptic reorganization was corroborated by quantitative analysis demonstrating 38.7% reduction in dendritic spine density within DG engram cells at 14 days post-training (11). These complementary observations collectively demonstrate bidirectional engram state transitions: Cortical engrams transition from latent to functionally dominant states across a ~2-week consolidation window. Hippocampal engrams paradoxically maintain stable synap-

tic connectivity during recent memory phases but undergo progressive functional silencing (Figure 4).

Transcriptional and Epigenetic Mechanisms Underlying the Dynamic Change in Engrams

Emerging evidence reveals that dynamic transformations in memory engram cells are governed by multifaceted molecular and epigenetic mechanisms. Chromatin plasticity emerges as a critical regulator, with enhanced nuclear flexibility increasing neuronal excitability to prime cellular recruitment into engram networks (120). Longitudinal analyses further demonstrate experience-dependent chromatin reorganization during memory formation and retrieval phases, suggesting structural genomic adaptations underlie engram functionality (121). DNA methylation patterns exhibit spatiotemporal specificity in memory processing. Cortical hypermethylation persists in the mPFC following CFC, with pharmacological inhibition of methyltransferases at remote timepoints impairing retrieval—a mechanistic demonstration of epigenetic maintenance of long-term memories (122). The differential DNA methylation alternations in hippocampus and mPFC at 1 h and 4 weeks after CFC correlates strongly with the dynamic temporal spatial location of associative memory (123), which could alter the expression and splicing of genes involved in functional plasticity and synaptic wiring. Increased DNA 5-hydroxy methylation levels have also been reported in mPFC for remote contextual fear memories (124). Using neuronal activity-dependent promoter to drive de novo DNA methyltransferase 3a2 (Dnmt3a2) overexpression within DG memory engram cells specifically during consolidation was sufficient to strengthen contextual fear memory, which suggests DNA methylation selectively within memory engrams as a mechanism of stabilizing engrams during consolidation that supports successful memory retrieval (125).

Histone modification during learning has also been shown to be important for the memory dynamic. The increases in histone H3 acetylation in the orbitofrontal cortex (OFC) were observed after social transmission of food preference learning, and interference with this cascade during the early postacquisition period could bidirectionally regulate remote memory retrieval (126). Histone H2A.Z, a variant of histone H2A, is actively exchanged in response to fear conditioning in the hippocampus and the mPFC, where it mediates gene expression and restrains the formation of recent and remote memory (127). How does synaptic transmission trigger transcriptional changes in engram cells to contribute to memory consolidation? DG engram neurons exhibit prominent CREB-dependent transcription features which are required for recent CFC memory consolidation (128). CREB-mediated transcription in mPFC engram cells has been reported to be required for remote memory consolidation (129).

Neuronal Excitability and Engram Dynamic

Neuronal excitability is an intrinsic property that determines the threshold for spike generation and regulates signal transmission (130). Studies have shown that neurons with inherently higher excitability during memory encoding are more likely to become part of the engram (28, 64). Patch-clamp recordings have revealed that synapses connecting hippocampal engram cells are selectively strengthened compared to those linking non-engram cells, as evidenced by increased excitatory postsynaptic current amplitude, enhanced spontaneous excitatory postsynaptic current amplitude, and an elevated AMPA-to-NMDA receptor ratio (19). Moreover, DG engram cells exhibit a transient increase in excitability following memory reactivation, a phenomenon mediated by NMDA receptor activation and a subsequent cascade leading to the downregulation of Kir2.1 channels (72). This rapid yet temporary modulation enhances the precision and efficacy of subsequent memory retrieval (72). In the context of social associative olfactory memory, the reorganization of GluN2B-containing NMDA receptors acts as a critical tuning mechanism, determining the fate and malleability of cortical memory engrams (131).

Dynamic maturation of memory engrams also depends on neuronal circuit activity. It has been demonstrated that the maturation of mPFC engram cells requires postlearning input from hippocampal engram cells (11). For example, chronic inhibition of hippocampal DG engram cell output via selective tetanus toxin (TeTX) expression initiated one-day post-training abolished the reactivation of mPFC engram cells during remote

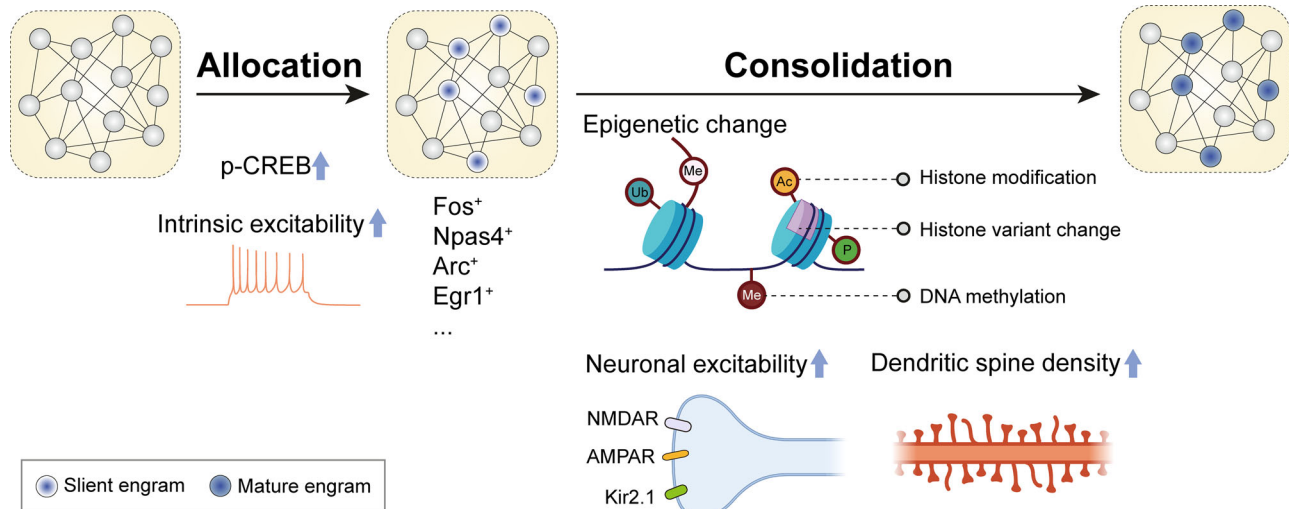


Figure 4. Dynamic mechanisms of engram maturation. During the allocation, engram allocation is primarily governed by enhancements in intrinsic neuronal excitability, driven primarily by increased phosphorylation of CREB, which primes these cells for selective recruitment. Following allocation, engram formation is molecularly marked by the expression of IEGs including Fos, Npas4, Arc, and Egr1. The consolidation phase is characterized by epigenetic reprogramming, such as DNA methylation, histone posttranslational modifications (e.g., acetylation, phosphorylation), and histone variant exchange. Concurrently, neuronal excitability is further modulated through synaptic recruitment of NMDA receptors, AMPA receptors, and inwardly rectifying potassium channels (Kir), while dendritic spine density increases to reinforce synaptic connectivity. Throughout this maturation process, engrams transition from a silent state to a functionally mature configuration, marked by enduring structural and molecular adaptations that support long-term memory storage.

exposure to a conditioned context and prevented the associated increase in dendritic spine density observed in control subjects. Furthermore, pharmacologically silencing hippocampal activity during early phases impaired remote social transmission of food preference (STFP) memory, stored in the OFC, indicating that early hippocampal activity is crucial for the subsequent maturation and stabilization of mnemonic traces (126). Disruption of hippocampal engram activity during recent recall at remote timepoints, or interference with CA1-to-ACC projections postlearning, impairs remote CFC memory, suggesting that functional connectivity between engrams is vital for their maturation during the transition from recent to remote memory (132). Additionally, overexpression of hippocampal Dnmt3a2 promotes the transfer of fear memory traces from the hippocampus to the cortex and facilitates the maturation of mPFC engrams, further supporting the role of DNA methylation-mediated hippocampal activity in cortical memory engram maturation (133). Finally, the consolidation of remote contextual fear memories has been linked to progressive strengthening of excitatory connections between PFC engram neurons active during learning, a plasticity process that is CREB-dependent and relies on sustained hippocampal signals (57).

Dynamic Components of Engrams

Several questions remain regarding the dynamic changes in engram cells. Engram neurons are typically defined as those activated during both memory encoding and retrieval. One common method for identifying activated neurons involves detecting the expression of IEGs such as Fos, Npas4, Arc, and Egr1, which serve as markers of neuronal activity (134). Notably, functional heterogeneity within memory engrams can be delineated by the differential expression of these IEGs. For instance, it has been reported that the Fos ensemble promotes the generalization of contextual fear memory, whereas the Npas4 ensemble is essential for its discrimination (135). Furthermore, developmentally distinct subpopulations of hippocampal neurons are differentially recruited into memory traces over time. Specifically, late-born neurons are preferentially recruited for retrieval shortly after CFC acquisition, while early-born neurons become more prominent at later stages (136). This divergent recruitment underlies the gradual reorganization of memory ensembles, thereby influencing memory persistence and plasticity. Computational models using spiking neural networks have revealed that neurons can both drop out of and join engrams during memory consolidation, with inhibitory synaptic plas-

ticity playing a critical role in refining engram selectivity (137). In addition, long-term potentiation (LTP), an activity-dependent and sustained increase in synaptic strength, is suspected to contribute to engram maturation via LTP-like mechanisms. Notably, inducing optical LTP shortly after fear conditioning has been shown to preferentially enhance memory encoding (42, 138). Moreover, the use of dual-enhanced green fluorescent protein reconstitution across synaptic partners (dual-eGRASP) has allowed researchers to monitor synaptic dynamics, revealing that changes at CA3-to-CA1 engram synapses are key modulators during fear memory states (139, 140). Despite these advances, how functionally distinct memory engrams are defined within a memory trace and how they dynamically evolve during consolidation and updating remain open questions. Numerous studies have demonstrated that reactivation of memory engrams during offline periods following learning is critical for both memory consolidation and updating (113, 141). For example, after a fearful event, memory encoding ensembles are reactivated and strengthened during post-conditioning sleep, and disrupting this engram reactivation during sleep impairs the consolidation of fear memory (49, 142). The intrinsic mechanisms driving offline engram activation warrant further investigation.

Questions to be Answered

The study of dynamic change of engrams across different memory processes such as encoding, consolidation, generalization, and updating has significantly contributed to our understanding of memory. However, there are still numerous fundamental questions that remain unanswered. For example, we now know that memory engrams undergo epigenetic changes related to their activation state during learning, which will subsequently influence both immediate and long-term transcriptional responses. However, there are significant gaps in our understanding of the crucial steps that connect these nuclear changes to the reinforcement of specific synaptic connections. Furthermore, across different memory processes such as consolidation, retrieval, generalization, and updating, mechanisms that drive neurons drop out of and drop into engrams network to modify our memory remains unknown. The neural ensemble fluidity in engram composition confers our memory stability and flexibility, which mechanism need further investigation. Finally, our knowledge of the intrinsic mechanism underlying the offline activation of memory engrams in an unconscious state is totally lacking, which might shed light on the understanding of our memory representations drift over time



depend on our experience and internal states. The ongoing development and optimization of new technologies for studying engram cells hold great promise for addressing these fundamental questions, which have the potential to revolutionize our understanding and treatment of memory-related disorders.

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Author Contributions

Z.Y.C. and S.W.T. conceptualized, wrote, and revised the manuscript and figures. X.L.C. contributed to the figure art.

Author Disclosures

The authors declare no competing interests.

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Heart rate modulation and clinical improvement in major depression: A randomized clinical trial with accelerated intermittent theta burst stimulation

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Intermittent theta burst stimulation (iTBS) is a promising noninvasive treatment for major depressive disorder (MDD), though significant variability exists in patient responses. This quadruple-blind, sham-controlled crossover randomized clinical trial investigated whether clinical improvement was influenced by the spatial selection of stimulation sites or early cardiac rhythm modulations. Seventy-five patients with MDD (33 women) were randomized to either personalized stimulation sites—identified via the strongest negative functional connectivity between the left dorsolateral prefrontal cortex and the default mode network—or fixed stimulation at the F3 position of the 10–20 EEG system. Electrocardiograms throughout stimulation monitored heart rate and its variability, focusing on heartbeat deceleration heart rate (RR) slope and changes in the root mean square of successive differences between heartbeats (RMSSD). Findings demonstrated that a higher RR slope within the first 45 s of stimulation predicted greater clinical improvement at 6 weeks, while a lower RMSSD change during the first 270 s correlated with improvement at 1 week. However, no significant differences in outcomes were observed between personalized and fixed stimulation sites. This study identified a significant relationship between early heart rhythm modulations and the antidepressant effects of accelerated iTBS in MDD. Although the spatial determination of stimulation sites did not enhance clinical improvement, iTBS-induced changes in cardiac rhythm during early sessions may develop into valuable biomarkers for stratifying patients, enabling more personalized and effective treatment strategies in the future.

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Keywords: Major depressive disorder, intermittent theta burst stimulation, personalized stimulation, F3 stimulation, heart rate, heart rate variability

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders and the leading cause of disability worldwide (1). With a lifetime prevalence of 16%–20%, MDD treatment is particularly challenging for approximately one-third of patients who experience treatment-resistant depression. These patients fail to respond to two or more antidepressant medication trials of adequate dose and duration (2). In this context, repetitive transcranial magnetic stimulation (rTMS) has gained attention as an effective treatment modality (3, 4). More recently, advances in stimulation protocols such as intermittent theta burst stimulation (iTBS) (5), along with the expansion of neurostimulation in clinical settings, have encouraged the application of rTMS as a first line of treatment for MDD (6, 7). Although access to and familiarity with iTBS has increased, clinical outcomes remains extremely variable and difficult to predict. In the field of precision medicine, neurobiological predictors have been proposed as potential markers of clinical improvement in patients undergoing rTMS. For example, the selection of customized stimulation sites based on individual functional connectivity and the identification of heart rhythm modulations at the onset of stimulation are very promising candidates (8–11). Thus, in this randomized clinical trial (RCT), we prospectively evaluated the clinical improvement of spatially personalized stimulation sites as well as subsequent heart rate (HR) and HR variability modulations. Both strategies suggest that the degree of commu-

nication from the site of stimulation in the left dorsolateral prefrontal cortex (DLPFC) to the subgenual anterior cingulate cortex (sgACC) is likely implicated in clinical improvement (12–14).

The most studied and successful coil position for the treatment of clinical depression has been in the left DLPFC (15). Historically, the position site was determined using the “5cm rule” or “7cm rule,” referring to the distance from the point where the resting motor threshold (RMT) was established to the prefrontal region. However, this motor system-based approach has been questioned over the years, as anatomical locations in the DLPFC have not been consistent (16, 17). More recently, the default mode network (DMN), and the sgACC in particular, has emerged as a promising references for coil positioning, given its relevance to the pathophysiology of depression and its association with clinical improvement (18–20).

One approach to optimize coil placement utilizes resting-state functional magnetic resonance imaging (MRI) connectivity of the individual. Building on evidence of a physiological anticorrelation between the frontoparietal network and the DMN (21), an rTMS study demonstrated that reducing the DMN hyperconnectivity in MDD, extending to the sgACC, was associated with symptomatic relief (18, 20). Subsequent studies have replicated an association between greater therapeutic success with rTMS and the degree of anticorrelation of the individual left DLPFC and a general sgACC seed (10). However, since a general sgACC seed may not reflect the individual sgACC site implicated in symptoms, we validated a protocol

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using the same anticorrelation concept, but with a focus on the strongest anticorrelation between the left DLPFC and the individual DMN. This approach demonstrated that rTMS resulted in functional disconnection of the DMN up to the sgACC region in healthy volunteers (22, 23). Translationally, we hypothesized that the closer the ideal stimulation site was to the individualized target, the greater the clinical benefit of the iTBS protocol would be for depressed patients and we tested both DMN and sgACC associations, as previously replicated.

A novel approach, termed neuro-cardiac-guided (NCG)-TMS, involves stimulating the left DLPFC and, possibly through the sgACC, exerting modulations on HR and HR variability. This is thought to reflect the successful activation of the frontal vagal pathway, which would enhance the vagal tone, reducing HR and/or increasing HR variability. Additionally, research in healthy volunteers has suggested that stimulation at the F3 position of the 10–20 EEG system is optimal for inducing early HR changes with rTMS (24). Compared to healthy controls (HCs), depressed patients exhibit altered HR and HR variability (25, 26), and these alterations are not always reversed by treatment (27). However, another study using iTBS observed a trend toward an association between HR decelerations and clinical improvement in depression (8), suggesting that HR modulations may serve as a predictor for treatment response.

In the current RCT, we rigorously tested the two previously suggested approaches to enhance the clinical benefits of rTMS treatment in depression: (1) spatial customization of coil position in the left DLPFC based on resting-state functional connectivity data and (2) early modulations of cardiac rhythm. The primary outcome was clinical improvement over a 6-week period, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) score in patients with major depression treated with accelerated iTBS. Based on the existing evidence, we hypothesized that both the personalized selection of stimulation sites (personalized > F3 site) and the early iTBS-induced modulations of HR (as measured by RR slope) and HR variability change [as measured by RMSSD (root mean square of successive difference) minus baseline] would be positively associated with greater clinical improvement.

Results

Of the 125 patients screened, 92 were enrolled in the study (Figure 1). Of the 33 patients who were not enrolled, 18 were excluded and 15 did not consent to participate, mainly due to time constraints. Of the excluded patients, 7 met the diagnostic criteria for bipolar depression, 3 did not meet the diagnostic criteria for MDD, 4 had claustrophobia, 3 were on recently adjusted medication, and 1 presented an incidental finding in the MRI scan. Of the 92 participants, 11 dropped out during the 6-week course of the study, with no reports of serious adverse effects (see Safety section below). The reasons for dropping out of the study were rTMS-unrelated issues (e.g., symptoms of a cold), time limitations, change in medication, etc. We also excluded 6 patients from the final analysis due to errors in the electrocardiogram (ECG) acquisition (incomplete acquisition, or extreme values detected as outliers), resulting in 75 participants.

Characteristics of the sample

We assessed the age, sex, years of education, medication use, treatment-resistant depression, comorbidities, and expectation of effect (blinding) of the participants in total and in each group (Table 1). Except for sex ($\chi^2(1) = 10.45, P = 0.001$), no other characteristic was different between groups. The number of patients on stable medication did not differ between groups ($\chi^2(1) = 0.03, P = 0.872$).

Safety and side effects

Of the 75 participants, 53.33% reported headache, 30.00% neck pain, 58.00% scalp pain, and 20.67% scalp irritation at the stimulation site. The intensity of daily pain/irritation experienced (Likert 0–10) was, however, very low on average in the active condition [M(SD): 1.47 (1.19) headache, 1.31 (1.35) neck pain, 2.31 (1.73) scalp pain, 1.40 (1.03) scalp irritation] as well as in the sham condition [M(SD): 1.01 (0.99) headache, 1.24 (1.32) neck pain, 1.06 (0.90) scalp pain, 0.81 (0.55) scalp irritation]. The intensity of daily pain/irritation between conditions differed ($P < 0.0125$) only for headache ($W = 3663.5, P = 0.007$ for headache, $W = 2688, P = 0.564$

neck pain, $W = 3369.5, P = 0.029$ scalp pain, $W = 2744.5, P = 0.718$ scalp irritation). No participant reported serious adverse effects.

Personalized versus F3 stimulation

We found no significant interaction effect of time and sex in the two groups [$F(4,295) = 0.733, P = 0.57$]. Furthermore, no two-way interactions were significant. There was a significant effect of time [$F(4,295) = 14.378, P < 0.001$]. In the pairwise comparisons, a significant reduction of MADRS was found in F3 from V1 to all visits except V3, whereas in the personalized, only V6 showed a significant reduction compared to V1 after Bonferroni correction. Most importantly, patients in the F3 when compared to the personalized stimulation displayed no significant difference in MADRS scores at the first as well as the last visit (pairwise comparison $P = 0.494, P = 0.490$) (Figure 2, panel 1). Therefore, there was a significant reduction in MADRS scores in both groups, but no significant difference between personalized and standard F3 stimulation was found in the V6 evaluation. Finally, although difficult to visualize, the within-week reductions in the overall MADRS score in the active condition were significantly larger than the sham in the linear mixed model (LMM) (Table 2), as seen earlier in (28).

Next, we investigated whether the MADRS score changed according to the distance between the stimulated and ideal sites. The mean Euclidean distance between ideal and stimulated sites was obviously shorter ($W = 4826, P < 0.001$) in the personalized ($M \pm SD: 7.27 \pm 4.76$ mm) as compared to the F3 ($M \pm SD: 18.20 \pm 9.17$ mm) group. However, the correlation values for active ($r = 0.17, P = 0.14$) and sham ($r = 0.08, P = 0.48$) conditions did not hint toward any relationship (Figure 2, panel 2). In addition, we projected the stimulation sites from the native to the standard space in order to visualize the spatial distribution of the areas in personalized and F3 groups coded with clinical response ranges (Figure 2, panel 3).

Heart rate and heart rate variability

We assessed whether iTBS-driven modulations in the RR interval (45 s) and RMSSD (270 s) would be associated with clinical benefit (delta MADRS score: 1 being a 100% reduction of depressive symptoms). Therefore, we correlated slopes and delta RMSSD with MADRS change and found a significant positive relationship for slope in the active condition only ($r = 0.27, P = 0.021$; Figure 3A), which was also significantly higher than the sham condition [$t(74) = 2.92, P = 0.005, d = 0.41$ (CI: 0.12–0.69); Figure 3B]. A relationship was not seen for correlation of delta MADRS score and RMSSD change in the active ($r = -0.17, P = 0.15$) or sham ($r = 0.05, P = 0.7$) conditions. When assessing the delta MADRS within a week, we identified a significant negative correlation with RMSSD change in the active condition only ($r = -0.29, P = 0.013$; Figure 3C), which was also significantly higher than the sham condition ($W = 3402, P = 0.017$) (Figure 3D). To confirm that the hypothesized timeframes were correct, we also conducted an exploratory investigation of timeframes 30 s, 45 s, 60 s, 180 s, 270 s, and 360 s to cover time regularly up to 6 min (Tables S1, S2, and S3; Figures S1 and S2). It is also important to note that no differences in HR or HRV were observed across any time intervals between the personalized stimulation group and the F3 group (Table S4).

Additionally, we performed LMM to explore the within-week effect of iTBS on delta MADRS score, which, in the context of hypothesis-generating, was not controlled for multiple testing. The first set of models with the three-way interaction between the condition, the distance, and the RR slope yielded a significant full-null comparison at 45 s [$\chi^2(6) = 13.09, P = 0.042$]. At all other timeframes (30 s, 60 s, 180 s, 270 s, 360 s), the full model was not significantly different from the null model. We consequently calculated the models for 45 s only. The three-way interaction was not significant ($P > 0.05$). We decided to reduce the model to the two-way interactions between the condition and the distance, the condition and the slope, and the distance and the slope. Again, we did not observe any significant interaction. We further reduced the 45 s model to the main effects and observed a significant effect for the age predictor ($\beta = 0.006, P = 0.012$). As the full-null comparisons did not yield any significant differences ($P > 0.05$), we could not replicate this finding with our secondary outcome measures [Hamilton Depression Rating Scale (HAMD) and Beck Depression Inventory (BDI-II)] as the dependent variables.

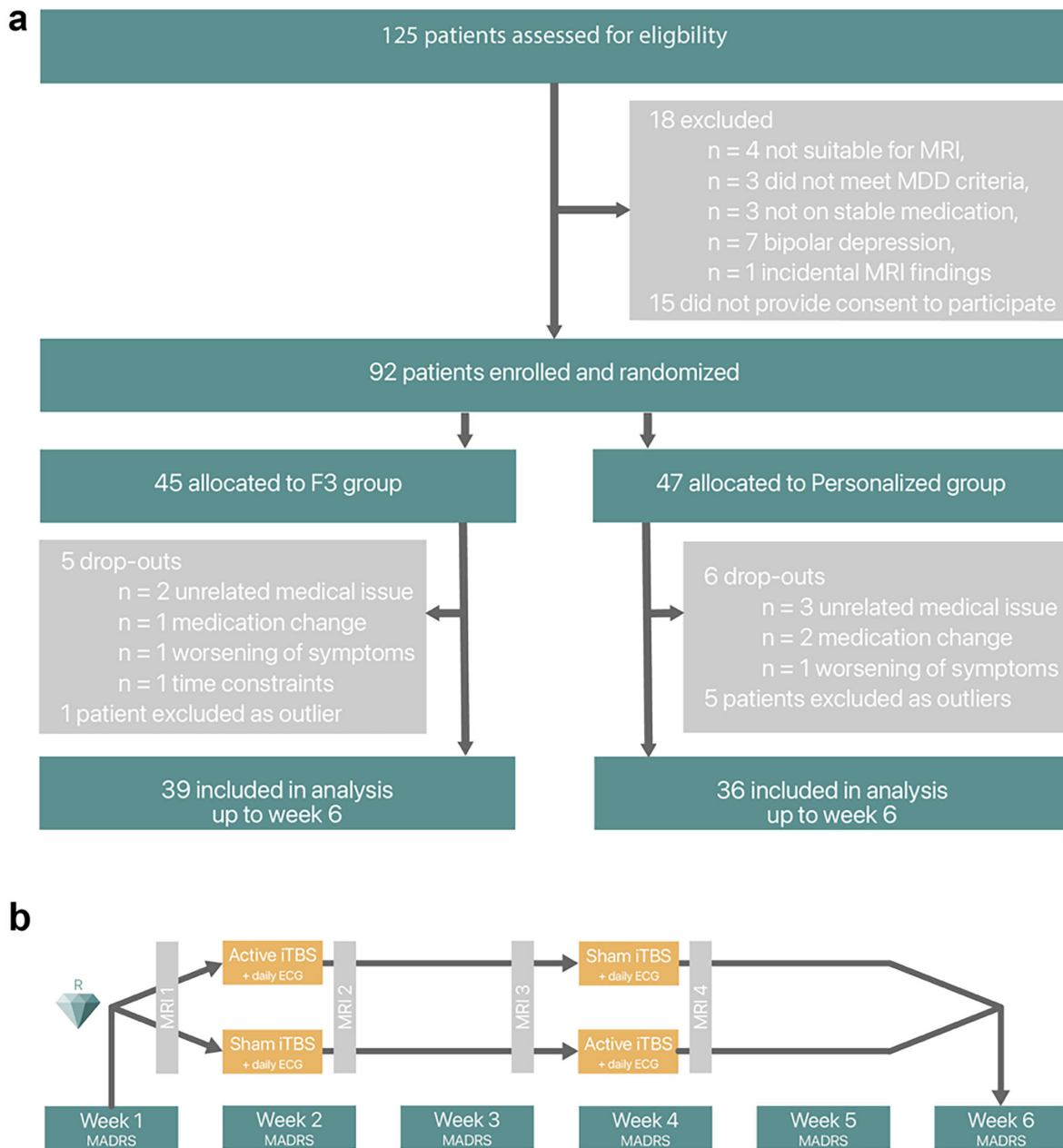


Figure 1. Participants and study protocol. (A) Study flow diagram and (B) study design.

The second set of models with the three-way interaction between the condition, the distance, and the RMSSD difference score was significantly different from the null model at all timeframes [$\chi^2(6) = 12.70, P = 0.048$ (30 s), $\chi^2(6) = 14.83, P = 0.021$ (45 s), $\chi^2(6) = 14.19, P = 0.028$ (60 s), $\chi^2(6) = 13.81, P = 0.032$ (180 s), $\chi^2(6) = 17.58, P = 0.007$ (270 s), and $\chi^2(6) = 24.67, P = 0.0004$ (360 s)]. Still, the three-way interaction was not significant ($P > 0.05$). We reduced the models by removing the insignificant interactions between the condition and the distance, and between the RMSSD change and the distance. In doing so, the two-way interaction was significant in the models for 180 s ($\beta = -0.015, P = 0.011$) and for 270 s ($\beta = -0.017, P = 0.008$, Table 2). We saw a trend in the model for 60 s ($\beta = -0.01, P = 0.075$). These estimated fixed effects were all negative, indicating that a greater iTBS-specific change in RMSSD led to worse treatment outcome in our sample. Regarding our secondary outcomes, none of the full null comparisons were significant in HAM-D. The set of models with BDI-II was significantly different from the null model at 180 s [$\chi^2(6) = 22.31, P = 0.001$], 270 s [$\chi^2(6) = 19.76, P = 0.003$],

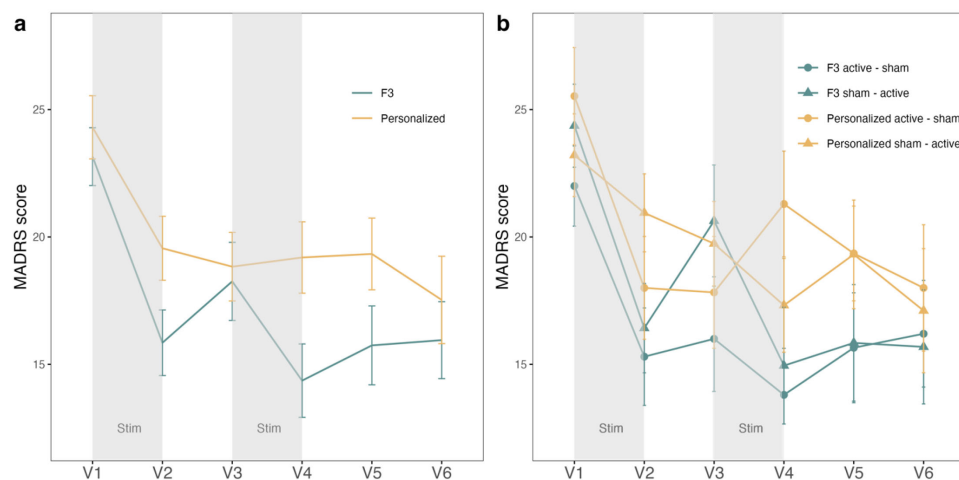
and 360 s [$\chi^2(6) = 21.19, P = 0.002$]. The three-way interactions were all insignificant. However, the two-way interactions between RMSSD change and active condition were significant for 180 s ($\beta = -0.022, P < 0.0001$), 270 s ($\beta = -0.020, P = 0.002$), and 360 s ($\beta = -0.022, P = 0.001$).

Discussion

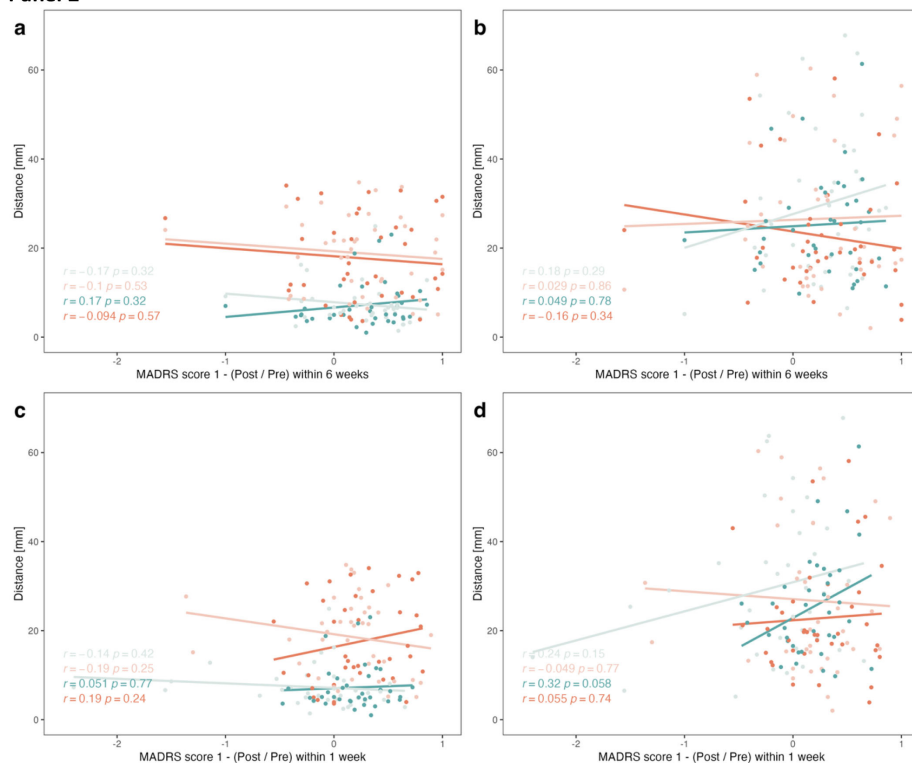
In this RCT, we investigated whether the clinical benefit of accelerated iTBS for treating depression could be related to personalization of left DLPFC stimulation sites and/or early heart rhythm modulations. As the largest prospective study to date to address these aspects, our findings show that clinical improvement driven by iTBS was associated with modulations of HR and HR variability—but not with personalized stimulation sites based on individual resting-state connectivity. As hypothesized, iTBS-driven modulations of HR were significantly associated with clinical improvement in depression. Specifically, greater HR deceleration (RR slope) within the first 45 s of the first stimulation day, the greater the clinical benefit, reflected in MADRS score changes up to 6 weeks of follow-up.



Panel 1



Panel 2



Panel 3

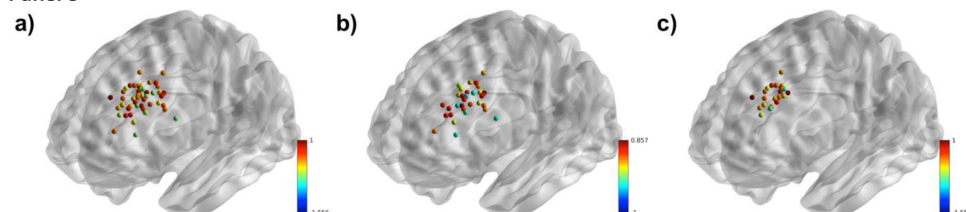


Figure 2. MADRS scores, stimulation site distance, and spatial distribution in F3 and personalized groups. Panel 1: Montgomery-Åsberg Depression Scale (MADRS) score from weekly visits V1 to V6 with active or sham stimulation between V1-V2 and V3-V4 visits (A) in F3 and personalized groups and (B) in F3 and personalized groups with sham-active and active-sham subgroups. Error bars represent mean $\pm$ SE. Panel 2: Relationship between clinical improvement (delta MADRS) and distance to ideal stimulation site calculated by (A,C) the default mode network (22, 23) and (B,D) the subgenual anterior cingulate cortex (9–11) methods. F3 stimulation in red (dark red: active, light red: sham), personalized stimulation in green (dark green: active, light green: sham); r indicates Pearson's correlation coefficient. Panel 3: Individual stimulation sites in native space projected to the MNI space in (A) whole sample, (B) personalized, and (C) F3 groups. Points are color-coded according to MADRS score 1 – (post/pre) within 6 weeks. Note the absence of a clear spatial pattern of color distribution. Also of note, projection to MNI space involves warping, which may limit the precision of individual native-space reconstructions.

**Table 1.** Characteristics of the participants. Demographic, clinical, and baseline characteristics of the participants included in the analysis

	Total		Personalized group		F3 group	
	N (%)	M ± SD	N (%)	M ± SD	N (%)	M ± SD
Number of subjects	75 (100.00)		36 (48.00)		39 (52.00)	
Order						
Active-sham	37 (49.33)		17 (47.22)		20 (51.28)	
Sham-active	38 (50.67)		19 (52.78)		19 (48.72)	
Sex ^a						
Male	42 (56.00)	33	15 (41.67)	21	27 (69.23)	12
Female	(44.00)		(58.33)		(30.77)	
Age		36.14 ± 13.09		33.83 ± 12.02		38.28 ± 13.74
Years of education		16.42 ± 3.48		16.70 ± 3.74		16.16 ± 3.24
Medication use						
Yes	57 (76.00)		29 (80.56)		28 (71.79)	
No	18 (24.00)		7 (19.44)		11 (28.21)	
Medication						
Load		1.91 ± 1.77		2.13 ± 1.95		1.71 ± 1.58
MADRS ^b at baseline		24.55 ± 7.26		24.32 ± 7.45		24.79 ± 7.09
Treatment resistance						
Yes	29 (38.67)		18 (50.00)		11 (28.21)	
No	46 (61.33)		18 (50.00)		28 (71.79)	
Number of subjects with comorbidities ^c						
Presence of	20 (26.67)		12 (33.33)		8 (20.51)	
generalized anxiety						
Panic disorder	7 (9.33)		3 (8.33)		4 (10.26)	
Eating disorder	3 (4.00)		-		3 (7.69)	
Social phobia	2 (2.67)		2 (5.56)		-	
Obsessive compulsive disorder	6 (8.00)		3 (8.33)		3 (7.69)	
PTSD ^d	2 (2.67)		1 (2.78)		1 (2.56)	
Somatoform	2 (2.67)		2 (5.56)		-	
ADHD ^e	1 (1.33)		1 (2.78)		-	
ADHD ^e	1 (1.33)		1 (2.78)		-	
Expectation of effect (VAS 0-1)						
Active		0.43 ± 0.29		0.45 ± 0.30		0.41 ± 0.28
Sham		0.38 ± 0.29		0.39 ± 0.29		0.38 ± 0.30

^a $P < 0.001$.^bMADRS: Montgomery-Åsberg Depression Rating Scale.^cComorbidities ($\chi^2(1) = 0.8, P = 0.371$): not included as covariates.^dPTSD: posttraumatic stress disorder.^eADHD: attention-deficit hyperactivity disorder.

Although iTBS-induced HR variability changes (RMSSD) within the first 270 s did not correlate with MADRS score change at 6 weeks, they did predict clinical benefit at a shorter follow-up (1 week), with patients showing lower RMSSD change experiencing greater MADRS score reductions. However, no clinical benefit was observed from using personalized stimulation sites based on individual functional connectivity (personalized site) compared to fixed stimulation sites (F3 site), nor was a relationship found between the distance from ideal sites on the left DLPFC and clinical improvement.

There is considerable anticipation regarding the identification of methods that maximize the therapeutic effect of rTMS (29, 30). The NCG-TMS approach suggests that when the frontal vagal pathways is subjected to high-frequency stimulation, HR deceleration can be observed, as demonstrated in healthy volunteers (24). In the context of MDD, often characterized by elevated HR (31), the HR deceleration observed early in the stimulation protocol could serve as objective evidence for potential effectiveness of the treatment. If this modulation in certain individuals is reactive, it possibly indicates successful activation of the frontal vagal pathway, thereby providing a means to predict which patients will benefit from the intervention. Our results support observation of increased RR slopes under real versus sham iTBS conditions, along with significant correlations between RR slopes and treatment improvement—findings that

were previously only observed as trends (8). In fact, this approach has been regarded as so promising that some researchers have suggested it could replace the use of motor output to determine individual stimulation intensity and/or coil positioning in patients with MDD (32). While the use of motor output to determine individual stimulation intensity is a well-established and valuable method for standardization, a clear link between motor cortex action potential thresholds and the left DLPFC remains uncertain. This raises concerns about the accuracy of transferring motor output intensity information to the level required for therapeutic effects. In other words, a model that considers the individual anatomy and function of the DLPFC would be more accurate, as the intensity determined in the motor cortex is dependent on its spatial characteristics, which may differ significantly from those of therapeutic targets. Therefore, a method grounded in the underlying mechanism by which appropriate stimulation of the left DLPFC probably targets the sgACC and triggers cardiac modulations appears highly promising for future clinical applications.

In addition, a meta-analysis identified lower RMSSD as a strong pathological finding in MDD in comparison to HC (33). Generally, HR variability is considered an indicator of well-being (34) and self-regulatory ability (12, 35), both of which are reduced in individuals with depression (33, 36). In this sense, an increase in RMSSD during iTBS could indicate

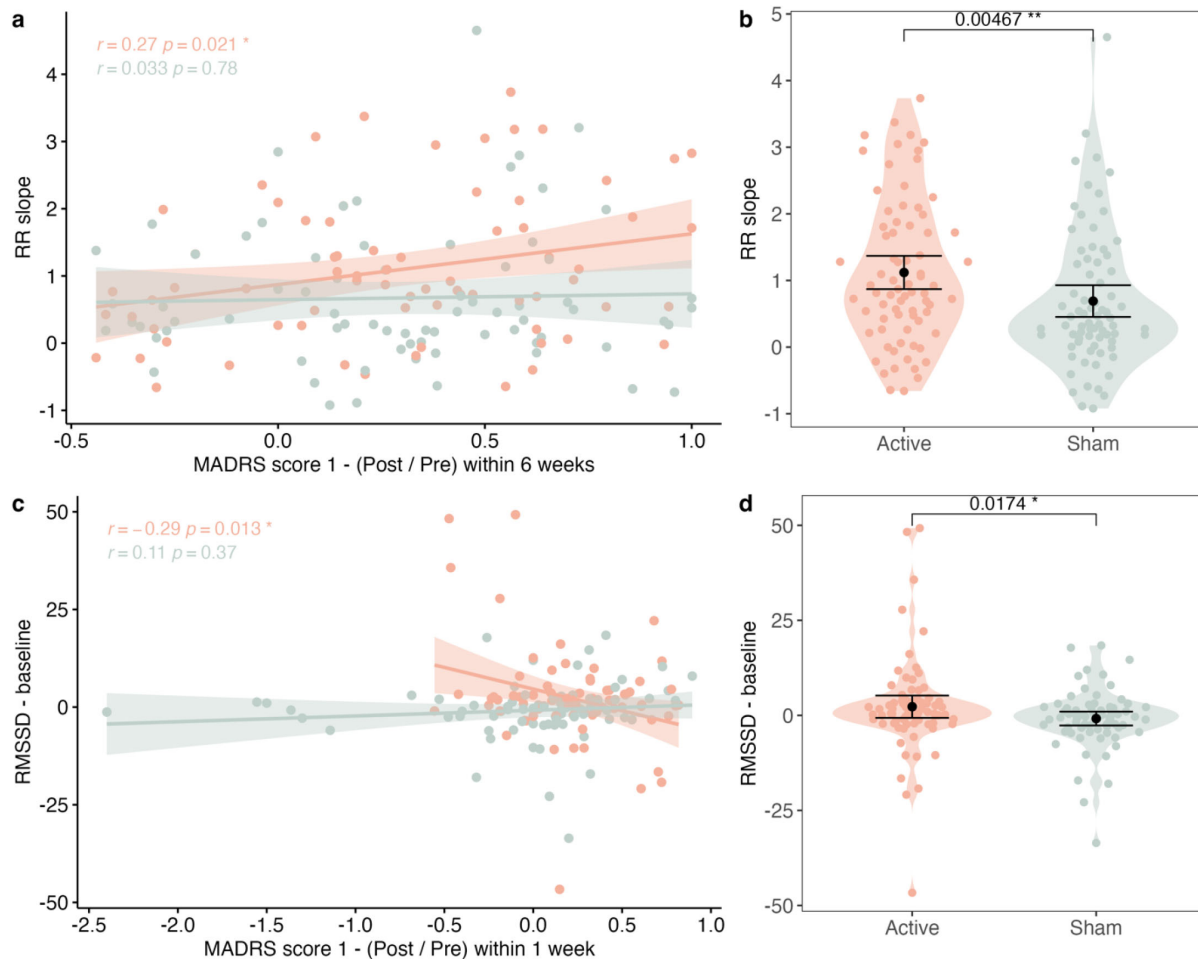


Figure 3. Stimulation-induced the RR interval (first 45 s) and RMSSD (first 270 s) modulations along with the corresponding Montgomery-Åsberg Depression Scale (MADRS) score changes. (A) The association between the RR slope and delta MADRS score within 6 weeks was seen in the active condition (red) only, and (B) the RR slope was stronger in active (red) versus sham (gray) conditions. (C) The association between the RMSSD change and delta MADRS score within 1 week was seen in the active condition (red) only, and (D) the RMSSD change was stronger in active (red) versus sham (gray) within 1 week. Error bars represent mean $\pm$ SE. * $P < 0.05$, ** $P < 0.01$.

greater frontal vagal modulations, from the DLPFC, through the sgACC to the brainstem and vagus nerve, reaching the heart (29), and thus serving as a potential predictor of clinical improvement. However, to the best of our knowledge, this mechanism has not been demonstrated in previous studies. While we were able to replicate the increase in RMSSD in active versus sham iTBS (8, 37), our exploratory results revealed an unexpected negative relationship. We found that the smaller the change in RMSSD, the greater the reduction in MADRS score. It should be noted that RMSSD assessed here likely reflects stimulation-induced, transient heart-brain coupling effects (8, 38), rather than resting-state RMSSD as an index of baseline autonomic tone. These findings, derived from a LMM, show a significant two-way interaction between the iTBS condition and RMSSD change in predicting delta MADRS score. To further investigate these early heart rhythm modulations, we conducted additional analyses. A direct comparison of baseline MADRS scores between two subgroups, divided by the median RMSSD, showed no significant differences ($P > 0.05$). This suggests that our results were not influenced by potential flooring effects (e.g., less depressed individuals with higher RMSSD having less room for improvement compared to more depressed subjects). Based on the negative association, we hypothesized that effective engagement of the frontal vagal network would initially result in less HR variability during stimulation, followed by increased HR variability afterward as a compensatory mechanism, aligning with clinical improvements. We further examined whether participants who improved clinically were also those who

exhibited higher RR slopes and lower RMSSD changes at different time points. Of the 10 participants with the most significant changes, only 2 showed the greatest clinical improvement, indicating that more complex mechanisms may underlie these modulations. Overall, our results underscore the complexity of RMSSD as an output (39), suggesting that systematic investigation is needed to better delineate the brain-heart pathways and potentially achieve even higher predictive accuracy (8) than that observed with RR slopes alone.

Equally important, regarding clinical improvement, interindividual variability could potentially be reduced, and the effect of iTBS maximized, by optimizing stimulation sites based on individual functional connectivity data. The sgACC has been proposed as a key marker for treatment response in depression (9, 20), and several studies have suggested that stimulation sites with the strongest negative connectivity to the sgACC could yield superior clinical outcomes (10, 13, 14). This method has been widely replicated and is considered the most established approach in the current literature for identifying patients who may benefit from rTMS. However, in our study, the use of functional connectivity data for personalized site selection did not show a clinical advantage. When comparing personalized stimulation sites on the left DLPFC to the fixed F3 stimulation site, no significant difference in MADRS score changes at 6 weeks of follow-up was observed. Additionally, no association between the distance from the ideal stimulation site and clinical improvement was identified. An inspection of the data revealed no spatial pattern of stimulation

**Table 2.** Linear mixed model analysis of the predictors of changes in Montgomery-Åsberg Depression Scale (MADRS) scores

Delta MADRS score ^a			
Predictors	Estimates	CI	P
(Intercept)	−0.158	−0.372 to 0.055	0.145
condition [active]	0.145	0.029–0.261	0.015^b
RMSSD ^c change 270 s	0.009	−0.002 to 0.019	0.096
distance to optimal stimulation site	0.003	−0.004 to 0.010	0.385
stimulation order [sham_first]	0.054	−0.064 to 0.172	0.370
Age	0.005	0.001–0.010	0.024^b
Sex [men]	0.027	−0.095 to 0.149	0.659
Medload	−0.017	−0.053 to 0.019	0.363
TRD ^d	0.002	−0.125 to 0.128	0.980
Condition [active]*RMSSD change 270 s	−0.017	−0.029 to −0.004	0.008^e
Random effects			
σ^2	0.12		
τ_{00} IDnew	0.00		
N IDnew	75		
Observations	143		
Marginal R ² /Conditional R ²	0.139 / NA		

^a1 being a 100% reduction of depressive symptoms.^b $P < 0.05$.^cRMSSD: root mean square of successive differences between heartbeats.^dTRD: treatment-resistant depression.^e $P < 0.01$.

in the left DLPFC that suggested a clinical advantage. Importantly, because the point on the left DLPFC with the strongest anticorrelation to each subject's DMN differs from the point with the strongest anticorrelation to a general sgACC seed, we repeated the analysis as described in previous studies (10). Again, no relationship between the distance from the ideal site and clinical improvement at 6 weeks was found (Figure 2) with accelerated iTBS. This finding contradicts the results of prior studies and may suggest that the profile of the MDD sample evaluated plays a critical role. Given that our study included a larger sample than those in previous studies showing positive results (9, 10), a sample size limitation is unlikely to explain the discrepancy. We also explored the changes in stimulation conditions within 1 week of the intervention but again found no evidence of a relationship. It is possible, however, that subgroups, such as biotypes (40, 41), may respond differently to this personalized approach, leading to better outcomes. Nevertheless, as it stands, we could not demonstrate any clinical benefit from the implementation of this personalization method. Our results align with Morriss et al., Our findings align with Morriss et al. (42); while they compared resting state functional MRI (rsfMRI)- and structural MRI-guided protocols without finding differences in clinical benefit, we compared personalized targeting with the F3 position of the international 10–20 EEG system—an approach that is simpler and more feasible in clinical practice. Similarly, Elbau et al. (43) reported only a weak association between sgACC–DLPFC connectivity and treatment response, highlighting the limited utility of such measures in larger, representative samples. Overall, it must be acknowledged that using resting-state functional connectivity data as the basis for this precision method was labor-intensive, expensive, and did not reveal a direct clinical advantage in this RCT. Future novel approaches (44) may provide new insights into this challenge.

Regarding the secondary outcomes (BDI-II and HAMD), a previous study found a negative correlation between baseline RMSSD and baseline HAMD–24 (43), which was not observed in our sample using the HAMD–17. Other findings could not be replicated, except for the two-way inter-

actions between RMSSD change and the active condition in delta BDI-II score LMMs.

The present study has several limitations. The heterogeneity of depression, due to variations in presenting symptoms, is well documented, prompting efforts to identify subtypes and their underlying neural correlates (40, 41, 45, 46). Due to limitations in sample size and insufficient representation of MDD clinical variations, we were unable to explore these important aspects. This should be a focus for future studies with larger and more diverse datasets. Additionally, we found no relationship between RR slopes or RMSSD changes and delta BDI-II or HAMD scores. This may be explained by the factor analytic approach of Uher et al. (47), who showed that the MADRS, BDI-II, and HAMD items load differently on three factors: the MADRS mainly on the observed mood factor, the BDI-II on the cognitive factor, and the HAMD on the neurovegetative factor. Given the dimensional complexity of MDD, it is not surprising that clinical improvement is not captured equally across all depression scales. Personalized connectivity-based targeting is highly dependent on the specific methods of data acquisition, analysis, and implementation; therefore, our results cannot be directly generalized to all targeting protocols. It should also be noted that in the personalized group, a small number of stimulated sites deviated by more than 10 mm from the calculated connectivity-based target. Such deviations are inherent to the practical implementation of neuronavigated targeting, where factors such as coil positioning, individual anatomy, and patient tolerance may limit exact placement. V6 corresponds to approximately 5 weeks after the start of active stimulation in the active-sham group and approximately 3 weeks in the sham-active group, due to the crossover design. This design was chosen as no alternative approach with comparable rigor and power exists to quantify sham effects. Both F3 and personalized groups were balanced across these intervals, and averaging over the full course provides a conservative estimate, avoiding overestimation of intervention effects. Nonetheless, the crossover design complicates the separation of long-term effects between iTBS conditions due to potential carryover (48). While placebo effects were not sustained, they were robust, indicating that the rTMS setup may enhance expectation effects (28, 49, 50), which future studies should carefully control for.

In conclusion, we demonstrated an association between HR deceleration during the first 45 s of stimulation and the degree of reduction in depressive symptoms up to 6 weeks after the aiTBS protocol. However, this relationship was not observed in HR variability modulation at 270 s, which correlated with clinical improvement only within the stimulation week, presenting important predictive limitations. Moreover, clinical improvement was not related to the distance between stimulation and ideal sites, and no benefit was observed between the personalized and F3 groups. In contrast, the use of online ECG emerges as a promising and cost-effective approach that could be further developed for MDD treatment with iTBS. Overall, the promise of precision medicine may be realized through improved targeted stimulation using a combination of neuronavigation and ECG, which could allow for the stratification of patients more likely to benefit from iTBS.

Methods

Participants and study protocol

We selected 125 depressed patients between April 2019 and July 2021, recruited through national advertisements, to participate in an rTMS study. Inclusion criteria were age between 18 and 60 years, diagnosis of MDD confirmed on site by medical assessment using the Structured Clinical Interview for DSM-5 Disorders–Clinician Version (SCID-5-CV), and moderate-to-severe depressive episode, according to MADRS score. The intervention was on an outpatient basis, although both inpatient and outpatient participants were included. Exclusion criteria were epilepsy or other neurological diseases, pregnancy, metallic implants, claustrophobia, as contraindications to MRI or rTMS, or, in case of regular psychopharmacological medication intake, change of type or dosage in the 2 weeks prior to participation or during the course of the study. To account for the psychotropic medication load (51–55), we summed for each individual the estimated intake dose of each substance at each visit, based on the interview or when possible on the circulating blood levels (below = 1,



normal = 2, or above = 3 of the expected dose). The study protocol (clinicaltrials.gov/ct2/show/NCT05260086) is in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Medical Center Göttingen (UMG). Prior to enrollment, verbal and written informed consent was obtained from all participants.

Once enrolled, the participant was randomized to participate in a 6-week quadruple-blind (patient, stimulation provider, principle investigator, clinical rater) crossover trial. We used the randperm function in MATLAB (The MathWorks, Inc., Natick, MA, USA) to generate a true random sequence that coded if the participant would receive the stimulation either at the F3 position of the international 10–20 EEG system (F3 group) or at personalized left DLPFC sites (personalized group) (Figure 1A), and either as active-sham or sham-active conditions (Figure 1B). At baseline and at the end of every week, a trained rater administered the MADRS (56) as a primary outcome measure, and additionally the Beck Depression Inventory (BDI-II) (57) and the Hamilton Depression Rating Scale (HAMD) (58) as secondary outcome measures.

Magnetic resonance imaging

We collected structural data with T1-weighted scans ($1 \times 1 \times 1$ mm) with a 64-channel head coil in a 3T MR scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany). We acquired the rsfMRI data using T2*-weighted gradient-echo echoplanar imaging with the following parameters (59, 60): repetition time of 1.5 s, echo time of 30 ms, flip angle of 70° , 69 axial slices with multiband factor of 3, $2 \times 2 \times 2$ mm, field of view (FOV) of 189 mm, with 10% interval between slices and posterior to anterior phase encoding. The rsfMRI data were acquired with 400 volumes in 10 minutes. The gradient-echo field map was acquired with a repetition time of 704 ms, echo times of 4.92 ms (TE 1) and 7.38 ms (TE 2), flip angle of 60° , 73 slices, FOV of 210 mm, $2 \times 2 \times 2$ mm, with a 10% interval between cuts and phase encoding from anterior to posterior.

Ideal and stimulated cortical sites

In accordance with prior publications (22, 23), we temporally concatenated the data for group independent component analysis (GICA). The GICA was performed with FSL 5.0.7 software (61) separately for the scans of the first, second, third, and fourth week, and separately for the F3 and personalized group. We identified components that best represented the DMN and the network that best covered the left DLPFC, and back reconstructed these into the normalized rsfMRI data of the individual patients. We then identified the left DLPFC region that most strongly anticorrelated to the DMN of the subject (ideal site) and projected the (x, y, z) coordinates from normalized to native space. Noteworthy, our method to determine the strongest left DLPFC anticorrelation to the DMN in each participant differs from a commonly used approach in which the area of strongest anticorrelation is found from seed-based connectivity analyses using a common sgACC seed derived from HCs (10). Therefore, we also extended the analysis to the seed method to explore whether this approach would yield different results.

Our neuronavigation systems (Visor 2 software, ANT Neuro, Enschede, Netherlands) recorded the stimulation coordinates in each session. We calculated the average of the first coordinate of each session in the week (x, y, z) and centered a region of interest (ROI) on it with spheres of 2 mm radius using MarsBar (62). To find the point on the cortex closest to the ROI on the skull, we calculated the Euclidean distance between the segmented cortex of each individual T1-weighted image and the center of the ROI using SPM12 and MATLAB. Finally, we calculated the Euclidean distance between the ideal cortical site and the stimulated cortical site for each observation and used this variable ("distance") in further analyses.

ECG acquisition and analysis

Participants were sitting quietly in a reclined chair for at least 10 min before recordings started. We acquired ECG data 2 min before (baseline) and throughout iTBS using the three electrodes of the neuroConn NCG-rTMS device (neuroCare, Munich, Germany)—ground electrode placed near the lower end of the sternum, red electrode placed on the first intercostal space on the right side, green electrode placed on the fourth or fifth intercostal space on the left side. The device recorded the ECG at 1000 Hz as

well as the iTBS bursts, allowing for exact synchronization of ECG and iTBS information. We analyzed the ECG data using the Biosignal Processing in Python (BioSPPy) toolbox, the heart rate variability (HRV) analysis toolbox, and the SciPy module (63) in Python 3.6. We used SciPy to remove power-line noise from the ECG signal and then used BioSPPy to remove band wander noise in the data and detect R peaks of the QRS complex as the maxima of the curve ± 25 ms. Then, we calculated the RR interval using the timestamps of detected R-peaks. We then preprocessed the RR interval by developing a Python correction of ectopic beats and other types of outliers as detailed in Lipponen and Tarvainen (2019) (64). Next, we selected the timeframe of 45 s from the start of iTBS for the RR interval, as the HR deceleration (represented by a positive slope) can be seen stronger in comparison to the sham condition (8). We also selected the root mean square of successive differences (RMSSD) in the time domain as an index of HRV due to being consistent and presenting the largest difference between MDD and HC among HRV parameters (33). The RMSSD is indicative of the parasympathetic influence of the autonomous nervous system on HR and lower values of RMSSD suggest lower parasympathetic (vagal) activity (65). Moreover, delta RMSSD showed significant decrease during cognitive stress (66). Based on criticism against ultra-short-term HRV and the recommendation of at least 4 min to draw accurate conclusions about HRV (67, 68), we selected the RMSSD timeframe of 270 s after stimulation starts. Importantly, RMSSD during stimulation likely reflects rTMS-induced entrainment of cardiac rhythm, also referred to as Heart-Brain Coupling (8, 38, 69), rather than resting-state HRV.

Accelerated intermittent theta burst and sham stimulations

Stimulation sessions took place during week 2 and week 4. We used a MagVenture X100 with Mag-option and a figure-of-eight MCF-B65 A/P cooled coil. The resting motor threshold was reassessed daily via electromyography in the right first dorsal interosseous muscle with the lowest intensity eliciting 50 mV motor reaction in 5 of 10 attempts, and the stimulation intensity was adjusted to 110%. In the active condition, we applied the stimulation parameters (4): stimulation ON lasted for 2 s, followed by 8 s of stimulation OFF, a volley composed of 10 units of three individual bursts with a frequency of 5 Hz and each burst with three single pulses with 50 Hz, performed 60 times, resulting in 1800 per session (7200 pulses daily and 36,000 pulses in total). In the sham condition, the same MCF-B65 A/P coil was blindly rotated 180 degrees, according to pre-coded sequences provided by the study principal investigator, who had no contact with the participants. Each daily visit included four sessions (accelerated protocol) of approximately 10 minutes per session, followed by at least 20-min pauses, according to the necessary intersession time described on previous literature (69). As part of the device, transcutaneous electrical nerve stimulation (tENS) electrodes placed in the scalp as close as possible to the coil mimicked tingling skin sensations simultaneously to the sound of pulses, regardless of the stimulation condition. After completion of all stimulation sessions, participants were asked to indicate their expectation about the effectiveness of the stimulation using a visual analog scale (VAS). As there was no significant difference between expectation levels under stimulation conditions [$t(70) = 1.47, P = 0.15$, see Table 1], we see the blinding procedure as effective.

Statistical analysis

Statistical analyses were conducted in RStudio (38), adopting a significance level of two-sided $\alpha = 0.05$. Participants were excluded from the analysis, if the baseline MADRS score < 7 or the z-standardized outcome score $> \pm 2.5$ SD. Levene's test was used to check the homogeneity of variance assumption and Mauchly's test was used to check the sphericity of variances. To investigate sample characteristics in the F3 and personalized groups, we used nonparametric Wilcoxon rank-sum (W) and chi-square (χ^2) tests. For investigating the MADRS scores and the interaction between groups over time, we conducted repeated mixed measures ANOVA (F) with the time as the within-subject factor and F3 or personalized groups as a between-subjects factor. Due to significant differences between groups in sex distribution, we added sex as an additional between-subjects factor.

We conducted independent analyses of Wilcoxon rank-sum (W) test between the F3 and personalized groups to investigate the Euclidean



distance. We further computed Pearson correlation coefficients between the distance and delta MADRS as well as between HR/HRV and delta MADRS. By conducting dependent *t* test (*t*) or Wilcoxon rank-sum (*W*) test, if the assumption of normality in the data is violated, we compared the ECG measures between the active and the sham condition. We calculated Cohen's *d* and the 95% confidence interval as effect size within and between groups and conditions. An effect size of *d* > 0.10 indicates a small, an effect size of *d* > 0.30 a medium, and an effect size of *d* > 0.50 a large effect (71). Delta MADRS score was computed as 1 – poststimulation score/prestimulation score. The primary outcome was delta MADRS score within 6 weeks, but we also investigated delta MADRS score within each stimulation week as an attempt to unravel possible carryover effects. For the later, we used the R packages lme4 (72) and lmerTest (73) to fit the LMMs using the restricted maximum likelihood method and to extract *P* values. We performed full-null comparisons using the chi-square (χ^2) test of our hypothesized full model and a corresponding null model with a random structure. To minimize the accumulation of α error, we only extracted and interpreted the estimated fixed effects when the full model was significantly different from the null model.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

All listed authors made substantial contributions to various aspects of the work. RGM funded and designed all experiments, oversaw the entire data collection and wrote the manuscript. JW and HMJ analyzed all data, made all figures, and wrote the manuscript. IA, VB, PD, LE, NH, VK, LEM, YM, CR, KS, AS, FW; JW, AW, VZ, and AZ made significant contributions to the acquisition and interpretation of data. MW, CSS, and TEG made substantial contributions to the analysis and interpretation of data and substantively revised the manuscript. TEG also collected data and oversaw the entire data collection. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere.

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Author disclosures

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NK3R antagonism reduces fear expression in a PTSD-like model of female mice

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The Tachykinin 2 pathway has been shown to modulate fear memory consolidation in healthy animals and humans. Here, we studied the Tac2 pathway antagonist Osanetant administered shortly after immobilization stress on fear memory consolidation in female mice. Osanetant reduced freezing during fear expression, indicating diminished fear memory consolidation. These findings support the potential preventive therapeutic role of Osanetant in a posttraumatic stress disorder-like model.

Fear is a survival mechanism triggered by certain threats that result in instant defensive responses, allowing one to preserve their well-being. Fear memory refers to the association between a neutral and an aversive stimulus (unconditioned stimulus). This results in the neutral stimulus (now termed conditioned stimulus) eliciting a fear response, which, before the association, was only triggered by the unconditioned stimulus. Despite being an adaptive response, fear memory can be altered and can manifest pathological characteristics as often seen in posttraumatic stress disorder (PTSD). Women are twice as likely as men to suffer from PTSD, as seen from their lifetime prevalence (5%–6% in men, 10%–12% in women) (1). Several studies highlight key differences in fear memory processing in males and females both in rodents and humans at anatomical, molecular, and behavioral levels. However, there is still a disparity in the number of studies in males compared to females (5.5:1), emphasizing the need to consider sex as a biological variable in research (2).

The Tachykinin 2 (Tac2) pathway is involved in neuromodulation and neurotransmission in the central nervous system. The Tac2 gene encodes Neurokinin B (NkB), a neuropeptide that binds to the Neurokinin 3 receptor (Nk3R). Previous studies have emphasized the importance of the Tac2 pathway in fear memory modulation (3, 4). Additionally, Tac2 is expressed in key fear-processing areas, including the centromedial amygdala, the bed nucleus of the stria terminalis, and the hippocampus. Blocking the Tac2 pathway could be a potential therapeutic approach for PTSD (3).

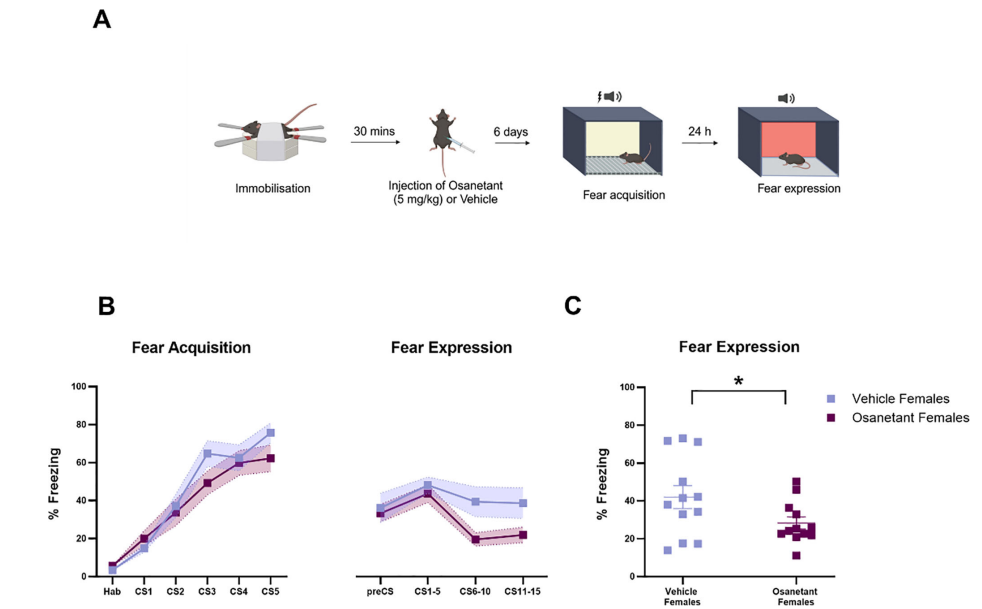


Figure 1. NK3R antagonism decreases fear memory consolidation. (A) Experimental procedure of fear memory consolidation after stress. Created with Biorender. (B) Fear acquisition and expression in mice administered with Osanetant. (C) Effect in the fear memory consolidation after administration of Osanetant (5 mg/kg, ip) or Vehicle 30 min after stress (IMO) in adult females ($n = 12$ per group) ($p = 0.038$, $\eta^2 = 0.798$). Analyzed by Generalized Linear Model with least significant difference (LSD) correction.

Previous work from our research group has demonstrated that Osanetant, an Nk3R antagonist shows a sex-opposite effect in fear memory consolidation in nonstressed mice, increasing fear expression in females and decreasing it in males (4). Here, we aim to study the effect of Osanetant on fear memory consolidation in female mice subjected to **immobilization stress** (IMO), a PTSD-like model.

Here, Osanetant (5 mg/kg) was administered systemically 30 min after IMO, and 6 days later the mice were subjected to classical fear conditioning (For further details see *supporting online material*). No differences were found in fear acquisition in females administered with Osanetant or vehicle. Interestingly, a treatment effect was seen in female mice ($\chi^2_{(1)} = 4.299$, $p = 0.038$), wherein female mice administered with Osanetant showed lower rates of freezing compared to the Vehicle group during fear expression, indicating decreased

fear memory consolidation ($p = 0.038$, $\eta^2 = 0.798$) (Figure 1).

This study highlights the potential therapeutic use of the Nk3R antagonist Osanetant administered immediately after trauma exposure such as car accidents or sexual abuse to prevent pathological alterations of fear processing in women. Among the limitations of this study are the lack of monitoring of the estrous cycle, the exclusion of male mice, and the absence of additional techniques beyond the behavioral protocol. A previous report demonstrated an increase in fear memory consolidation in nonstressed females administered with Osanetant, in apparent contradiction to our current findings (4). We hypothesize that the high intensity of the stressor might be triggering neural changes that are not seen when mice undergo fear acquisition with no previous stress exposure (5). For instance, restraint stress showed to modulate the BDNF, GSK-3 β ,





and β -catenin pathway, decreasing the expression of phosphorylated GSK-3 β , and β -catenin in the hippocampus of rats (6). However, non-stressed female mice administered with Osanetan after fear acquisition showed an increase in the β -catenin levels (4). This interplay between the levels of β -catenin and potential involvement of other synaptic plasticity factors like mTOR and CREB could be one possible explanation for a decrease in fear memory consolidation in female mice, contrary to nonstressed mice. Further research on the molecular changes of the Tac2 system in the brain under different stress conditions could potentially lead these findings to be translated to the clinic, since Osanetan is a well-tolerated drug in humans (7).

Data Availability

Data will be shared upon reasonable request.

Author Contributions

N.A. and J.F.N. performed the behavioral experiment, analyzed the data, and wrote the manuscript. R.A. conceptualized and oversaw the project, helped writing the manuscript and obtained the funding.

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Author Disclosures

R.A. declares a potential conflict of interest with the patents PCT/US2015/037629 and EP25160662.0. The other authors declare no competing interests.

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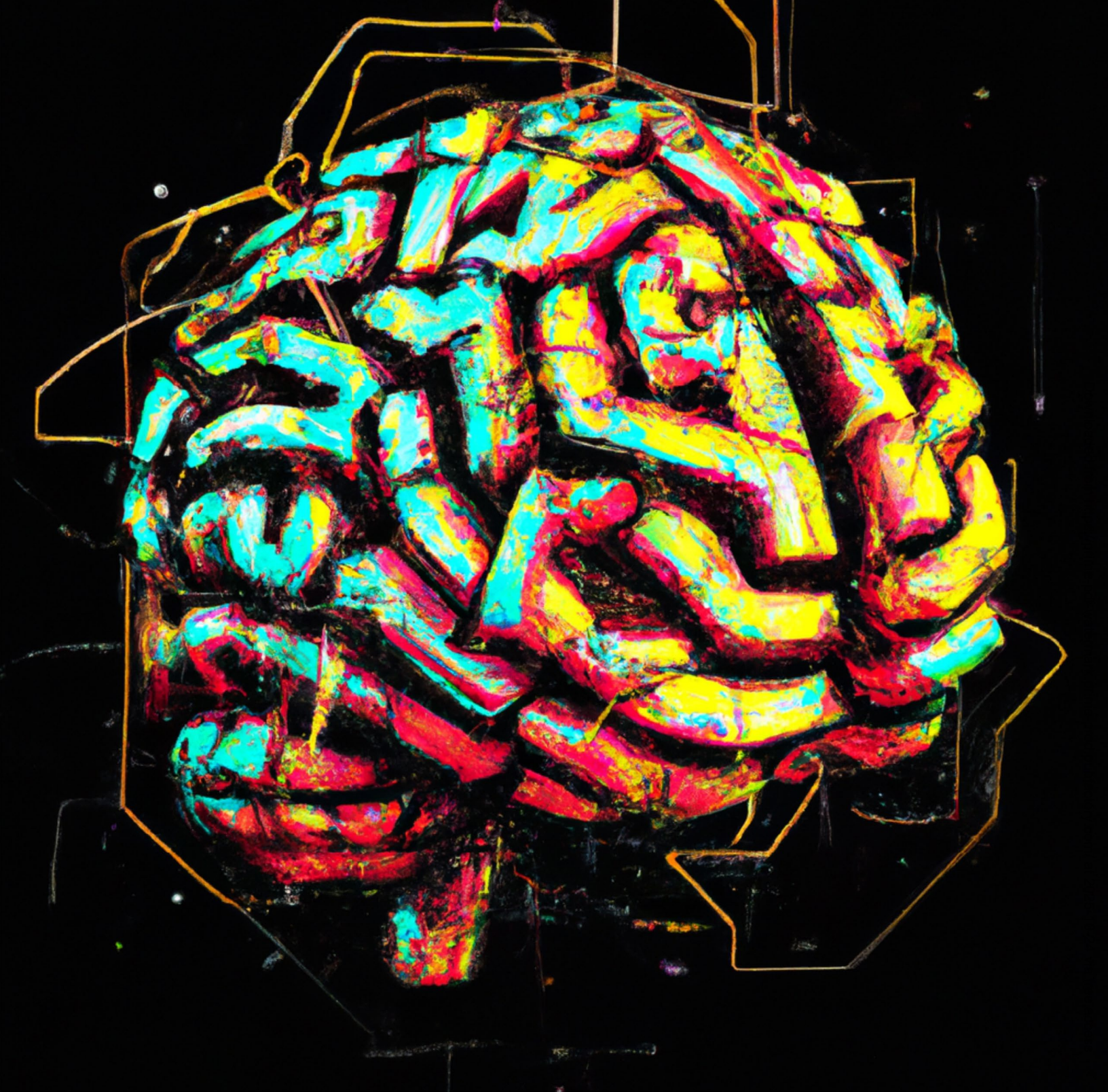
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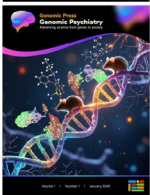
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