Can you remember silence? Life in the aftermath of trauma

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> Pierre Janet commented in 1919: "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).

About a decade ago, when I (Lloyd) had only recently started a project on behavioural epigenetics with a primary research site in Montreal (a group Lutz has been affiliated with), I stumbled upon an article with a provocative title: "Remembering Silence" (2000) by the molecular biologists Leonie Ringrose and Renato Paro. The article focused on how epigenetic traits that were activated through a variety of means, could subsequently return to their silent state.

Though the article was on fruit flies and regulatory factors affecting growth and physical development, the article struck me as asking a question of considerable importance to the research emerging from my research site: if you experience a traumatic event and, as a result, acquire an epigenetic state that is considered pathological, can you free yourself of that state? This question interested me because a lot of the running narratives in behavioural epigenetics then, and to date, did not seem much less deterministic than many of the "gene for" arguments that had preceded them. In these narratives, once critical windows of developmental neuroplasticity are closed, epigenetic changes remain permanent. In contrast, the article on remembering silence was interested in the dynamic processes that might differentiate epigenetic narratives of risk and development from genetic or other deterministic frameworks.

The interests at the Montreal research site build on a century of research that has characterized and recharacterized the post-traumatic state described by the French psychologist Janet in 1919 in the citation that opens our chapter. Overall, this research has sought a means to help people return to a state of supposed silence, freed of distress and torment believed to be caused by past experiences. Considerations of 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 are the target of a panoply of clinical tools and interventions aimed at liberating people from the resulting suffering. On the side of diagnoses, tools include physical and clinical evaluations based on well-established criteria. On the side of interventions, they include pharmacotherapy (e.g., antidepressants) and psychotherapy (e.g., cognitive behavioral therapy).

More recently, and alongside these developments, two decades of research in neurosciences and environmental epigenetics most specifically have offered a range of 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 temporal and molecular scales. The ability to encode episodic memories (the memory of one's life events and experiences) is a core interest of some researchers. It is believed to include a range of physiological cognitive functions that remain poorly

understood, but that likely rely on a network of interacting brain structures. 'Molecular memory,' by contrast, is more loosely defined in research agendas. It is used to refer to molecular mechanisms correlated with any event leading to long-lasting cellular changes or adaptations, whatever their implication in episodic memories or virtually any other brain property. It remains uncertain to what extent these two types of memories — whatever their nature — might best be considered fleeting or indelible and to what extent they interact.

Our primary focus in the present chapter is not the cognitive encoding, consolidation or recall of episodic memory, but instead the molecular changes considered to be acquired through the experience of traumatic events (i.e., *molecular memory*). For instance, how a chemical tag is thought to be added to specific genes such as those associated with the regulation of the stress response, thereby epigenetically modifying gene expression. These effects are, in turn, thought to contribute to the risk of psychopathology as biomarkers that play a role in affective and behavioural regulation. To date, the processes involved in these correlations are only incipiently understood, and currently remain based on observational studies conducted in humans, model organisms in laboratory settings, or post mortem tissues, as will be detailed below.

In this chapter, we draw on published scientific literature as well as findings from long-term engagement with an epigenetics research unit in Canada and multisite interviews. Our primary research site is a research group whose work focuses on the relationship between early life adversity and subsequent development of psychopathology (such as depression) and how these conditions and associated affective states and behavioural profiles might lead to suicide. We are interested in epigenetic states as they pertain to their correlations with the experience of past adversity, regardless of whether they may be considered to affect subjective memories of experiences, or other physiological systems such as stress responses. Specifically, we are interested in molecular memory as the persistence of an active or silent state of gene expression. We bring together the perspectives of medical anthropology and molecular biology to consider (1) how a subset of molecular and clinical researchers envision the activation of epigenetic molecular memories at a biological level in response to specific experiences, (2) whether and under what conditions it is believed that such memories can subsequently be silenced, and (3) situate how researchers – from specialists in life sciences to humanities – suggest that silencing might hypothetically impact personality, affect, and identity, and whether such an intervention might enable someone to remember silence (i.e., be freed of the torment of memories of past events).

Remembering silence

In their article, Remembering Silence, Ringrose and Paro considered the implications of emerging research which indicated 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 specific regions within genes where, under control of epigenetic changes, proteins that regulate gene activity may act differentially. The authors noted that silenced states can be remembered over several cell generations, during which time the elements are active. Ringrose and Paro explained that existing research only allowed them to hypothesize as to how or why regulatory factors would return to their silenced state. This article dates from the early days of environmental epigenetics research, yet more than twenty years later, the same questions persist: how do regulatory factors, under the influence of specific environments, affect gene activation or deactivation and how does this relate to molecular memories of experiences?

The research discussed by Ringrose and Paro yielded findings on the varying effects of single alterations depending on the type and timing of the modification, and raised broader questions about the stability and reversibility of epigenetic states and their effects on subsequent development. 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 time, which may have longer-term consequences than the bout of epigenetic plasticity itself. We will return to this point later in the chapter. Ringrose and Paro observed that certain experimental results suggested that a restoration of silence was not possible after a significant period of activation, while other results pointed to the possibility of silencing even after cell division (2000: 569). Thus, there was a trend toward stability, but with notable exceptions.

Ringrose and collaborators extended this research using mathematical models of epigenetic memory of both silent and active states (Reinig et al. 2020). Acknowledging that an overall model has emerged in which specific elements are thought to increasingly maintain silent *or* active states of epigenetic memory as development proceeds, the processes conferring biological stability that they identified "do not conform to the above criteria." (ibid: 2) Genes targeted by the regulatory elements underlying molecular memories may switch status late in development or may switch dynamically and have expression patterns that are far more complex than on or off states (ibid: 2). In line with their previous findings, this research suggests the possibility of complex dynamic shifts of epigenetic memories that need to be examined at the level of individual genes and in their specific biological context. While biological context here refers to the way functional activity of genes are determined by regulatory elements, for other environmental epigenetics research that we consider in this chapter, biological context includes life experiences such as early life adversity (ELA), which is seen to enact physical changes on a person's epigenome.

Research on the persistence and reversibility of epigenetic states has rapidly expanded to include work at a variety of biological scales and experimental frameworks using multiple types of model organisms, work on human tissues, and in vitro models. Key areas of research include the determination of cellular identity during embryological development. Developmental processes are integral to related studies of molecular memory in induced pluripotent stem cells (iPSC). Research on iPSCs relies on a method whereby differentiated cells – such as a fully developed skin cell – can be reprogrammed to an undetermined state. iPSC have significant potential for the development of new experimental models ('organoids', i.e. small organs in a dish), as well as for regenerative medicine. Part of the enthusiasm for these cells comes from the fact that reprogramming to the undifferentiated state does not implicate any manipulation of the genome itself, but rather relies on epigenetic plasticity triggered by the re-expression of specific genes acting at multiple regulatory elements implicated in cellular identity. The underlying assumption related to researchers' enthusiasm is that such programming might be reversible. In other words, this research suggests that precise interventions (Guan et al. 2022) could rewrite cell fates – including memories of their pasts – to produce cells perfectly identical to 'true' stem cells.

However, it is now clear that iPSC retain epigenetic traces of their previous differentiated state (Lister et al. 2011), suggesting a form of molecular memory that resists reprogramming. Therefore, silence, in these experiments, is only partially restored, despite interventions meant to thoroughly wipe clean the epigenetic landscape. This fundamental research into molecular plasticity underlying cellular identity, over the cell lifespan, argues against a binary model grounded in a discussion of epigenetic states as active or inactive (or, on/off). It supports, instead, a gradual, context-dependent balance between persistence and reversibility. This balance is visible in Ringrose and Paro's findings

regarding dynamic shifts and studies of the persistence of epigenetic traces of the past that seem impervious to experimental efforts to effectively erase a cell's history. It may also be visible in therapeutic or experimental interventions that aim to silence molecular traces of past adverse events. As in the case of undifferentiation, these interventions may shift the cell's towards another path of differentiation and identity through the reversal of some epigenetic states, while failing to entirely undo all traces of this history.

Through these examples, the highly ambitious nature of behavioural epigenetics research that attempts to translate reasoning about the activity and silencing of molecular traits to the human lifespans and the relationship between life experiences and brain function becomes clear. Such research attempts to correlate specific epigenetic states with both earlier traumatic experiences and downstream molecular consequences on brain function. Changes in people's profiles – biological, affective, and behavioural – are considered potentially durable, though possibly dependent on the type and timing of the experience. Durable epigenetic states believed to result from traumatic events, at our primary research site and elsewhere, have been associated with a variety of pathologies, from cardiovascular to suicide risk, including for anxiety and depressive disorders, addiction, bipolar disorder, psychosis, and more (Gilbert et al. 2009; Nemeroff 2016). Models of neuropsychiatric risk suggest that epigenetic states activated by earlier trauma can set off a variety of brain adaptations that notably affect, for example, specific cell types (e.g., oligodendrocytes or astrocytes) or neuromodulators (e.g. opioid and oxytocin systems). It is these adaptations that are considered to lead to a variety of psychological traits, such as impulsivity, that are ultimately associated with mental illness, such as depression, or behaviours such as suicide. Our interest, in this chapter, is a consideration of the potential silencing of these molecular adaptations and what silence might resemble for someone experiencing these post-traumatic conditions. Before moving onto these considerations, however, the question of memory needs to be clarified. Below, we discuss the challenges associated with conceptual leaps from such molecular memory to episodic memory and from cellular to organism scales.

What's in a memory?

Ringrose and Paro's work is situated within a century of research in psychology, psychiatry, and the neurosciences that has attempted to characterize the processes and experiences associated with memory. Yet despite this substantial research and more recent work on subjects ranging from indelible memories of life experiences to associated molecular mechanisms, memory remains a category that eludes explanation (Young 1995; Meloni and Reynolds 2020).

The term memory has been mobilized in a variety of ways. A subset of researchers interested in memory and epigenetics have worked across scales of neurobiology to explore what they call the "'epigenetic code' in the central nervous system that mediates synaptic plasticity, learning, and memory." (Day and Sweatt 2011) Neuroscientists Jeremy Day and David Sweatt argue that "Investigation of the precise molecular mechanisms in both cellular development and memory has increased over the past two decades, and 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, emphasis added)

In their models of how memories are formed at a molecular level, Day and 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) Sociologists Elsher Lawson-Boyd and Maurizio Meloni suggest that Day and Sweatt's resuscitation of the concept of the engram resonates "with influential late nineteenth and early twentieth century models of organic memory, although not necessarily adhering to the same neo-Lamarckian framework." They add that "contemporary ideas of plasticity, brain receptiveness, experiential inscription and traces were a major part of these post-Darwinian debates that were later challenged by the rise of genetics (Chiapperino and Panese, 2019)," though these understandings of plasticity have become more influential in epigenetic models (Lawson-Boyd and Meloni 2021: 4) Overall, in models of episodic memory formation, "The epigenome is said to be 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." (2021: 4)

In these models, two characteristics of epigenetics are proposed, both of which we suggest should be approached with caution. Specifically, Day, Sweatt, and others have proposed that [1] molecular memory may be homologous to episodic memory and [2] epigenetics makes an exceptional contribution to the chain of events leading from life experience to gene regulation. The first proposition may be particularly misleading. Recent research has produced increasing evidence that virtually every function of the nervous system, from the regulation of autonomous functions to feeding, sleep, nociception, locomotion or the perception of stimuli, to name a few, may all implicate changes in gene expression under epigenetic regulation (Nanduri et al. 2017, Guo et al. 2017, Richard et al. 2017, Niederberger et al. 2017, MacKay et al. 2019, Gaine et al. 2019, Vucetic et al. 2012). In these studies, the levels of scientific evidence do not appear lower than that achieved in relation to the implication of epigenetic molecular processes in *episodic memory*. As such, it is difficult to identify any specificity in the relationship between *epigenetic memory* and *episodic memory*, given that epigenetic processes may be involved in all brain processes, other than the use of a common word. Accordingly, we argue 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 trauma or stress are complex and multiscalar. In case of life-threatening or traumatic events, their perception and encoding starts with sensory processing of e.g., sounds or movements, which are then interpreted at higher cognitive level by devoted brain areas, triggering negative emotions. Each of these aspects rely on a set of specialized cellular processes. At sensory level, these notably include chemical (e.g., release of neurotransmitters by neurons in brain regions getting activated), physical (e.g., light sensing in the retina), or mechanical (e.g., transduction of sound wave by the tympanic membrane) properties that act on temporal and spatial scales not necessarily compatible or dependent upon any form of epigenetic plasticity. It is the overall psychological impact of emotional distress associated with early adversity, downstream of this series of processes, that is ultimately thought to trigger epigenetic changes. The latter may in turn retroactively act on and modulate the activity of some of these neuronal processes, as well as others, potentially contributing to heightened sensitivity to later stress in life, and increased psychopathological risk. Thus, epigenetic plasticity is likely recruited by early adversity both *after* and *before* several types of biological processes, at every level of the molecular, cellular and tissue organization of the brain, and, most importantly, does not occur in isolation. Their conceptualization as exceptional contributors to brain adaptiveness, in this context, appears to reflect rather 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) Finally, a third aspect to consider relates to the fact that neurons, a major type of brain cell, present highly specialized, if not unique, epigenetic properties. These properties likely reflect the fact that neurons are post-mitotic cells that no longer divide, in which the epigenetic molecular machinery may have progressively subserved distinct requirements in these "immortal" cells compared to that during embryological development or cellular differentiation (Lutz et al. 2017). In those cells, it remains largely unknown how knowledge inferred from studies of the type of epigenetic plasticity implicated in actively dividing or differentiating cells, during the later processes (by far the most thoroughly investigated), may be pertinent. To navigate the specific role of epigenetics to these complex processes, researchers ground these models in the imperfect triangulation of incongruent forms of experimental designs (e.g., post-mortem brain tissue of people who have been classified as having experienced early adversity or not, analysis of non-brain samples in longitudinal cohorts, animal models).

In the case of the experience of early adversity (as well as potentially all brain functions enumerated above), several types of interacting epigenetic mechanisms are likely involved at molecular level. This includes modifications of the structure and activity of chromatin, i.e., the degree of compaction of genes and DNA, in part through modification of histone proteins and modulations by networks of non-coding RNAs. This is also the case for DNA methylation, the most frequently investigated candidate as molecular epigenetic memories of these events, which will be our prime focus. In animal and rodent models, early-life adversity is frequently objectivized in the form of naturally-occurring variations in maternal care, or the experimental induction of some form of stress to either mother dams, their progeny, or both. Most often, this results in behavioral deficits that manifest in adult animals long after weaning and initial triggering events, and bear some analogy with psychopathology associated in humans with early adversity (e.g., childhood maltreatment). In these well-controlled settings, such delayed or long-lasting perturbations have been associated with a host of molecular adaptations at histological, cellular, or molecular levels, including epigenetic changes, reminiscent of the propagation of multiscalar adaptations emphasized above. Building on this, studies in humans have been conducted using either post-mortem brain tissues, or more accessible peripheral 'liquid' biopsies (blood, saliva). In animal studies, causal attribution of behavioural abnormal manifestation to epigenetic changes would require dedicated experiments during which the epigenetic substrate under study would be specifically manipulated in order to prevent or reverse the abnormal behavior. Another important aspect would relate to the examination of how these traits might shift dynamically without specific interventions (e.g., passive return to their silent state or as a result of subsequent life experiences). This is currently difficult, even with some of most modern tools and approaches that are briefly exemplified and discussed below. In humans, such associations between adversity and epigenetic adaptations are even more questionable, as they may be rather due to unaccounted sources of variability. These limitations warrant caution when considering available evidence for the remembrance of epigenetic silence in the context of adversity and psychopathology.

In sum, there is a lot in a memory. Given the profound uncertainty of the relationship between epigenetic changes and episodic memory, we will stay with one specific type of memory in this text, that of the molecular changes that are correlated with the experience of early life adversity. These are considered the persistence of the experience of past events in the form of epigenetic modifications that may not be implicated in cognitive recollections of those events, nor in associated behavioural dysfunctions (e.g., higher reactivity to stressful life events). Even when limited to the question of molecular effects of past experiences, setting aside questions of episodic memory, it is only possible

to say that there are epigenetic states that are correlated with the past experience of trauma and adversity. Individual epigenetic modifications are likely only some among many effects at different scales (e.g., neurobiological patterns of synaptic connectivity). They may be durable or reversible, either passively or actively. And it matters when events occurred. We will return to this last point in the next section. However, we want to make it clear that the molecular changes that are tracked as active or silenced in this research are only single examples of systemic changes, at least in terms of the nervous system, that result from experiences.

The epigenetics of remembering silence

Epigenetics researchers continue their efforts to identify the mechanisms that may be associated with the experience of trauma and subsequent psychopathology. Concomitantly, they are also attempting to identify interventions that might silence or block modified epigenetic states.

Some of this research focuses on classic interventions such as antidepressants and psychotherapy, now studied for their effects on epigenetic mechanisms in addition to their effects on psychiatric symptoms. On the side of antidepressants, researchers have associated a number of different epigenetic modifications with a positive response to antidepressants. They are now, furthermore, attempting to identify which epigenetic states might be able to predict responsiveness to these medications (Menke and Binder 2014; Lopez et al. 2017). In terms of psychotherapy, researchers have suggested that epigenetic mechanisms may constitute "dynamic biological correlates of therapeutic interventions" and that epigenetically driven neuroplasticity (may) underlie responses to psychotherapy. (Ziegler et al. 2016: 5-6). The processes, directionality, or interactions linking symptom alleviation, intervention, and epigenetic states, however, are not yet clearly understood. For example, this research does not demonstrate whether [1] it is an intervention that reduces a person's symptoms and that it is this symptom reduction which subsequently affects epigenetic profiles, [2] whether interventions directly affect epigenetic plasticity thereby affecting symptoms, or, [3] more likely, some combination of the two. This raises important questions about inference of causality, as distinguishing between these three possibilities and assessing their respective implications would require direct and specific manipulation, or "editing", of the epigenome.

To address the challenge of causal inferences, some experimental approaches have been recently implemented in animal models. While their application to human health remains highly speculative, this work with model organisms nevertheless represents an important step toward addressing some of the theoretical questions raised by behavioral epigenetics. A subset of researchers tackling these issues, such as Elizabeth A. Heller and Eric J. Nestler, are attempting to carry out locus-specific (i.e., affecting only a specific location in the genome) epigenetic editing in rodent models (Hamilton et al. 2018: 273). The interventions they have developed modify chromatin state and change the expression of a specific gene (*fosb,* investigated at non-epigenetic level by this group, and others, for three decades) in a specific brain region in the mouse. Using this method, Heller and collaborators report having epigenetically reprogrammed this gene to modify behavioural responses to *later* stress exposure, promoting susceptibility to this experience and subsequent depressive-like behaviour, or alternatively, promoting resilience. They argue that the putative specificity of their approach allows them to understand how locus-specific epigenetic states may act in opposing ways and be causally implicated in the modulation of stress responses. The extent to which such manipulations are truly precise, and specifically affect the targeted gene only, has not been definitely evidenced yet, and raises difficult technical and experimental challenges that need to be addressed. Nonetheless, the

significance of these research findings is that, even if they are not aimed at inducing a return to silence, they demonstrate the potential feasibility of intervening in targeted ways on the molecular processes implicated in stress or trauma responses.

In parallel with these highly technical experimental endeavours, other researchers are trying to use more classical approaches to target part of the molecular machinery that is thought to either mediate or result from 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 believed to be associated with the disorder. They then manipulated the expression of one of the 2 main enzymes responsible for methylating the DNA in the mammalian brain (Dnmt3a) to undo behavioural PTSD-like traits observed in their experimental model. Yadid et al. directly manipulated enzyme expressions in the brains of model organisms. While results offer strong support to the hypothesis that DNA methylation changes may contribute to PTSD-like behavioural traits, the level of evidence for epigenetic causality is weaker compared to previous studies by Heller et al. For instance, it is possible that the enzymatic manipulation may have had effects in the brain that affected the PTSD-like behaviour but that they did not measure. Additionally, they did not identify if or how their enzymatic manipulation directly affected the DNA methylation states that were triggered in their PTSD model, but instead reasoned by inference that the enzyme must have affected these states. Yadid et al. suggest that similar therapeutic effects may be possible in humans using a systemic therapy. They propose the use of the chemical donor for methyl groups in our diets (SAM). While the authors' assertion about the therapeutic potential of a methyl donor is compelling, as in the case of the epigenetic editing carried out by Heller et al, it raises questions about the specificity of the intervention. Indeed, the systemic administration of SAM would likely affect every cell in the body (in the brain as well as in other organs) in which methylation of the DNA affects their activity. Such an induction of epigenetic plasticity using SAM would be expected to have broad effects across many brain functions as well as physiological functions of other organs and tissues. This may include potentially detrimental side effects. Ultimately, even if such an intervention allowed a person to remember silence, i.e., to reverse or erase a specific epigenetic state associated with PTSD, it also raises unresolved questions as to the psychological and behavioural consequences of the silencing.

Compared to existing therapeutic strategies, whether epigenetic editing interventions act at different spatial and temporal scales is an open question. The development of epigenetic interventions that target the molecular imprints of traumatic memories reflect a departure from therapeutic efforts to free people of the emotional impact of distressing, indelible memories. Instead, they attempt to allow a person to remember the affective silence of an epigenetic landscape unmarred by (mal)adaptive shifts in trajectories brought on by stressful or traumatic events. Such interventions would hypothetically target a range of regulatory elements, in effect bringing to the toolkit of psychiatry interventions discussed by Ringrose and Paro over twenty years ago. Systemic global methyl donor treatments, for instance, may represent a significant departure from previous treatments insofar as they have the potential, to use an analogy, to open up the equivalent of developmental critical windows of neuroplasticity among people. In other words, the canalization that has taken place to date in a person's life, setting them on a particular life trajectory based on their environments and experiences, might be reopened. (Lloyd, Larivée, and Lutz: under review) While hypothetically interesting in terms of the potential of such induced plasticity, according to one researcher we spoke with, opening or maintaining neuroplasticity may pathologically open our perceptual field. This researcher argued that under normal developmental circumstances, in adulthood, this perceptual field is narrowed by past experiences. The result of such an induced

plasticity, according to the researcher, could raise the spectre of destabilizing a person's personality, cognitive abilities or biographic integrity. (On critical periods and plasticity see Reh et al. 2020) In other words, in the process of smoothing an epigenetic landscape, basic knowledge of what is important about the relationship between self and environment could be neglected.

In sum, any single one of these molecular traces may have a range of cascading effects that are only beginning to be understood. Silencing these traces may be able to cease their activity in the future but (presumably) may not fully undo the cascades previously activated by the trait, or alternatively may trigger unwanted consequences. These latter effects may be significant depending on the time passed between activation and silencing. For the moment, what is important is that to talk about a memory and its association with active and silent states requires a great deal of clarification and specificity, more than is often reflected in scientific or social scientific considerations of these subjects.

Biography at the intersection of memories and silence

To date, the term "memory" has often served as much to hinder as to facilitate questions of biological embedding of experiences and biographical continuity. The concept nevertheless remains a crucial point of entry to conceptualize diverse processes, from sensory development to mental disorders.

In this chapter we focused on the enduring influence of the concept of memory and the moral weight of Ringrose and Paro's observations twenty years ago. Experimental interventions that aim to target specific parts of the epigenome are now looking to take their place in a long history of therapies that attempt to lessen the torment and distressing effects of what have often been described as indelible memories of traumatic events, now tightly associated with the diagnostic category PTSD (Lloyd and Larivée 2020). Altogether, these therapies, from anti-anxiety and antidepressant medications to epigenetic editing, share a common goal of lessening the emotional and affective burden of people. To conceive of the potential significance of emerging epigenetic therapies, it is important to understand them within a history of other interventions that have targeted post-traumatic states.

Conventional therapies seek to mitigate the effects of past traumas through the alleviation of symptoms (e.g., anxiety) in the present. Widely used interventions such as cognitive and behavioural therapy and medications may acknowledge the role that memories are believed to have in a person's symptomatology, but these therapies intervene somewhat adjacent to episodic memories of events. Other therapies have been developed that seek to intervene more directly on episodic memories of trauma. Propranolol is one of these. Propranolol is an experimental medication that attempts to reduce the emotional charge associated with a traumatic memory. It is administered while a traumatic memory is reactivated, and some researchers suggest that it blocks part of the process of reconsolidation in such a way that the emotions associated with a past experience are reduced, while not interfering with the memory of a specific event. (Brunet et al. 2018) The therapy is considered to most effectively reduce fear and promote extinction learning (the gradual decrease in response to a conditioned stimulus that is thought to occur when the stimulus is regularly presented without an associated negative experience) in the immediate aftermath of a negative experience or even prophylactically, prior to a traumatic experience. Propranolol has generally been found to have little effect if a person has already experienced PTSD for some time. (Giustino et al. 2016; Henry et al. 2007) However, the literature documenting the effects of propranolol presents inconsistent results

and some concerns about its potential side effects on memory or emotional associations. (Kredlow et al. 2018)

The use of psychopharmaceuticals (e.g., antidepressants) and cognitive and behavioural therapy for different forms of anxiety and depression have raised long standing questions about the extent to which their use become integrated in normative ideals and performative expectations. (Lloyd and Moreau 2011; Ehrenberg 2008) Use of propranolol for the treatment of PTSD and its potential association with the extinction of the negative emotions associated with traumatic memories has triggered ethical debates about the possible "over-medicalization of bad memories." (Henry et al. 2007: 13) Broader debates about propranolol and episodic memory have focused on the significance and the potential dangers or pitfalls of being able to create a more malleable self. While ethicists acknowledge that other interventions, such as psychopharmaceuticals or electrical stimulation, also provide means to modify ourselves, they insist that technologies to modify memories differ and that their specificities are key to assessing their impact. 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 would tilt the concept of authenticity toward one of what she identifies as its two constitutive elements. Specifically, in favour of self-creation at the expense of self-discovery, opening up new ways of being ourselves through a modification of t our self-narratives. (2022: 13-15) Leuenberger suggests that narrative identity always involves a negotiation with life experiences such that certain elements of our pasts are drawn upon to produce an identity in the present. This process of self-discovery – how we draw on these events to produce a narrative – leads to self-creation. Within these negotiations, there are traditionally elements of our pasts that, even though integrated selectively in the present, cannot be changed. However, Leuenberger suggests that memory modification technologies would tip the balance in favour of self-creation because essential elements of our memories of our pasts could be changed, and would therefore no longer be part of our subsequent self-discovery. Ethical discussions of memories and their potential extinction situate them between tormenting and essential to who we are. More broadly, these interventions raise questions about how our past experiences and emotions associated with them affect our identities.

Interventions directed at molecular memories of early trauma and how the effects of early trauma might be undone aim to do something different compared to conventional or experimental interventions that target episodic memory and their effects on psychopathology. Epigenetic therapies that target molecular effects of early negative experiences *may* affect episodic memories, given the implication of the former in the latter. However, the therapies are meant to target the molecular processes associated with behavioural traits and basic levels of reactivity to stress considered typical to PTSD. What is being silenced, then, is not 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. (Leys 2011) This conceptualization of the neuropsychiatric risk associated with post-traumatic subjectivities focuses on affective responses to triggers. As we have argued elsewhere, these triggers are considered both devoid of exceptional qualities and at once 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 different types of therapies – one oriented to or tacitly considering the effect of episodic memories of traumatic memories and the other oriented to acquired affective responses – reflect a fundamental disjunction in their approaches to post-traumatic subjectivity. These

differences are fundamentally associated with how researchers believe they might most effectively intervene on memories (episodic or molecular) of traumatic events and offer people silence. One form of silence targets emotions and the other targets affective states. Silence, then, is as polysemic as memory in this research.

Beyond questions of types of silence, questions remain as to whether any of these therapies could offer silence and provide people with the possibility of no longer being tormented by the distress of past experiences. While all of these interventions may, some only theoretically, help people to live in the aftermath of trauma, there may be an unbridgeable gap between a post traumatic state and a return to silence through epigenetic means.[1] At the extreme end of wiping memories clean, as in the case of iPSCs, it is clear that even efforts to epigenetically reprogramme cells back to, for instance, stem cell states, are unable to completely remove molecular traces of past events (i.e., molecular memories). Furthermore, such an intervention would be far from specific, with destructive effects on a person's identity. Translating this reasoning to experimental efforts at epigenetic editing, it becomes clear that even these targeted effects have the potential to both miss their mark, in terms of removing the molecular memories associated with past trauma, and the potential to destabilize people's affective identities in unforeseen ways. Moreover, as noted earlier in the text, biological mechanisms underlying such critical periods do not rely solely on epigenetic plasticity, but rather on finally coordinated sequences of events at multiple biological levels. The above analogy with critical periods should be considered critically, as associated molecular effects are likely to impinge on an otherwise 'static' brain (e.g., at cellular or tissular levels), creating unpredictable and potentially non-physiological interactions among those biological levels of organization across time and space. In the long term, overcoming these issues will require much deeper knowledge on: 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 tailored approaches for diagnosis and intervention, which will need to be both more precise (targeting pathophysiological substrates only) and broader (acting on multiple regulatory networks that underlie, perhaps differently in each affected individual, the expression of subtle, fleeting but also recurring symptoms of suffering). It should be underscored that any *return* to silence aspired for in this research is hypothetical. Epigenetics research on the effects of stress/trauma is grounded in comparison of model organisms that were subject to trauma/stress or not, but the animals are not tested prior to interventions to provide a "before" view that would hypothetically reflect a state of silence. In research with 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)

As we noted earlier in the text, researchers have suggested that episodic memories and molecular memories may be physically homologous. (Day and Sweatt 2011) While subsequent research has made this proposition unlikely (Roy et al. 2022), we would like to note a different homology that could be considered implicit in reasoning about molecular memories of life experiences: that of the relationship between a particular social experience and molecular traces of the experience. For instance, between early adversity and specific epigenetic traits. Sociologist Megan Warin and collaborators have extended sociologist Pierre Bourdieu's concept of habitus. Bourdieu's definition

[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.

of habitus relies on an analogy between biology and the social world, in which social traits uniting a class of individuals are considered to have been produced by previous experiences and are homologous to those they will reproduce. This integration of the social world is proposed to be unconsciously embodied to allow members of a class to be pre-adapted to a social context (Bourdieu: 61). In their extension of Bourdieu's analogy, 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 while *habitus* has a certain reproductive angle, it is not deterministic but flexible, open to change at both an individual and collective change. The concept of biohabitus allows us to think about the impact of social factors and the way they are perpetually reenacted and embedded at a biological, molecular level. In the context of trauma and ELA, factors such as poverty, structural violence and discrimination in medical contexts play an important role in the way memories and the distress associated to them are handled both by patients, researchers, and clinical care providers (McKenzie 2015; Bloom et al. 2018). If social structures might be seen as having enacted changes on a person biologically, might we not also consider how social structures might shift a person's subsequent life path (subjectively and biologically) in addition to looking at how one might edit molecular memories of these social structures?

Our lives are tightly bound up with our past experiences and with the lives of other people. (Lloyd and Larivée 2021) They haunt our present and affect our future. Given the number of choices, existing and in development, to remember the silence of a past state prior to trauma, perhaps the more pertinent question moving forward is what type of silence a person might seek and whether interventions would realistically bring about this type of biographic shift. If we return to the people who are at the centre of the research programme at our project's site – people who die of suicide after having experienced early abuse – what is silence to them? We do not have their words, but our project has included interviews with their family members. According to these people, their deceased family members wanted their torment to stop. This included living with their own affective and emotional tendencies that may have contributed to unstable relationships or other life decisions and with specific memories of traumatic events. These things added on cumulatively over their lives. No single intervention discussed in our chapter offers a means of undoing these sources of distress. If it might one day be possible to reverse a single epigenetic trait, it remains impossible to reverse an epigenetic landscape or a person's developmental trajectory.

Within these limits, the more pertinent question might be how people could use emerging tools to create new paths forward. What each of these interventions offers, perhaps, is a tool to think through what certain forms of silence might resemble and the role they might play in people's lives: in the process, a consideration of the molecular and lived aspects of post traumatic subjectivities might be used to make "theory out of science" (Paxson and Helmreich 2014, Landecker 2016) of relevance to social science and humanity scholars as much as to clinicians or molecular biologists.

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