Can you remember silence? Epigenetic memory and reversibility as a site of intervention

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> All the famous moralists of olden days drew attention to the way in which certain happenings would leave indelible and distressing memories - memories to which the sufferer was continually returning, and by which he was tormented, by day and by night (Janet 1919/1925: 589, quoted in van der Kolk and van der Hart 1989:1530).

Just over twenty years ago, molecular biologists Leonie Ringrose and Renato Paro published an article with a provocative title: "Remembering Silence" (2001). The article focused on how epigenetic elements, which are modulated through a variety of means, could subsequently return to their silent state, operationally defined as their epigenetic status before their modulation by experimental or environmental factors.

Though Ringrose and Paro's article was on fruit flies and factors affecting embryological growth, the article asked a question of considerable importance to the rapidly expanding research in neuroepigenetics: if you experience a traumatic event and, as a result, acquire an epigenetic trait that is considered pathological, can you free yourself of that trait? This question was, and still is, particularly compelling beyond research on epigenetics, and including DOHaD research which has been deeply influenced by epigenetics findings since its origins (Waterland and Michels 2007). By interrogating widely held beliefs about reversibility and plasticity, Ringrose and Paro's research avoided running narratives in which epigenetic effects of early-life experiences on long-term health and disease risk were not much less deterministic than many of the "gene for" (i.e., genetic determinism) arguments that preceded them. In deterministic narratives, experiences thought to have epigenetic modulatory effects are largely considered permanent. The orientation of Ringrose and Paro's research, by contrast, foreshadowed more recent shifts in some DOHaD research agendas, that are moving away from causal models of early life experiences leading to diseases later in life, to frameworks focused on conditioning, which imply a possibility for change and eschews deterministic arguments (Hanson and Gluckman 2014). As sociologists Ruth Müller and Georgia Samaras have argued, these two conflicting perspectives – a deterministic emphasis on epigenetic programming vs. an emphasis on epigenetic conditioning and malleability – are characterized by significantly different epistemic formations and biopolitical implications (Müller and Samaras 2018). This crucial tension is intimately tied to questions of reversibility and, while it has received limited attention in the broader context of DOHaD studies, its consideration appears essential for future research.

Early millennium narratives of epigenetics and risk built on a century of research on the post-traumatic state described by the French psychologist Janet in the epigraph. This research has sought means to help people "remember silence" – to frame the sought-after transformation in the language of reversibility used by Ringrose and Paro – by returning to a subjective state prior to a traumatic experience, freed of distress and torment originating in that experience. Considerations of this subjective silence are conceptually bound to questions of past events and memories of those events. Since the past events cannot change, it is the memory of these experiences that may be the

target of a panoply of clinical evaluations and interventions (whether pharmaco- or psychotherapy). Recent research in neuroscience and epigenetics have offered new hypotheses on how traumatic experiences might be etched into memories. The use of the term memory in this research is polysemic, referring to processes at different scales:

- 'Episodic memory', the ability to encode one's life events, includes a range of cognitive functions that rely on interacting brain structures.
- 'Molecular memory,' by contrast, is more loosely defined. It refers to molecular mechanisms correlated with any event leading to long-lasting cellular changes, whatever their implication in episodic memory, or any other brain property. It remains uncertain to what extent these two types of memories interact or are reversible.

In this chapter, our primary focus is molecular memory, more specifically the molecular changes considered to be acquired through the experience of traumatic events and thought to contribute to the risk of psychopathology. We discuss the ways in which molecular memory has been viewed through a deterministic lens and how the concept of reversibility challenges these frameworks. These perspectives open new ways for DOHaD research to think about the relationship between environment and conditioning, the types of therapies and resources made available for people who experience trauma, as well as how we think about human subjectivity.

Drawing on current literature, we are interested in epigenetic states as they correlate with the experience of past adversity (regardless of whether they may affect episodic memory or other physiological systems), and how they may maintain – or not – a molecular modulation of gene activity. We bring together the perspectives of medical anthropology and molecular biology to consider (1) how behavioural epigeneticists envision the activation of molecular memories in response to specific experiences and their contribution to later risk for disease, in particular psychopathology (2) whether and under what conditions it is believed that such memories can be silenced, and (3) what impacts on personality development, affect, and identity such silencing might have.

Persistence and reversibility in epigenetics research

From the perspective of embryological growth, biologists Ringrose and Paro considered emerging research indicating that, in *Drosophila*, regulatory elements that are experimentally switched to their active state can "'remember' and restore their previous [silent] state." These "regulatory elements" are defined as regions within genes where, under epigenetic control, proteins that regulate gene activity may act differentially. The authors noted that silenced states can be remembered after several cell generations during which those elements were active. They could only hypothesize as to how or why regulatory factors would return to silence. This article dates from the early days of epigenetics research, yet the same question persists: how do regulatory factors, under the influence of early-life experiences, modulate gene activity and contribute to health and disease?

The research discussed by Ringrose and Paro yielded findings on the varying effects of single epigenetic alterations depending on the type and timing of the modification and raised questions about the stability and reversibility of epigenetic states and their developmental effects. For instance, even if an epigenetic state is only modified for a limited period of time, it will nonetheless affect downstream biological processes during that period, which may have longer-term consequences than the bout of epigenetic plasticity itself. Ringrose and Paro also observed that while certain experimental data suggested that a restoration of silence was not possible after a significant period of

activation, other results pointed to the possibility of silencing even after cell division (2000: 569). Moreover, genes implicated in molecular memories may switch status surprisingly late in development, or may switch dynamically and have regulatory patterns that are far more dynamic than a single transition between on or off states (ibid: 2). Thus, there was a trend toward stable effects of epigenetic traits on development, but with notable exceptions.

Research on the reversibility of epigenetic states now spans multiple types of in vitro models, model organisms, and work on human tissues, as well as both physiological and pathological contexts. Key areas of research include the determination of cellular identity during embryological development, modelled using induced pluripotent stem cells (iPSC). iPSCs rely on a method whereby differentiated cells – such as a fully developed skin cell – can be reprogrammed to an undetermined state, and then redirected to a new developmental path. Part of the enthusiasm for these cells came from the fact that reprogramming to the undifferentiated state does not implicate any manipulation of the genome, but relies on triggering epigenetic plasticity at regulatory elements implicated in cellular identity. In other words, interventions targeting the epigenome (Guan et al. 2022) may potentially rewrite cell fates – including memories of their pasts – to produce cells perfectly identical to 'true' stem cells, with the hope of full reversibility. However, it is now clear that iPSCs retain epigenetic traces of their previous differentiated state (Lister et al. 2011), suggesting a form of resistance to reprogramming. Therefore, what scientists have referred to as silence (i.e. the return to undifferentiation), in these experiments, is only partially restored. This molecular plasticity underlying cellular identity over the cell lifespan argues against a binary on/off model, and instead supports a gradual, context-dependent balance between persistence and reversibility. This is visible in Ringrose and Paro's findings regarding highly dynamic shifts, or epigenetic traces of a cell's history that resist experimental erasure.

In studies at the scale of the human lifespan, and in DoHD research, these nuanced understandings of the dynamics of epigenetic states are less present. Instead, researchers have argued that durable epigenetic states result from traumatic events that show epidemiological association with a variety of pathologies, from cardiovascular to suicide risk, including anxiety and depressive disorders, addiction, and more (Nemeroff 2016). These epigenetic states are considered to set off brain adaptations that contribute to psychological traits, such as impulsivity, that ultimately potentiate the risk of mental illness. Research on reversibility – whether on *Drosophila* or iPSCs – provides a different, critical angle to human lifespan and DOHaD researchers, as they attempt to conceptualize how reversibility of epigenetic traits may occur, as well as how therapeutic intervention might silence molecular traces of past adverse events. On the last point, it is likely that even extreme interventions may be unable to entirely undo targeted traces of a person's history.

<u>The epigenetics of memory formation and its effects</u>

A subset of researchers interested in memory and epigenetics have explored the so-called "'epigenetic code' in the central nervous system that mediates synaptic plasticity, learning, and memory." (Day and Sweatt 2011) In their models, neuroscientists Jeremy Day and David Sweatt evoke "the controversial theory of the 'engram' - a (hypothetical) biophysical change in the brain that accounts for the material existence of memory (Josselyn et al., 2015: 201)... [and] suggest that epigenetic mechanisms, such as DNA methylation, may be a window into the brain's memory." (Lawson-Boyd and Meloni 2021: 4) In other words, they and other researchers became interested in how memory can be traced through epigenetic mechanisms in the brain, at a molecular level. Drawing mostly on research on model organisms, Day and Sweatt further argue that "an interesting

new understanding has emerged: developmental regulation of cell division and cell terminal differentiation involve many of the same molecular signaling cascades that are employed in learning and memory storage. Therefore, cellular development and cognitive memory processes are not just analogous but homologous at the molecular level." (2011: 813-14) Their research presents cellular epigenetic and developmental mechanisms, and cognitive memory processes, as intertwined, and thus potentially actionable on a molecular level. In this understanding of molecular memory, the epigenome is "a crucial 'missing link' between life experiences and gene expression, which in turn will influence the ways in which neuronal circuitry and brain structures develop." (Lawson-Boyd and Meloni 2021: 4)

In these models, two characteristics of epigenetics are put forward, both of which we suggest should be approached with caution. First, that molecular memory may be homologous to episodic memory and second, that epigenetics makes an exceptional contribution to the chain of events leading from life experience to the molecular memories of these events and their subsequent effects.

The first proposition may be particularly misleading. Recent research indicates that every function of the nervous system, from the regulation of autonomous functions to feeding, sleep, or nociception may implicate changes in gene expression under epigenetic regulation (see e.g. Guo et al. 2017, Richard et al. 2017). In these studies, the degree of implication of epigenetic modulation appears similar to what has been identified in relation to episodic memory. As such, it is difficult to identify any *specificity* or *homology* (besides the use of a common word) in the relationship between *epigenetic* and *episodic memories*, given that gene expression changes and underlying epigenetic plasticity likely contribute to all aforementioned brain functions, without necessarily being homologous to them.

The second proposition is similarly debatable. Responses to life experiences are complex and multiscalar. In case of trauma, their perception and encoding starts with sensory processing of, for instance, sounds or movements, which are then cognitively apprehended by devoted brain areas, triggering negative emotions. Each of these operations relies on specialized cellular processes. At the sensory level, they include chemical (e.g. release of neurotransmitters in activated brain regions), physical (e.g. light sensing in the retina), or mechanical (e.g. transduction of sound wave by the tympanum) properties that act on temporal and spatial scales not necessarily compatible or dependent upon any epigenetic plasticity. Ultimately, it is the overall psychological impact of adversity, downstream of these multiscalar processes, that is considered to trigger epigenetic changes.

At molecular level, DNA methylation is arguably the most frequently investigated candidate and, while other substrates are also studied and likely implicated, it will be our primary focus below. Changes affecting DNA methylation are considered not only to reflect past experiences, but also contribute to behavioural changes through the modulation of neuronal processes, heightened sensitivity to stress, and increased psychopathological risk. In terms of experimental designs, research on these processes is grounded in the triangulation of incongruent experimental designs. Animal studies of epigenetic consequences of early-life adversity, on the one hand, objectivize how such embodied epigenetic memories may manifest in adulthood, long after initial triggering events, in controlled settings that limit interfering factors. Even then, causal attribution of abnormal behaviour to epigenetic changes would require dedicated experiments during which the proposed epigenetic substrate would be manipulated to prevent or reverse the abnormal behaviour (see next section). The behavioural changes in these models are believed to bear some similarity to

psychopathology in humans who experience early adversity (e.g., childhood maltreatment), and at least some of the same molecular processes may be involved. In humans, on the other hand, associations between adversity and epigenetic adaptations are even more questionable, as sources of unaccounted variability over the lifespan, following trauma, are incomparably higher, with studies typically involving analysis of post-mortem brains (of people retrospectively classified as having experienced early adversity), or peripheral 'liquid' biopsies (blood, saliva) in living subjects (which, although more accessible, are less relevant for the understanding of brain epigenetics). Thus, there is only a tenuous, associative relationship between epigenetic memories of early experiences and drivers of later behaviours, both in animal and human studies.

Ultimately, any delayed or long-lasting biological perturbations are associated with multiscalar adaptations at histological, cellular, or molecular levels, which include but are not exclusively encoded by epigenetic changes. Epigenetic processes are likely recruited, over the lifespan, during early adversity and later when a host of related biological consequences mediate the impact of more recent life events. But they do not operate in isolation. Influential conceptualizations of epigenetic processes as exceptional contributors to molecular memories of past experiences, in this context, appear to reflect an inability to place them in these long chains of back-and-forth, across temporal and spatial biological timescales, rather than a solid epistemic property. (Lloyd, Larivée, and Lutz under review) These limitations suggest caution when translating available evidence about the relationship between epigenetic modifications and memory in the context of adversity and psychopathology.

Experiments in reversibility

In parallel to efforts to understand the molecular mechanisms that may be associated with the experience of trauma and subsequent psychopathology, researchers are attempting to identify interventions that might reverse or modify epigenetic states and the psychopathology correlated with them.

Some of this research focuses on well-established interventions such as antidepressants and psychotherapy. These therapies seek to mitigate the effects of past traumas through the alleviation of symptoms (e.g., anxiety) in the present, and are now also studied for their effects on epigenetic mechanisms. Concerning antidepressants, researchers have associated a number of different epigenetic modifications (again, in aforementioned peripheral samples, not the brain) with a positive response to antidepressants and are attempting to identify which epigenetic states might be able to predict responsiveness to these medications (Menke and Binder 2014). In addition, researchers have suggested that epigenetic mechanisms may constitute "dynamic biological correlates of [psychotherapeutic] interventions". (Ziegler et al. 2016: 5-6). However, the processes, directionality, or interactions linking symptom alleviation, intervention, and epigenetic states are far from being understood. For example, such research does not demonstrate whether [1] it is an intervention that reduces a person's symptoms or whether it is symptom reduction that subsequently affects epigenetic profiles, [2] interventions directly affect epigenetic plasticity thereby affecting symptoms, or [3] some combination of the two. This raises important questions about inference of causality, as distinguishing between these possibilities would require direct and specific manipulation, or "editing", of the epigenome.

Experimental approaches are being developed in rodent models to address this challenge of causal inference. Researchers such as Elizabeth Heller and Eric Nestler, are attempting to carry out

locus-specific epigenetic editing (i.e., affecting only a specific location in the genome [Hamilton et al. 2018: 273]). The intervention modifies epigenetic regulation of the expression of a specific gene (*fosb,* largely investigated at non-epigenetic level by this and other groups). Using this method, Heller and collaborators epigenetically reprogrammed this gene in a specific brain region to modify behavioural responses to *later* stress exposure, promoting susceptibility, or alternatively resilience, to this experience. They argue that the specificity of their approach allows them to understand how locus-specific epigenetic states may be causally implicated in the modulation of stress responses. The extent to which such manipulations are truly specific – affecting the targeted gene only – is unclear, with difficult technical and experimental challenges ahead. Nonetheless, these findings demonstrate the potential feasibility of intervening in targeted ways on the molecular processes implicated in stress or trauma responses. In effect, potentially silencing molecular memories of past experiences.

Other researchers are drawing on more classical approaches to target the molecular machinery that may mediate epigenetic reprogramming. A team led by Moshe Szyf and Gal Yadid recently investigated a rat model of post-traumatic stress disorder (PTSD), in which they identified changes in DNA methylation (Warhaftig et al. 2021). They then directly manipulated the expression of one of the two enzymes responsible for methylating DNA in the mammalian brain (Dnmt3a) in an attempt to undo PTSD-like behaviours in their model. While results offer support to the hypothesis that DNA methylation changes may contribute to PTSD-like behaviours, the level of evidence for epigenetic causality is weaker compared to the previous study by Heller et al. For instance, they did not identify if or how their manipulation of the enzyme directly affected the DNA methylation states that were triggered in the model, but instead reasoned by inference that the enzyme must have affected them. Yadid et al. suggest that it may be possible to translate their intervention to humans, using a systemic therapy rather than direct manipulation in the brain. They propose the use of the chemical donor for methyl groups in our diets (SAM), which raises questions about the specificity of the intervention. Indeed, systemic SAM administration would likely affect every cell in the whole body in which methylation of DNA affects their activities. Such an induction of epigenetic plasticity may have broad and potentially detrimental effects across physiological functions of the brain and other organs. Limitations notwithstanding, such an intervention evokes the possibility of inducing silence, as discussed by Ringrose and Paro twenty years ago, but now in the case of humans and the silencing of the effects of traumatic experiences.

Departing from existing symptom-oriented therapeutic efforts to free people from the emotional impact of distressing, indelible memories, the proposed epigenetic interventions are meant to target the molecular imprints of traumatic memories. In theory, they would be more akin to a cure, allowing a person to remember the affective silence of an epigenetic landscape unmarred by (mal)adaptive shifts brought on by adversity. Such interventions would hypothetically target a range of regulatory elements, bringing to the toolkit of psychiatry the reversibility discussed by Ringrose and Paro. Systemic global methyl donor treatments, for instance, may have the potential – to use an analogy – to reopen critical windows of neuroplasticity among people who are biologically beyond the developmental period when such plasticity initially occurred (Reh et al. 2020). In other words, the canalization that takes place in a person's life and presumably sets them on a particular life trajectory based on their environments and experiences, might be rendered shallow, and move to another trajectory. (Lloyd, Larivée, and Lutz: under review) While the potential of induced plasticity is far-reaching, according to one researcher, induced or uncommonly prolonged neuroplasticity could be a double-edged sword (personal communication). She argued that under normal circumstances, in adulthood [the] perceptual field is narrowed by past experiences: "it probably wouldn't be good to leave the window [of neuroplasticity] open when we're older because… I

wouldn't be having a discussion with you. I'd be listening to the furnace going on or off… We narrow our perceptual field according to our experience." From this perspective, the stabilization of neural traits is essential for 'normal' development and the solidification of one's identity. Therefore, the promise of epigenetic editing, for all of its therapeutic possibilities, raises the spectre of destabilizing a person's personality, cognitive abilities or biographic integrity.

Experimental interventions to reshape epigenetic molecular traits are, thus, only beginning to emerge. Potential implications for the reversal of the behavioural traits correlated with the experience of trauma are poorly understood, with concerns that they could result in the loss of fundamental aspects of our identities. For the moment, it is clear that understandings of the association between memory and active and silent epigenetic states – and their reversal – still require a great deal of clarification and specification, more than is often reflected in current considerations within fundamental research and its translation to other research and policy spaces.

Discussion

In this concluding section we focus on social and political implications of efforts to assuage traumatic memories, including through the reversal of epigenetic traits.

Following a long history of interventions, new experimental strategies hope to target specific parts of the epigenome to lessen the torment and distressing effects of traumatic events (Lloyd and Larivée 2020). Pharmacotherapy (e.g., antidepressants) and cognitive and behavioural therapy have raised long-standing questions about the extent to which their use has become integrated in normative behavioural and affective ideals and performative expectations. (Lloyd and Moreau 2011; Ehrenberg 2008) Propranolol provides a compelling example to consider, as an experimental medication that attempts to reduce the emotional charge associated with traumatic memories (Brunet et al. 2018). Its use for the treatment of PTSD has triggered ethical concerns about the possible "over-medicalization of bad memories." (Henry et al. 2007: 13) and, more broadly, about the potential dangers of modifying episodic memory and creating a more malleable self. While ethicists acknowledge that other psychopharmaceutical or psychosurgical interventions may modify the self and our relationship to our memories, they insist that the impact of technologies to directly modify memories is different. Ethicist Muriel Leuenberger argues that "memories of the past are constitutive of the boundaries we find ourselves in today." (2022: 14) She argues that the use of memory modifying technologies destabilize the traditional balance of what she considers the two constitutive elements of authenticity – self-creation and self-discovery – at the expense of the first. Leuenberger argues that this re-equilibration will result in new self-narrative processes. (2022: 13-15) In particular, she asserts that identities are always based on selective relationships to past life experiences, but that self-discovery is grounded in the assumption that there are nonetheless elements of our pasts that cannot be changed. However, memory modification technologies, potentially including epigenetic editing, by enabling people to change essential elements of their memories, may free them from the necessity of self-discovery, and tip the balance in favour of self-creation. Overall, ethical discussions of memory modification insist that despite the torment they might cause, they are fundamental to our identities and narratives of our lives.

Interventions that aim to modify or reverse molecular memories of early trauma may, should they affect episodic memories, be critically assessed through the same lenses that have been brought to bear on existing therapies. However, beyond their potential effects on episodic memory, epigenetic editing interventions aspire to modify the fundamental molecular processes associated with the past

experience of trauma. Researchers hope that these modifications will affect neurobiological processes and, as a consequence, behavioural traits and reactivity to stress (e.g., as in the case of PTSD). The primary target, then, of these interventions would not be the factual or emotional content of an episodic memory (i.e., the emotional relationship between the person and a specific object/event), but rather an affective state related to behaviour. (on affect and trauma, see Leys 2011) This conceptualization of the neuropsychiatric risk associated with post-traumatic subjectivities is framed in terms of affective responses to triggers. As we have argued elsewhere, these triggers are considered both devoid of exceptional qualities and sufficient to set into motion pathological responses. At their extreme, these affective responses are thought to be sufficient to lead to suicidal acts. (Lloyd and Larivée 2020) The two types of therapies – one oriented to or tacitly considering the effect of episodic memories of trauma, the other to acquired affective responses – reflect a fundamental difference in their approaches to post-traumatic subjectivity, or how the experience of trauma is thought to affect a person. The difference also reflects researchers' beliefs about how one might most effectively intervene on memories (episodic or molecular) of traumatic events and offer people silence.

While interventions that seek silence through the reversal of epigenetic states may, theoretically, offer novel opportunities for neuropsychiatric and developmental researchers to help people to live in the aftermath of trauma, there may be an unbridgeable gap between a post-traumatic state and this return to silence.[1] At the extreme end of wiping cellular memories clean, as in the case of iPSCs, even efforts to epigenetically reprogramme cells back to stem cell states are unable to completely remove molecular traces of their past differentiated identity. In addition, it is clear that epigenetics is only one part of multiscalar responses to life experiences. Furthermore, systemic interventions that may offer the opportunity to modulate epigenetic processes, come with the potential for sweeping effects on our bodily processes. Even targeted epigenetic-oriented interventions may either miss their mark (being unable to remove the molecular memories associated with past trauma) or destabilize people's affective identities in unforeseen ways. In the long term, overcoming these issues will require deeper understandings of: the kinetics, particularities and potential reversibility of epigenetic processes in the brain; their reciprocal interactions with other levels of biological organization; and, finally, the development of more precise interventions, targeting pathophysiological substrates only.

It should be underscored that any *return* to silence aspired for in this research is hypothetical. Epigenetics research on the effects of trauma is grounded in comparison of model organisms that were exposed or not, but the animals are not tested prior to exposure and interventions to provide a "before" view that would hypothetically reflect a state of silence. In humans, these before states are not tested either, given that brain tissue can only be studied postmortem. Moreover, research on inter- and transgenerational effects of trauma and long-term evolutionary inheritance of epigenetic states raises additional questions of how "before" or "silence" might be conceived. (Pentecost and Meloni 2020) In light of current understanding of molecular memories, while it might one day be possible to reverse a single epigenetic trait, it may remain impossible, or counterproductive, to reverse a full epigenetic landscape or a person's developmental trajectory.

[1] The multiple scales at which memories of experiences exist mean that there is no single easy or clear link between the end of suffering and silence.

Beyond the different biological and temporal scales explored in this article, a growing body of work in Science and Technology Studies focuses on the ways the biological and social levels are intertwined. This endeavour found echo in DOHaD research, after researchers followed the historian of science Evelyn Fox-Keller in her call to revisit the mirage of a space between nature and nurture (Fox-Keller 2010; Hanson and Gluckman 2014). Working in a similar vein, sociologist Megan Warin and collaborators recently extended sociologist Pierre Bourdieu's concept of habitus, in which social traits uniting individuals are considered to have been produced by previous experiences and to be reproduced in future experiences. The social world is conceived of as unconsciously embodied to allow members of a social group to be pre-adapted to their particular context (Bourdieu: 61). In their extension of Bourdieu's work, Warin and her co-authors proposed the concept of *biohabitus* to explain how certain types of risks are "structurally embedded in socio-cultural contexts" and subsequently become a part of people's bodies. (2015: 65) These experiences lead to somatic memories, which inform people's future trajectories. While these will tend to shape a person's future, Warin and colleagues point out that though *habitus* has a certain reproductive angle, it is not deterministic but flexible, open to change at both individual and collective levels. The concept of *biohabitus* encourages us to consider the impact of social factors and the way they are perpetually reenacted and embedded at a biological, molecular level. Epigenetics research has yet to address such complexity.

In the context of DOHaD-associated policies, clinical interventions, or research agendas interested in freeing people from the distress of past memories, alongside questions of the feasibility of any targeted epigenetic editing in terms of having the desired effect without destabilizing individual identity, we propose two key considerations moving forward. First, in the context of interventions that target memories through different means (i.e., their emotional weight or their molecular origins and associated presumed affective consequences) and that reflect fundamentally different perspectives of identity and experience, it is essential to consider the type of silence a person might seek, informed of the potential effects of returning to this silent state. Interventions would also need to factor in the way targeted biomarkers are impacted by elements such as poverty, structural violence, and discrimination in medical contexts (Bloom et al. 2019). These factors are not only in people's pasts and incarnated in molecular memories, but also in people's presents and futures, as new or repeated negative life experiences. Second, alongside efforts to undo the effects of traumatic pasts, an at least equal investment is warranted in supporting people as they define their futures.

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