Chapter 26

The Promise of Reversibility in Neuroepigenetics Research on Traumatic Memories

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26.1 Introduction

Just over 20 years ago, molecular biologists Leonie Ringrose and Renato Paro published an article with a provocative title: 'Remembering Silence' [1]. The article focused on how epigenetic elements, modified through a variety of means, could subsequently return to their silent state. Silencing is operationally defined as their epigenetic status before modulation by experimental or environmental factors. Ringrose and Paro's article described research on fruit flies and factors affecting embryological growth. Yet it asked a question of considerable importance to parallel and rapidly expanding research in human neuroepigenetics, that of *reversibility* of the molecular impact of the environment on an individual's biological profile. In the case of epigenetic modifications that are thought to be mediators between life trauma and the risk of psychopathology, this question would be translated as follows: if you experience a traumatic event and, as a result, acquire an epigenetic state considered to place you at higher risk, can you free yourself of that state? Through a critical assessment of contemporary neuroepigenetics research, in this chapter we consider researchers' ambitions to account for the indeterminacy of life and the speculative possibility of reversing acquired epigenetic states. Bringing together the perspectives of medical anthropology and molecular biology, we are interested in clarifying how reversibility – a return to silence – is envisioned, how therapeutic interventions purported to bring about that silence might function, and what this might mean for the mental health of people who live in the aftermath of trauma.

The question of reversibility is compelling for a wide range of research agendas in epigenetics, a science that has produced an evidentiary base of significant importance for the field of Developmental Origins of Health and Disease (DOHaD). Indeed, epigenetics research has provided insights into the molecular means by which life experiences might be associated with risk and resilience for the subsequent development of pathology. While the concepts of risk and resilience have received increasing attention in developmental research in recent years, little is known about their purportedly associated epigenetic states, such as their durability. In neuroepigenetics research, resilience is conceived of as a mechanism that may recruit different biological pathways than those triggered by adversity. It is often assessed in two ways: behaviourally and molecularly. Behavioural resilience has been conceived of as the possibility of not being affected by a negative experience at psychological and clinical levels; in other words, as being able to actively counteract what are considered pathological molecular states. Molecular resilience has been studied as the

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failure to be negatively affected, in terms of acquired epigenetic states, by adverse circumstances. The two conceptualisations of resilience are drawn together in experimental contexts, most often with model organisms, in which molecular profiles are sought to explain why different animals might exhibit what are seen as at-risk or resilient states. Risk, for its part, has been framed as the development of an epigenetic state associated with psychopathology, following a traumatic event; in effect, a molecular memory of that event.

Yet neuroepigenetics researchers only have speculative models to guide studies of the type or number of epigenetic states considered sufficient to confer risk or resilience in the face of adverse experiences, alongside the means by which one might reverse acquired risk. Efforts at reversibility – or remembering silence – by necessity include considerations of the relationship between subjective states, past events, and memories of those events. Since 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). Neuroepigeneticists consider mapping these processes an urgent priority given the prevalence of trauma; for instance, approximately 80 per cent of the American population is thought to have experienced trauma-level events [2]. These statistics are deemed particularly worrying given research that suggests that the epigenetic effects of traumatic events may contribute to a variety of pathologies, from cardiovascular to suicide risk, including anxiety and depressive disorders, addiction, and more [3].

Researchers hope that a greater understanding of molecular memories (i.e. epigenetic states) thought to be acquired through the experience of traumatic events, and their relationship to subsequent risk of psychopathology, might allow the development of targeted interventions to help people 'remember silence': to reverse the effects of presumably acquired pathological traits. While pre-existing and emerging models alike tend to presume the durability of epigenetic states acquired during early life, Ringrose and Paro's evaluation of epigenetics research remains productively provocative as it conceptually fuels the hypothesis of the potential for epigenetic reversibility. It also foreshadows more recent shifts in some DOHaD research agendas that are moving away from deterministic models of early-life experiences leading to diseases later in life and are instead focused on conditioning, which implies the possibility for change [4].

Through the following sections, we discuss polysemic understandings of memory and how research on reversibility is entangled with metaphors of silence as a subjectively untroubled or unaffected state. We begin with a consideration of the tensions between narratives of reversibility and persistence in epigenetics research to sketch out what is currently known and unknown about these processes.

26.2 Persistence and Reversibility in Epigenetics Research

In 2001, biologists Ringrose and Paro evaluated 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 have different functional impacts. The authors noted that silenced states can be remembered after several cell generations during which those elements were active, though they could only hypothesise as to how or why regulatory factors would return to silence. This article dates from the early days of epigenetics research, yet Ringrose and Paro's interests in how epigenetic elements change, with what effects, and whether they are reversible persist. In their contemporary version, they might be:

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how might epigenetic states acquired through exposures contribute to health and disease? And are the molecular traces of those experiences reversible?

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. Each of the studies 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, 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 the restoration of silence was not possible after a significant period of activation, other results pointed to the possibility of silencing even after cell division [1]. Moreover, genes implicated in molecular memories may switch status surprisingly late in development or switch dynamically and have regulatory patterns that are far more complex than a single transition between on or off states [1]. Thus, there was a trend towards stable effects of epigenetic states on development, but with significant variability.

Research on the reversibility of epigenetic states has since moved beyond fruit flies, and spans multiple types of in vitro models, model organisms, and work on human tissues, in situations of both health and disease. Key areas of research include the determination of cellular identity during embryological development, modelled using induced pluripotent stem cells (iPSCs). 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 comes 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 [5] may potentially rewrite cell fates by erasing or reversing memories of their pasts to produce cells perfectly identical to 'true' stem cells, which would amount to a process of full reversibility. However, it is now clear that iPSCs retain epigenetic traces of their previous differentiated state [6], suggesting an only partial reversal. 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 model (e.g. with an epigenetic landscape as either mature or immature) and instead supports a gradual, context-dependent balance between persistence and reversibility. This emerging research echoes findings discussed by Ringrose and Paro regarding highly dynamic shifts or epigenetic traces of a cell's history that resist experimental erasure.

Researchers working at the scale of the human lifespan do not necessarily depict such nuanced portraits of the dynamics of epigenetic states. Instead, they have argued that durable epigenetic states result from traumatic events [3]. (See also Keaney et al. in this volume, Chapter 14.) These epigenetic states are described as setting off brain alterations that contribute to psychological traits – such as impulsivity, interpersonal difficulties, or emotional lability – that ultimately potentiate the risk of mental illness. Research on reversibility – on a variety of species and scales – provides critical insights into human lifespan and DOHaD researchers. A careful review of this work reveals the considerable uncertainty about the dynamics of these processes. Yet it is only through a fine-grained understanding of such processes that scientists may conceive of how reversibility of epigenetic states may occur and how therapeutic interventions might silence molecular traces of past adverse events.

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26.3 The Epigenetics of Memory Formation and Its Effects

Recent neuroepigenetics research advances that traumatic experiences may increase the risk of psychopathology through acquired molecular states etched into memories. The use of the term 'memory' in neuroscience research is polysemic, referring to a range of processes at different scales. In particular, it is often evoked in ways that are consistent with its common sense description, which roughly overlaps with the concept of episodic memory. Episodic memory, formally, refers to the ability to encode one's life events and includes a range of cognitive functions that rely on interacting brain structures. The term molecular memory, by contrast, refers to molecular mechanisms correlated with any event leading to lasting cellular changes, whatever their implication in episodic memory, or any other brain property.

In this chapter, we are interested in epigenetic states as they are thought to correlate with the experience of past adversity (regardless of whether they may affect episodic memory or other physiological systems, for example reactivity to stress), and how they are believed to maintain – or not – a molecular modulation of gene activity: in effect, producing at-risk states. In order to determine which notions of memory are implicit or explicit in researchers' hypotheses about whether molecular memories and their effects might be silenced, it is necessary to examine the uses of the concept of memory in epigenetics research.

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' [7]. 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' [8]. 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 signalling 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. [7]

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' [8].

In these models, two characteristics of epigenetics are advanced, 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. Any proposition to silence memories of traumatic events would hinge on these relationships and the possibility of an intervention acting specifically on them. While Day and Sweatt put these ideas forward most explicitly, they implicitly inform many other researchers' models of epigenetic memory and its potential reversal [9].

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Day and Sweatt's first proposition may be particularly misleading. Recent research indicates that every physiological function of the nervous system – such as feeding, sleep, or nociception – may implicate molecular mechanisms occurring in part through gene expression changes, under epigenetic regulation [10, 11]. In these studies, the role of molecular and epigenetic processes in the emergence and long-term regulation of those states appears similar to what has been identified in relation to the physiological function of episodic memory. This complicates any assertions of *specificity* or *homology* (besides the use of a common word) in the relationship between *epigenetic* and *episodic memories*. Episodic memory, instead, might be seen as affected by gene expression changes and epigenetic plasticity, much as the aforementioned other physiological functions, without necessarily being homologous to them.

The second proposition is similarly debatable. Responses to life experiences are complex and multi-scalar. In the case of trauma, their perception and encoding start 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 specialised 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 waves by the tympanum) properties that act on temporal and spatial scales not necessarily compatible with or dependent upon any epigenetic plasticity. Moreover, it is the overall psychological impact of adversity, downstream of these multi-scalar processes, that is considered to trigger epigenetic changes.

Neuroepigenetic mechanisms are nonetheless widely considered to be implicated, to some extent, in the formation of molecular memories. Most of this research investigates DNA methylation, which we will focus on below. Changes in DNA methylation are considered not only to reflect past experiences but also to contribute to behavioural changes through, for example, 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. On the one hand, animal studies document how embodied epigenetic memories of early adversity may manifest in adulthood in controlled settings that limit confounding factors. Even in these studies, causal attribution of abnormal behaviour to epigenetic changes would require dedicated experiments that manipulate the proposed epigenetic substrate to prevent or reverse the abnormal behaviour (see next section). In humans, on the other hand, associations between adversity, epigenetic alterations, and later psychopathology are even more questionable. Sources of unaccounted variability over the lifespan, following trauma, are incomparably higher as studies typically analyse post-mortem brains of people who often die decades after experiencing adversity. Alternatively, peripheral 'liquid' biopsies (blood and saliva) that can be taken throughout life are more accessible but are less relevant for understandings of brain epigenetics. Thus, there is only a tenuous, associative relationship in animal and human studies between early adversity, epigenetic memories of these experiences, and drivers of later behaviours.

Ultimately, based on existing evidence, any delayed or long-lasting embodied memories are likely associated with multi-scalar adaptations, which include but are not exclusively encoded by epigenetic changes. Therefore, while epigenetic processes are plausibly recruited over the lifespan, during early adversity, and later when a host of

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related biological consequences mediate the impact of more recent life events, they do not operate in isolation. In this context, influential conceptualisations of epigenetic processes as exceptional contributors to molecular memories of past experiences appear to reflect an inability to place them in these long chains of back-and-forth, across temporal and spatial biological scales [12]. These limitations suggest caution when postulating relationships between life experiences, epigenetic modifications, and memory, particularly in the context of human adversity and psychopathology. Moreover, current understandings of this relationship might encourage attentiveness to the ways in which slippage between different types of memory explicitly or implicitly populates research on epigenetic plasticity and its potential silencing. This slippage contributes to conclusions that too easily conflate behavioural and molecular risk or resilience.

26.4 Experiments in Reversibility

In addition 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. The most targeted epigenetic editing interventions aspire to modify the fundamental molecular processes associated with past experiences 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 of these interventions is not considered to be the factual or emotional content of an episodic memory such as the emotional relationship between the person and a specific object/event, but rather an affective state thought to be related to behaviour associated with past experiences of trauma. Affective states, in this perspective, are conceived as triggered neurobiological dispositions 'operating outside the domain of consciousness and intentional action' [13]. In this conceptualisation of neuropsychiatric risk, triggers are considered both devoid of exceptional qualities and sufficient to set into motion pathological responses. At their extreme, in certain neuroepigenetic research agendas, affective responses to triggers are thought to be sufficient to lead to suicidal acts [14].

Some of the research on the reversal or modification of epigenetic states 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 in the present (e.g. anxiety) and are now also studied for their effects on epigenetic mechanisms. This involves a reconceptualisation of these interventions as modulating basic affective states underlying clinically measured symptoms. Concerning antidepressants, researchers have associated several different epigenetic modifications (in the 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 [15]. In a similar line of reasoning, researchers have suggested that epigenetic mechanisms may constitute 'dynamic biological correlates of [psychotherapeutic] interventions' [16]. However, the processes, directionality, or interactions linking symptom alleviation, intervention, and epigenetic states are far from comprehensively understood. For example, such research does not demonstrate whether (1) it is the intervention that reduces a person's symptoms and this reduction subsequently impacts

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epigenetic profiles, (2) the intervention directly influences epigenetic plasticity, thereby modifying symptoms, or (3) some combination of the two. Therefore, at present, reasoning about the reversibility of behavioural and molecular states – and how they might relate to states of risk or resilience – remains muddled. This raises important questions about the 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 the 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 [17]). Using this method, Heller and collaborators epigenetically reprogrammed a 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 to potentially silence molecular memories of past experiences.

Other researchers are drawing on different 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 [18]. In an attempt to undo PTSD-like behaviours, they manipulated the expression of one of the two enzymes responsible for methylating DNA in the mammalian brain (Dnmt3a). While the results offer support for the hypothesis that DNA methylation changes may contribute to PTSD-like behaviours, the evidence of causality through epigenetic reversibility may be considered more indirect than in 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. Despite these limitations, 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 [18]. They propose the addition of a chemical donor for methyl groups to our diets, which raises further questions about the specificity of the intervention. Indeed, systemic therapy 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 throughout the body.

Together, these approaches bypass existing symptom-oriented therapeutic interventions that are aimed at alleviating the emotional impact of distressing and presumably durable memories, and instead aim to directly reverse the molecular imprints of traumatic memories. In theory, they are more akin to an intervention targeting the aetiology of post-traumatic states, returning a person to 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. 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 associated with early-life plasticity, when the effects of negative experiences are

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considered to be particularly harmful (Reh et al. 2020). In other words, the treatment is conceived of as affecting the canalisation that presumably takes place in a person's life and sets them on a particular life trajectory [12].

It should be underscored that any judgement of a *return* to silence in this research might be considered arbitrary. 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 multi-scalar responses to life experiences, and whether the latter would be able to return to silence upon epigenetic editing is unknown. In terms of particular interventions, systemic therapies that aspire to modulate epigenetic processes come with the potential for sweeping effects on our bodily processes. Even targeted epigenetic editing interventions may either miss their mark (being unable to remove the molecular memories associated with past trauma) or destabilise people's affective identities in unforeseen ways. The limitations of these interventions place the appraisal of a return to silence in a relative framework.

In addition, epigenetics research on the effects of trauma is grounded in the comparison of model organisms that were exposed or not. Yet the animals are not tested prior to exposure and interventions, an assessment that would be necessary to provide a glimpse of 'before', which would hypothetically reflect a state of silence. In humans, these before states are not tested either, given that brain tissue can only be studied post-mortem. Further complicating judgements of before, after, or a return to a previous unaffected state, research on inter- and transgenerational effects of trauma and long-term evolutionary inheritance of epigenetic states raises additional questions of whether before should be considered a state during an individual's life or whether it should include in utero or preconception experiences, including potentially those of parents, or even longer time scales [19]. Thus, the before state to which a person would return is rarely assessed in this research, and questions remain as to when before should be identified in a person's or a lineage's trajectory. In the light of current understanding of molecular memories, it might one day be possible to reverse a single epigenetic state with a richer understanding of the processes involved, but we are not there yet. These understandings would necessarily include the kinetics, particularities, and potential reversibility of epigenetic processes in the brain; their reciprocal interactions with other levels of biological organisation; and, finally, the development of more precise interventions, targeting pathophysiological substrates only.

Limitations notwithstanding, the silence envisioned in these interventions for stress or PTSD spans ideas about memories and silencing through interventions targeting reversibility and plasticity, with epigenetic manipulations proposed as the key means of undoing the effects of past adversity. These perspectives integrate beliefs about the tendency towards stability of epigenetic states, as discussed by Ringrose and Paro over 20 years ago. They presume that molecular profiles are fixed and in need of molecular interventions to be righted. What is set aside, in terms of Ringrose and Paro's analysis, is indeterminacy and the context and variability of epigenetic states: whether, and under what conditions, acquired epigenetic states may be reversed and with what effect.

26.5 Conclusion

The interventions described in this chapter aim to silence memories of the past to create an unencumbered present and future: by wiping a person's past slate clean – whether in a

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targeted or more generalised way, depending on the intervention – it is assumed that the problem lies in the individual and only in their past as an isolated event/biomarker. Our goal has been to assess the state of knowledge about memories and their silencing and to consider the complexity of reasoning between molecular and experiential levels. We contend that researchers who aim to help people 'remember silence' should carefully reflect on the tenuous relationship between potential epigenetic and behavioural states of risk or resilience. We also argue for closer attention to the multi-scalar processes that may affect this relationship. Indeed, even if the trauma occurred in the past and a therapy was able to reverse an epigenetic state correlated with it at a later date, this does not mean that the multitude of multi-scalar processes associated with the traumatic event would also be silenced. Moreover, for many people who experience early-life adversity, ongoing trauma is as much an experience of the present as of the past [20, 21].

Ultimately, Ringrose and Paro's essential provocation concerning the indeterminacy of epigenetic states remains a powerful reminder for research that frames epigenetic trajectories as linear and fixed. While we may seem closer to the possibility of remembering silence based on claims in emerging research about epigenetic reversibility, there remains a chasm between understandings of epigenetic reversibility and the emotional and affective states associated with what are considered states of neuropsychiatric risk or resilience.

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