Homeorhesis: Envisaging the logic of life trajectories in molecular research on trauma and its effects

Abstract

What sets someone on a life trajectory? This question is at the heart of studies of 21st-century neurosciences that build on scientific models developed over the last 150 years that attempt to link psychopathology risk and human development. Historically, this research has documented persistent effects of singular, negative life experiences of people's subsequent development. More recently, studies have documented neuromolecular effects of early life adversity on subsequent life trajectories, resulting in models that frame lives as disproportionately affected by early negative experiences. This view is dominant despite little evidence of the stability of the presumably early-developed molecular traits and their potential effects on phenotypes. We argue that in the context of gaps in knowledge and the need for scientists to reason across molecular and phenotypic scales, as well as time spans that can extend beyond an individual's life, specific interpretative frameworks shape the ways in which individual scientific findings are assessed. In the process, scientific reasoning slides between understandings of cellular homeostasis and organisms' homeorhesis, or life trajectory. Biologist and historian François Jacob described this framework as the "attitude" that researchers bring to bear on their "objects" of study. Through an analysis of, first, historical and contemporary scientific literature and then ethnographic research with neuroscientists, we consider how early life trauma came to be associated with specific psychological and neurobiological effects grounded in understandings of life trajectories. We conclude with a consideration of the conceptual, ontological, and ethical implications of interpreting life trajectories as the result of the persistence of long-embodied biological traits, persistent life environments, or both.

Keywords

neuroscience, life trajectories, homeorhesis, behavioural neuroepigenetics, early life adversity, trauma

> When you read the literature you see these words, *reversibility*, *flexibility*… obviously there's a lot of interesting use and interesting misuse of these words. Another one's *memory*, in the sense that it evokes a lot. It allows us to make conceptual links we might not have been able to, but it also has a lot of baggage, each of these terms. ... We use them in papers but it doesn't mean anything really, because it's too broad. And the same is true for *plasticity* as far as I'm concerned. It doesn't mean anything.
> (McGill Group for Suicide Studies [MGSS] postdoctoral fellow)

> Beyond each structure accessible to investigation, another structure of a higher order is revealed, integrating the first and giving it its proper-ties. The second can only be reached by upsetting the first, by decomposing the organism and recomposing it according to other laws. Each level of organization thus brought to light leads to a new way of considering the formation of living beings. (Jacob 1970 cited in Méthot 2020, 239[1])

What sets someone on a life trajectory? How do you reason between vastly different scales of evidence – from phenotypic to molecular – to model at-risk trajectories? These questions sit at the intersection of what biologist and historian François Jacob has referred to as attitudes and objects: attitude understood as the perspective that researchers bring to bear on the objects of their studies, or, their evidence (Méthot 2020). Jacob believed that each object in biology is a "system of systems" that "obeys rules that cannot be deduced" by its own analysis (Méthot 2020: 239) He developed these ideas in his book *La Logique du vivant* (*The Logic of Life*) (1970), which was a history of the study of living beings grounded in an examination of objects. According to Jacob, each period of scientific thought can only operate in the space assigned by the attitude of the moment and around the objects available for analysis (Méthot 2020: 253). Attitudes, then, can be seen as an overall conceptual framework within which scientists understand the objects they study, which extend beyond what can be deduced from a discrete finding.

The type of analytic perspectives described by Jacob permit researchers to situate individual findings and reason between scales. Jacob, for instance, credited Charles Darwin's thinking about evolution to a particular form of reasoning grounded in statistics. In fact, contrary to other accounts of the history of statistics, Jacob attributed Darwin a key role in the development of statistical thinking given his reasoning between individual artifacts and population level trends. In doing so, Jacob framed Darwin's contribution in a particular way: as grounded in thinking in terms of populations and the laws of large numbers, but guided by intuition and common sense rather than "complex mathematical thinking." (Jacob 1970 cited in Méthot 2020: 256) These intuitions and common sense provide the foundation for Darwin's "attitude."

[1] All translations of Jacob taken from Jacob, 1973. Translations of Méthot are our own.

The framework Jacob developed in *The Logic of Life* provides a novel perspective from which to examine scientific inquiries at our primary research site, the McGill Group for Suicide Studies (MGSS), as researchers attempt to reason across scales, or systems, that span the molecular functioning of the brain to the clinical expression of symptoms and mental distress. The MGSS is perhaps best known for its environmental epigenetics models of the effects of early trauma on trajectories of neurobiological risk (e.g., Barnett Burns et al., 2018). It is the first research group to have translated highly influential animal research on the brain-based epigenetic effects of early life adversity (ELA) to human cohorts, identifying shared biomarkers that correlate early adversity with modifications in DNA methylation, a major epigenetic mark (e.g., McGowan et al., 2009, in Barnett Burns et al., 2018). Overall, studies of model organisms carried out by other research teams and the work of the MGSS suggest that ELA leads to elevated stress reactions later in life (see also Lloyd and Larivée, 2020). While researchers at the MGSS are particularly interested in the association between ELA and depression and suicide later in life, they do not contend that their models explain all instances of these states or behaviours (which they see as complex states or behaviours with many contributing factors) but rather that early trauma and chronic stress are correlated with them. This observation is at the origin of their interest in identifying the molecular traces of negative experiences in the body.

To identify whether people experienced early abuse, MGSS researchers carry out psychological autopsies with the kin of people who have died by suicide. This permits them to classify people within their typology of suicide with two subgroups of people who did (roughly 30-40%) or did not suffer from ELA. Psychological autopsies collect information from medical charts, information about medications people were prescribed, and reports from youth protection services and the coroner. Moreover, psychiatrists offer diagnostic impressions of the deceased based on this information and further insights gathered from their family members. Parallel studies at the MGSS, led by psychologists in collaboration with neuroepigenetics researchers, document the cumulative effects of negative life experiences that often precede suicide (Séguin et al., 2011). Thus, while the presence or absence of severe early abuse is of greatest interest to MGSS researchers, additional information gleaned about people's lives often documents lifelong experiences of mental health difficulties, addiction, socioeconomic and professional challenges, and personal loss (Séguin et al., 2013; see also Lloyd and Larivée, 2021).

The effects of life experiences are central considerations in environmental epigenetics, the study of how environments modulate the architecture and functional expression of the genome, with implications across biological and medical fields (Stotz and Griffiths, 2016; Moore, 2015). At the intersection of environmental epigenetics and neuroscience is behavioural neuroepigenetics (on neuroepigenetics, Day and Sweatt, 2010; Crews, 2008), a discipline that seeks to understand neuropsychiatric diseases through a study of brain physiology. Whereas neuroscience has long attempted to understand how life experiences affect histological, cellular and even molecular characteristics, behavioural neuroepigenetics aims to understand those processes at the level of functional regulation of genes. While much of the research in these fields focuses on plasticity -- how our brains respond dynamically to environmental cues -- it equally attempts to document the long-term effects of certain experiences on people's bodies. Efforts to understand the effects of plasticity necessarily also involve a study of stability, and how plastic and stable processes may influence life trajectories.

In this text, we draw on the words of the scientists at the MGSS, where we have carried out research since 2013, including sixty-seven interviews with MGSS researchers, complemented by observations and notes from four years of regular attendance of lab and journal club meetings,

shadowing researchers during their lab work, and ongoing exchanges with group members. In interviews with MGSS scientists, we asked them to reason beyond the limits of their laboratory research to describe why they believe that some people are at elevated risk of suicide – in other words, why they believe that the consequences of ELA are stable and thereby able to affect the rest of a person's life. Our aim was to better understand the ways in which researchers assemble and interpret data, or, approach research findings from particular perspectives. Researchers' accounts incorporate reasoning about plasticity (how ELA induces development of a biological trait) and stability (why the biological trait may persist and be associated with elevated suicide risk) to explain how environments interior and exterior to the body set people on different life trajectories.

Our interest is in the logic of life that emerges from these interpretive processes. We argue that researchers' "attitudes" reflect specific narrative choreographies (Müller and Kenney 2021) that situate their findings as molecular evidence of long-established research models. These narrative choreographies lend credibility to their findings and the adoption of particular attitudes facilitates researchers' [1] reasoning between different scales of data, and [2] population of the gaps in knowledge between their discrete molecular findings and purportedly associated clinical profiles. We suggest that a particular interpretive framework, or attitude, has contributed to an understanding of people's subsequent life trajectories as being disproportionately affected by ELA. Specifically, we suggest that historically informed trajectory-based thinking shapes the interpretation of studies of the neuromolecular effects of singular early life experiences, particularly negative ones. This interpretation of life trajectories dominates research agendas despite little evidence of the stability of the presumably early-developed molecular traits and in the face of significant difficulty by researchers to situate these traits and their potential effects on phenotypes within multiscalar and multiple temporal perspectives (Cecil et al., 2020). Instead, discrete findings, often associated with different neuronal processes, are read as contributing to the same or a stable phenotypic outcome rather than as being part of a series of dynamic and possibly impermanent shifts. This is the case despite researchers' evidence that different molecular (e.g., epigenetic) characteristics may produce opposite rather than cumulative effects and that comprehensive understandings of the dynamics of stable and unstable epigenetic processes and their effects remain out-of-reach of current experimental methodologies.

In light of these characteristics of neuroepigenetics studies, we encourage a reconsideration of the attitude that currently dominates neuroepigenetics research and we advocate for attention to experiences beyond singular events. Specifically, we want to call attention to the potential effects of ongoing negative experiences of "slow violence" (e.g., Ahmann, 2018; Nixon, 2011) in the life trajectories of people who previously experienced ELA, corresponding to the accumulation of protracted adverse situations or exposures. A consideration of the role of these experiences in people's life trajectories raises questions as to the origin of the potential durability of molecular traits, namely whether they simply persist or whether they are actively maintained, and potentially augmented by, ongoing adversity. The different visions of life trajectories that result from these two perspectives have significantly different implications for interpretations of the malleability of life trajectories and commitments to support people in shaping their trajectories.

This article begins with a historical examination of the ways in which trauma came to be associated with specific psychological and physiological effects. We then consider the ways in which behavioural neuroepigeneticists at the MGSS build on this history, and how they now envision the relationships between ELA and elevated suicide risk later in life. We conclude with

a consideration of the conceptual, ontological, and ethical implications of framing life trajectories as the result of the persistence of long-embodied biological traits, persistent life environments, or both.

A history of explosive events

For over 150 years, clinical and fundamental researchers have sought to identify the physiological and psychological effects of extreme events on people, and the relationship of these events with later psychopathology (Leys, 2010). This work has built on centuries of interest in the anatomical, physiological, and psychological effects of traumatic events (Ben-Ezra, 2011; Ellenberger, 1994). Significant shifts in etiological reasoning about mental disorders occurred in the nineteenth century, along with a growing interest in the structure, function, and reactivity of the nervous system (Lerner and Micale, 2001: 10). Research ranged from empirical studies of hysteria, in which the hereditary and anatomical locus of hysteria moved "from the reproductive zone to the brain, the mind, or the nervous system as a whole" (Micale, 1990: 366), to investigations of the psychic effects of railway accidents and other awful events, many of which involved injuries "without apparent mechanical lesions" (Page, 1883, cited in Young, 1995: 17). These changing interests and understandings of the relationship between life experiences and psychopathology led researchers to study the regulatory processes thought to underlie this relationship and how they came to be dysregulated.

Through this historical retrospective, we draw on the work of the neurophysiologist Jacques Paillard, alongside that of Jacob, to describe changes in scientific reasoning that conjoined adversity, life trajectories and increased risk of psychopathology. In 1976 Paillard argued that the heuristic devices that scientists use to infer the significance of biological processes for observable phenotypic outcomes often have the effect of obscuring important aspects of the processes themselves. In particular, he suggested that concepts such as plasticity may blind people to the potentially dynamic processes underlying states of apparent plasticity and stability. He pointed out that the ostensible functional invariance of systems are, for example, maintained by a vast number of micro-reorganizations at various subsystem levels: "Thus, one has instability as a condition of stability, random disorder as generating organization, diversity as being at the source of unity: all these seemingly contradictory notions are compatible with what one may call the "logic of life" (Paillard, 2008[1976]:9). While these processes may be compatible with what is known about biological life, Paillard appeared concerned with the cognitive effects of the interpretive frameworks that accompany terms such as plasticity and asked, "In its present form, is the term one of those generalizations condemned by Bachelard?" (Paillard, 2008[1976]:9), promoting over-determined interpretations of biological processes.

Along with Paillard and Jacob, we are interested in the interpretive processes and attitudes that become stabilized in reasoning about life sciences research. Most specifically, we wish to explore how more than a century of psychological and physiological research and theorizing about the singular effects of trauma on people's lives is reflected in contemporary behavioural neuroepigenetics research on life trajectories.

Extreme fright and homeostasis

Mid-nineteenth-century observations of emotional instability following the experience of extreme or abnormal events prompted efforts to understand potentially associated physiological

mechanisms. Surgeons such as John Erichsen ascribed increasing etiological importance to the experience of fear or extreme fright in the development of pathologies (e.g., surgical shock and nervous shock), each thought to operate through a specific yet vaguely defined anatomical pathway (Erichsen, 1859 and 1866, cited in Young, 1995: 13-14).

Shortly after, physiologist Claude Bernard described the physiological processes that were thought to be mobilized in the face of negative external environments. He proposed the maintenance of an internal environment as the result of a "fully arranged mechanism for equilibrium" that "can continually compensate for and counterbalance external variations." (Bernard, 1876 and 1878, in Cooper, 2008: 421-22) Physiologist Walter Cannon later coined the term homeostasis to describe these processes, and specifically "the coordinated physiological reactions which maintain most of the steady states in the body." (Cannon, 1929: 400) Cannon's definition of homeostasis shifted attention away "from the *state* of the internal environment (characterized in life by its relative constancy) to a more detailed study of those *control factors* which intervene to ensure the maintenance of the steady conditions of the body." (Cooper, 2008: 424, italics in the original). In particular, he described the role of the autonomic nervous system in reciprocally regulating the effects of intense emotional responses (e.g., fear) and reactions (e.g., running or fighting) to an external threat (Cannon, 1929: 422-423, see also Arminjon, 2016: 8). According to Cannon, "the *milieu intérieur* is the condition that permits the adaptive stability of the organism." (Arminjon, 2016: 8, italics in original)

Building on the work of physiologist Charles Richet, one of the critical features of Cannon's conception of homeostasis (Arminjon et al., 2010: 273) was the "apparent contradiction" through which the living being "maintains its stability only if it is excitable and capable of modifying itself according to external stimuli and adjusting its response to the stimulation. In a sense,… slight instability is the necessary condition for the true stability of the organism." (Cannon, 1929: 399) Physiological systems of regulation were increasingly seen as affected by long-term exposure to traumatic events. Cannon, along with surgeon George W. Crile, proposed that these might have a summation effect (Young, 1995: 24-5).

By contrast, physiologist Ivan Pavlov considered that recurrent trauma altered regulatory processes such that, beyond the effects during exposures, between exposures organisms could develop a new state of homeostasis. In other words, recurrent trauma produces "a transformation rather than summation." (Pavlov, 1927, cited in Young 1995: 25) He drew on research on the excitatory and inhibitory processes in the development of conditioned reflexes in animals to explain traumatic neurosis in humans. Pavlov argued that situations such as intense grief or bitter insults could lead to "profound and prolonged loss of balance in nervous and psychic activity" (Pavlov, 1927: 397) including neuroses and psychoses. Yet, he added that "we know that the same influence may produce a profound disturbance in some individuals and show no trace of effect on others, according to the power of the resistance of the nervous system in each case." (Pavlov, 1927: 397) Thus, these early researchers' theories were already oscillating between findings from the studies of experimental models and clinical profiles to envisage how physiological processes may result in psychological profiles, similar to current work in the field of behavioral neuroepigenetics.

While a great deal of this research focused on pathological circumstances and reactions, Pavlov nonetheless believed that the body's regulatory processes, even after trauma, in addition to being individualistic, were not fixed. Indeed, he concluded that

> [t]he chief, strongest, and ever-present impression received from the study of higher nervous activity by our method, is the extreme plasticity of this activity, its immense possibilities:

> nothing remains stationary, unyielding; and everything could always be attained, all could be changed for the better, were only the appropriate conditions realized. (Pavlov, 1932: 127)

This theorizing, then, already drew analyses of model organism research into beliefs or attitudes about shifts in people's life trajectories. Though some researchers displayed interest in flexible or indeterminate trajectories that were dependent on people's ongoing environments, most experimental psychology research remained oriented toward the circumstances that were seen as leading to pathological outcomes, and characterizing those outcomes.

Through the mid-20th-century, these understandings of the consequences of negative experiences, and the long-term effect of chronic stress on regulatory processes (e.g., Selye, 1950), were increasingly influenced by conceptualizations of pathology as a "disease of adaptation" (Young, 1995: 40). This form of thinking, then, already envisioned life trajectories as modulated by environmental circumstances and permitted a form of reasoning in which the source of pathology could be sought in earlier adaptations to adversity.

Organisms, environments, adaptations, and the psyche

During the last decades of the nineteenth century, a parallel set of fundamental and clinical researchers conducted controlled studies of the relationship between individual phenotypes and the environment. A subset of experimental psychology researchers studied unicellular microorganisms to investigate how organisms orient themselves toward their environments and with what effects (Carroy and Schmidgen, 2006; Schloegel and Schmidgen, 2002). They were interested in how these models could help address "psychological questions about the evolution of individuality, consciousness, and agency in the living world." (Schloegel and Schmidgen, 2002: 617) In the late 1890s, psychologist Alfred Binet drew on his studies of protozoa to elaborate theories of individual and developmental psychology, focusing on "the human individual as an organic being that interacts continuously with respect to its environment." (Schloegel and Schmidgen, 2002: 640) Similarly, Herbert Spencer Jennings applied his research on adaptation in microorganisms to issues of child education and welfare (Jennings, 1917). He argued that the maintenance of good environmental conditions (particularly good nutrition, the absence of germs, proper heat, and fresh air) would "enable the child to acquire the ability to adapt to diverse situations as they arose in the course of his or her development" (Schloegel and Schmidgen, 2002: 641). Adverse experiences, such as malnutrition, were thought to result in development being "directly weakened or pushed into wrong channels." (Jennings, 1917: 32)

Historians Jacqueline Carroy and Henning Schmidgen argue that such studies of, and theorizing about, experimental model organisms and their environments influenced psychological reasoning from behaviourism to child psychology and psychoanalysis. (2006: 177) Among the most striking examples are Sigmund Freud's speculations based on physiological research on protozoa (see Schloegel and Schmidgen, 2002 for details):

> Let us picture a living organism in its most simplified possible form as an undifferentiated vesicle of a substance that is susceptible to stimulation. Then the surface turned towards the external world will from its very situation be differentiated and will serve as an organ receiving stimuli. It would be easy to suppose, then, that as a result of the ceaseless impact of external stimuli on the surface of the vesicle, its substance to a certain depth may become permanently modified, so that excitatory processes run a different course in it from what they run in the deeper layers. A crust would thus be formed which would at least have been so thoroughly "baked through" by stimulation that it would represent the most favourable

> possible conditions for the reception of stimuli and become incapable of any further modification. […] We describe as 'traumatic' any excitations from outside which are powerful enough to break through the protective shield. (Freud, 1920, 1961: 20, 23-24)

Such theorizing diverged from efforts by Cannon and others to understand the impact of trauma on organisms' internal regulatory processes and instead proposed an explanation of how environments shaped individual organism's psyches. Freud promoted an understanding of the psyche as an organ subject to permanent modifications or wounds as a result of traumatic shocks (Malabou, 2007; Araneda, 2015). Once breached, he believed the psyche could not prevent itself from being flooded with large amounts of stimulus, resulting in a large-scale disturbance of the organism's functioning (Freud, 1920, 1961: 23-24).

These forms of thinking about organisms, environments, adaptation, and the psyche provided the foundation for researchers' increasing preoccupations with the effects of trauma on developmental processes, and for some researchers, the effects of trauma on subsequent psychopathology.

Diatheses and development

Consideration of the effects of trauma began to be set in developmental perspective during the early to mid-twentieth century. Studies of children's psychological trauma during the Second World War explored reactions to experiences such as evacuations and the impact of separation from parents as well as the effects of maternal nervousness on children during bombings (Terr, 1990, cited in Olafson et al., 1993: 11). From the 1920s forward, researchers examined the impact of negative environmental influences or events, ranging from prenatal exposure to radiation to mercury poisoning, fetal alcohol exposure, and maternal smoking, on early brain development (see Ashwal and Rust, 2003: 356). These studies can be seen as the foundation for subsequent longitudinal, epidemiological studies of the effects of the experience of adversity in the form of deprivation (e.g., famine, war; see Stein et al., 1975 for a classic example) or inequality and their correlation with patterns of mental and physical illness (e.g., the "Glasgow Effect", the Dutch Hunger Winter Study).[2] These studies framed early life as a moment of susceptibility to environmental influences with durable effects.

Attention to the effects of traumatic experiences on youth grew alongside increasing interest in theorizing organism development. In the 1930s, developmental biologist Conrad Waddington investigated how genes develop into physical traits. Working at a time when DNA had not yet been characterized and during which Mendelian understandings of evolution held sway, Waddington observed that genes tended to interact non-randomly with one another to produce developmental trajectories. This led him to believe that these processes needed to be studied with respect to the organism as a whole in its environment, rather than by focusing on single genes. Overall,

> According to the view I have been developing, organism and environment are not two separate things, each having its character in its own right, which come together with as little essential interrelation as a sieve and a shovelful of pebbles thrown on to it. The fundamental characteristics of the organism are time-extended properties, which can be envisaged as a set

[2] More recently, some of these studies have sought to identify the molecular substrates associated with these processes and their possible correlation with conditions ranging from elevated risk of disease to specific behavioural traits and types of mental illness.

> of alternative pathways of development, each to some degree, greater or lesser, a chreode[3] towards which the epigenetic processes exhibit homeorhesis. (Waddington, 1957: 189, cited in Cox, 2013: 381)

Only from this comprehensive perspective, Waddington believed, could one understand "the causal roles of single genes and the robustness of causal pathways" (Baedke, 2019: 303), such as how a genetic profile affects an organism under the pressure of the environment and developmental constraints overall (Cox, 2013: 381). Consequently, Waddington believed that development had to be studied through the optic of self-regulation (Baedke, 2019: 312), but this type of self-regulation differed from the homeostasis described by Cannon and others. While Cannon was interested in the *state* and *regulatory mechanisms* of body processes, Waddington was interested in homeorhesis, or, the tendency of a dynamic system to adopt and return to specific *trajectories* despite external perturbations.

Waddington developed a series of visual depictions of homeorhesis, in the form of the "epigenetic landscape", which were meant to represent the effects of interactions between multiple genes and the environment (see Nicoglou, 2018 for details). Depending on an organism's genetic makeup and prevailing environment, Waddington argued that either shallow (i.e., more easily changeable) or deep (i.e., resistant) canalization might be more optimal for an organism's development.

In his analysis of development, then, Waddington brought together a synthetic understanding of organisms in which neither environmental factors nor single genes alone had a singular effect on canalization (Cox, 2013: 381). The result was a functional analysis of organism-environment that provided a framework and metaphor allowing individual trajectories to be seen as emerging from the intersection of personal characteristics and environmental factors, with trajectories becoming stable over time. The essential elements of these forms of reasoning were reflected in subsequent research programmes focused on how negative environments shape people's biological profiles and phenotypes. In their most contemporary iteration, these include models of how ELA is seen to produce specific epigenetic traits leading, for some people, to a trajectory characterized by mental health problems and risk of suicide.

The 20th century work of Waddington and others definitively brought theories of early adversity and life trajectories together to explain how these negative experiences affected people over time with lasting results. These latter considerations were concerned not only with *what* might lead to vulnerability, but the importance of *when* it occurred. It was at this point in history that the concept of critical periods (defined as time points when the emergence of physiological brain properties is dependent on internal stimuli, life experiences, or environmental influences; Nelson and Gabard-Durnam, 2020) came to the fore, alongside an increasing interest in childhood trauma.

From the mid-20th century onward, increasing attention to child abuse and its effects drew and elaborated on studies of developmental trajectories in an effort to identify the mechanisms and processes that shift one person's trajectory but leave another person unaffected (e.g., the presence or absence of a congenital vulnerability). Studies of child physical abuse in the 1950s and 1960s (Dorahy et al., 2010: 6) documented the high incidence of specific psychological traits and dysfunctions among abused children (Green et al., 1981: 130), while research in the late 1980s and early 1990s associated childhood sexual abuse with long-term, diverse, negative

[3] The term chreode, or chreod, was coined by Waddington Greek roots for "necessary" and "path" (Humphrey, 2019).

physiological and psychological effects (Trickett and Putnam, 1993). From this point forward, it was generally accepted that severe and prolonged abuse in childhood was "one of the major factors predisposing a person to become a psychiatric patient" later in life (Herman, 1992: 379; see also Lloyd and Larivée, 2020).

Diathesis-stress models, first developed by the neurologist Jean-Martin Charcot, gained influence as a means of understanding how sources of vulnerability (e.g., congenital traits, early experiences) and later life experiences tended to set people on stable trajectories associated with mental illness and other negative traits. These models served as a blueprint for neurobiological research on childhood trauma and its relationship with mental illness later in life (Perry, 1994), which certain researchers saw as signalling a shift "toward a psychobiology of posttraumatic stress" (van der Kolk et al., 1985), in which early stress was thought to exert profound changes over a wide range of biological structures and functions in a way that stood outside all "ordinary stress response[s]" (van der Kolk, 2000: 13; see also Lloyd and Larivée, 2020). Stress hormones and neuroendocrine responses were drawn into molecular explanations of vulnerability and the effects of traumatic experiences on homeostasis and homeorhesis. From this perspective, elevated stress responses in adulthood are seen as a part of broader developmental processes.

Increasingly, research focused on how negative environments in youth or adulthood interact with predispositions to produce relatively stable phenotypes, or life trajectories, characterized by elevated stress responses. Yet the elephant in the room in these explanations, which oscillate between seemingly targeted biochemical responses and discussion of people's responses to stressful or traumatic circumstances, is the nature of the apparent alterations and their specific relationship to homeorhesis, or the development of a life trajectory and its persistence. The relationship between the micro processes and phenotypic outcomes remains nebulous in behavioural neuroepigenetics. However, accumulated understandings about the durable effects of significant trauma on later life trajectories permits a defensible association of the two despite considerable uncertainties about the impacts of adversity itself, the durability of any biological effects of adversity, and how any biological effects may be reflected in resulting phenotypes.

The objects of epigenetic research

In the past decade, the rapidly expanding body of research on the molecular effects of ELA has drawn attention to the multiple ways in which lived experiences affect the brain. At the MGSS, their investigations build on longstanding studies of the effects of negative environments. MGSS research suggests a "massive dynamism" in the brains of the people they study, according to a geneticist in the group. Yet despite this dynamism, epigenetic changes associated with ELA are hypothesized to be potentially stable over the lifespan and contribute to suicide later in life. Among the range of neuronal processes studied at the MGSS, we focus most on research on epigenetic mechanisms, including DNA methylation. DNA *methylation* refers to the addition of a methyl group to the DNA, while DNA *demethylation* refers to its removal. Both likely modify, or reflect changes in, the expression of a gene or its biochemical reactivity. We also examine how these processes are considered to mediate neuroanatomical consequences of ELA.

Since the 1980s, epigenetic processes have been primarily investigated for their role in cellular identity (Jeggo and Holliday, 1986), either through cellular differentiation during embryological development – for example, whether a stem cell becomes a skin cell or a neuron – or, more recently, during pathophysiological processes such as cancer (excessive cell division). In both cases, epigenetic mechanisms such as DNA methylation have been studied alongside

cellular division, the building block of the formation and functional specialization of multicellular organisms, including the transmission of genetic material. Cellular division is an essential part of such studies because the modern definition of the term epigenetic still refers to heritable changes that do not imply changes in the DNA linear sequence, where heritable refers to cellular division (either mitotic or meiotic; the latter refers to the forms of cellular division during gametogenesis, the formation of reproductive cells). The conditions by which epigenetic patterns are inherited from one cell generation to the next were thought to be the main determinant of their stability (with e.g. a passive loss of DNA methylation during the mitotic divisions that follow fertilization). As a result, these processes were little studied in postmitotic cells, such as neurons, which no longer divide: the assumption was that once cells have stopped dividing, the epigenetic plasticity that was causing or reflecting developmental processes would wane.

Although the process of DNA methylation was identified over half a century ago (Hotchkiss, 1948), the processes governing whether, how, and when loss of DNA methylation occurs (active demethylation) were not identified until just over a decade ago (Tahiliani et al., 2009). It is now clear that DNA methylation and demethylation activities persist in the brain in postmitotic neuronal cells. Most recent data indicate that neurons show some degree of epigenetic plasticity, including, and perhaps even particularly, during brain maturation and infancy (Lutz et al., 2017). Research further suggests that postmitotic neuronal cells, which live for decades, have developed, over evolutionary time, atypical forms of epigenetic plasticity (Jeong et al., 2021; de Mendoza et al. 2021). For instance, although DNA methylation primarily affects CG dinucleotides (a C followed by G in the linear DNA sequence), a non-canonical form of non-CG DNA methylation progressively accumulates during the first two decades of human life. This non-CG methylation, referred to as CH methylation, reaches levels an order of magnitude higher in the brain than in other organs, and preferentially occurs in neurons (Lister et al., 2013). Most recently, CH methylation has been shown (Zhang et al., 2021) sufficient for predicting where a neuronal cell is located within the brain, and to which other parts of the brain it is connected. Through these processes, CH methylation therefore appears to determine or reflect, at high resolution, cell fate specification and neuroanatomical organization.

During the developmental window during which CH methylation emerges, it is considered potentially susceptible to life experiences such as ELA. For this reason, scientists believe that it may represent a molecular vehicle for the persistent effects of experiences during critical periods of plasticity (Lutz et al., 2021). Drawing on findings from research using tightly controlled rodent paradigms (Zhang et al., 2018), studies with human subjects conducted by the MGSS, argue that some DNA methylation changes correlate with ELA in both CG and non-CG contexts[4] which potentially contribute to long-lasting alterations in fundamental cellular processes (e.g., synaptic plasticity, myelination) and physiological processes (e.g., regulation of reward and pain by opioidergic signalling), while acknowledging the limitations of retrospective postmortem investigations (Lutz et al., 2018; Lutz et al., 2021).

Yet, evidence of early neuroplasticity notwithstanding, epigenetic profiles captured in experimental settings represent only a snapshot of epigenetic dynamics at the moment of tissue sampling. In the context of MGSS post mortem studies, these snapshots likely reflect the results of cumulative molecular imprints of all life experiences, including ELA as well as more recent

[4] Other epigenetic processes are likely altered by early life adversity but are less studied and not considered here (see Barnett Burns et al., 2018 for a review).

stressors, psychopathological episodes, and their respective epigenetic embedding. Whether, and how, these series of events trigger distinct DNA methylation changes, possibly in non-additive or even conflicting mechanisms, cannot be inferred from MGSS studies. In other words, given current methodologies and knowledge, the postulate that some epigenetic changes associated with ELA may persist until adulthood is a reflection of the impossibility of detecting transient effects of ELA in such human retrospective studies, rather than of an empirically founded observation.

From this perspective, research centred on early life as exerting an exceptional effect on a person's life trajectory might be seen as the result of circular reasoning. First, long-standing models of the development of psychopathology have demonstrated that early life experiences may be implicated in trajectories of psychiatric risk. As a result, researchers are now studying the effects of similar experiences on biological processes believed to stabilize in the early years in search of evidence of neuropsychiatric risk. Therefore, evidence continues to accumulate about the effects of early life adversity on life trajectories. This pattern of research is typical. However, it leaves other timelines and processes that occur both within and outside of these time frames relatively unexplored and could be considered the scientific attitude of the present era, informed by past models, that is drawn upon to formulate hypotheses and consider the implications of objects defined in the research process.

Moving from ontogeny to phylogeny, recent research has found that epigenetic differences among distinct cell types (in particular, neuronal as opposed to non-neuronal cells), when compared across species that diverged relatively recently (e.g., human and non-human primates [Jeong et al., 2021]), are enriched at sites where genomic variation is associated with brain diseases, including schizophrenia and bipolar disorder. Researchers increasingly believe that both the DNA code and specific epigenetic traits (patterns of DNA methylation specific to the human brain) contribute to evolutionary processes that have allowed for the emergence of particular emotional or cognitive traits, and associated psychopathology. From a conceptual point of view, such neuron- and species-specific DNA methylation signatures blur the distinction between a strict definition of epigenetics (phenotypes transmitted through cell divisions with no change in DNA sequence) and the looser version adopted by behavioural epigeneticists (functional genomic adaptations driven by life experiences and the environment, with no change in DNA sequence). These specific signatures only affect postmitotic neurons and are not found in the germ-line, implying that they cannot be physically transmitted to the offspring through actual cell division. Nevertheless, they re-emerge at each generation, possibly as a result of self-organizing properties that are reminiscent of Waddington's chreodes (interactions among genes and environmental factors), but whose mechanisms are not yet understood. Importantly, these signatures may also retain some degree of plasticity as a function of environmental conditions. Altogether, these properties, while not consistent with the strict molecular definition of epigenetics, nevertheless fit with the concept of homeorhesis, as conceived of by Waddington. These signatures are also seen as shaping individuals' development and life trajectories, yet on a significantly different and longer time scale than is usually considered in the reasoning surrounding the studies of the effects of ELA on life trajectories.

In light of this, DNA methylation patterns may be considered substrates that are both stable (over successive generations of a given species) and unstable (in neurons, during onto- and phylogeny). These and other provocative recent findings related to environmentally-driven

changes in the DNA sequence itself[5], orient attention toward the notion that there may not be any chemical or physical biological characteristics or substrates that are perfectly stable and that might ground models of life trajectories. A consequence of which is that current definitions and concepts of structure-function relationships (e.g., those that inform the attitude through which the relationships between the biological behaviours of discrete molecular substrates and that of psychological trajectories later in life will be interpreted) and their links to specific time frames in relation to the biological effects of early life experiences on DNA methylation patterns, might be considered to be anchored in ever-shifting ground. This possibility carries implications within behavioural neuroepigenetics as well as the interpretations of this research in socio-economic, political, and policy-making settings (Müller and Kenney, 2021; Lappé et al., 2019).

Thus, researchers are only beginning to characterize the nature of organism-environment dynamics and how they may lead to stable trajectories, which may include "instability as a condition of stability," in Paillard's words, or vice versa. Yet the attitude driving models of the psychological and biological effects of ELA nonetheless reflect long-standing psychological and physiological models which suggest that experiences during critical moments of development can lead to life trajectories of neuropsychiatric risk. Based on this perspective, significant connections are conceived of between instances of ELA and negative mental health outcomes later in life (e.g., personality disorders, depression, suicide), with neuroepigenetic changes as one of the mediating mechanisms in the developmental processes that lead from one to the other (Barnett Burns et al., 2018).

Theorizing the logic of post-traumatic life in neurobiological and psychological registers

Brain studies conducted by the MGSS are producing evidence of the kinds of material processes that neuropsychiatric researchers have sought for over a century. Yet such detailed insights force scientists to grapple with the question of which elements of these data are significant in terms of personal trajectories of neuropsychiatric risk. Datasets that count in billions of "reads" of small chunks of DNA sequences reflecting the methylation status at specific genomic loci, create well-known traps for biologists seeking significant findings. For instance, recent approaches enable statistical comparison of groups of individuals with or without a history of ELA at > 25 million DNA methylation sites in the genome. Even if purely randomly distributed, data at such massive scales generate "chance" findings (i.e., false positives). Accounting and correcting for these represents a research field unto itself. In addition, the avalanche of data they collect using brain tissue samples is usually about one epigenetic trait (e.g., DNA methylation) in a single brain region.

These discrete findings reflect only one among innumerable molecular processes that might be related to the behavioural outcomes potentially associated with the experience of trauma (Barnett Burns et al., 2018). Moreover, MGSS researchers' analyses are based on limited snapshots of the final moment of people's lives and recollections of different moments of their life trajectories gathered in interviews with the kin of the deceased (Lloyd and Larivée, 2021). Thus, the current challenge for MGSS researchers is to interpret how empirical data intersect, or not, with existing theory. These researchers endeavour to draw associations between molecular profiles and life trajectories and document how they emerge at the intersection of biological,

[5] See research on the effects of early adversity on retrotransposons and shifts in the linear sequence of DNA in neurons (Breuss et al. 2020).

social, or psychological domains, while remaining vigilant for confounding factors, artifacts of the research process, and the necessity to refrain from causal inferences.

In this section of the paper, we turn to the words of MGSS researchers as they reason across scales and systems. In the process, we illustrate how their interpretations of their findings reflect perspectives emerging from influential models of the 19th and 20th centuries presented in the previous section concerning the durable impact of early traumatic events on life trajectories.

Between the regulation of states and trajectories

When researchers at the MGSS recount the effects of adversity, they describe processes that span the neurobiological (e.g., DNA methylation) and psychological (e.g., impulsivity, aggressivity) and that implicate responses across multiple neuromodulatory systems, brain structures, and cellular populations. Some of these systems may reduce the body's response to an experience, while others might augment it. To envision these processes, which have been only partially described at a molecular level, MGSS researchers draw on findings from their own research and that of colleagues (e.g., molecular biologists, neuroanatomists, psychologists), fundamental research in animal models, established physiological and psychological theories, and the canon of knowledge gleaned from their education and training. These sources are drawn upon continually through exchanges in lab meetings, journal clubs, collaborations with animal model researchers, and attention to emerging publications. A geneticist in the group drew on these sources to describe how he sees these processes occurring generally and, potentially, specific to an individual, with two main models (active coping as opposed to desensitization/passive coping). For the first, he suggested that:

> negative experiences might be severe enough to set off cascades of reactions, where there's little bumps in gene expression and in certain neurocircuits in your brain, because you're in shock… And then you're thinking [about the experience], and your cognitive processes might also start affecting where the neurosignals go and in what networks.

He reasoned that for some people, these temporary biological responses and associated cognitions and emotions might conclude with the return to their pre-trauma baseline, with little or no effect on their developmental trajectory. However, this stable response would be accompanied by a newly developed adaptation to particular contexts to avoid being overwhelmed by stressful circumstances. These people would make up a subpopulation who demonstrate few discernible consequences of their stress responses following the experience of trauma. This interpretation of biological and psychological processes corresponds with the belief of a molecular biologist in the group that some people are more "elastic" or "resilient" than others. Of note, while this type of reasoning about adaptability and resilience is documented in animal models, it is not directly informed by human postmortem work from the MGSS, whose studies mostly draw on comparisons between individuals with no history of abuse who died of suicide and those who are thought to have developed pathological responses to ELA and later died of suicide[6]. Despite this limitation, the geneticist specified that MGSS research suggests that this reaction is not common to all people:

> Somebody else… instead of responding with these little bumps of gene expression, for example, in the neural network… [they] might have a massive response in the cell… that is

[6] Investigations of groups of resilient subjects, exposed to ELA without any psychopathological impact, have not been conducted to date

> the shock and emotion they feel, and it is long-lasting [because of] this initial, crazy, huge increase in gene expression, which comes with mass release of hormones, which then feeds forward and makes it worse and worse and worse.

He described this as a "terrible" and "body-wide" response of cells and neural circuits. Drawing on experimental findings on acute and chronic stress using cellular models and behavioural paradigms in rodents, he argued that the desire to avoid biologically catastrophic responses to future stressful or traumatic situations and the recurrence of "terrible" experiences can lead to altered genome expression that will result in a blunted biological response to the same experience in the future. According to the geneticist, this means that people's experiences of future traumatic events will hopefully be less violent. He summarized that the cell is "always on a quest for stability – this is my feeling – like, the cell wants to be baseline, using as little energy as it can." He concluded that "this is basically homeostasis, is what I'm referring to here."

The MGSS geneticist's explanation draws on Bernard's theories of the constancy of the *milieu intérieur* and Cannon's theories of the body's mechanisms for the maintenance of equilibrium within extreme environments. This multiscalar reasoning and extrapolation between micro processes and an organism's behaviour has become prevalent in studies of child development that have played an influential role in contemporary psychological and physiological theories of the effects of trauma. Psychiatrists Bruce Perry and Ronnie Pollard, for instance, argue that when stress-response mechanisms are activated by severe, unpredictable, prolonged, or chronic environmental factors,

> the [body's] compensatory mechanisms can become overactivated or fatigued and incapable of restoring homeostasis, and so the physiologic system reorganizes its basal patterns. ... Trauma-induced homeostasis consumes more energy and is maladaptive compared with 'normal' homeostasis. By inducing this expensive homeostasis and compromising full functional capacity, trauma robs the organism. It has survived the traumatic experience, but at a cost. (1998: 35-36)

Perry later elaborated on this understanding, recalling Freud's theorizing of the effects of the breaching of protective shields on microorganisms:

> The physiological system reorganizes its 'basal' patterns of equilibrium. An event is 'traumatic' if it overwhelms the organisms, dramatically and negatively disrupting homeostasis. In a very real sense, trauma throws the organisms 'off balance', and creates a persisting set of compensatory responses which create a new, but less functionally flexible state of equilibrium. (Perry, 2007: 2)

Perry suggests that "In some cases, the stress-response systems do not return to pre-event homeostasis. In these cases, the signs and symptoms become so severe, persisting and disruptive that they reach the level of a clinical disorder. In a new context and in the absence of any true external threat, the abnormal persistence of a once adaptive response becomes maladaptive." (Perry, 2007: 3)

Themes from the work of Freud, Cannon, and Waddington are visible in this form of reasoning about the effect of adversity on subsequent life trajectories, shaping the attitudes that specialists adopt toward fundamental and clinical objects. The references are not direct, in the sense of referring to specific foundational texts that inform their reasoning, but this is rarely the case in the work of researchers or clinicians (Luhrmann 2001; Gibbon 2018). Anthropologist Sahra Gibbon has documented how, in contexts of emerging and uncertain information about the role of specific genes in the development of cancer, specific theories and knowledge come to "resourcefully populate" gaps between findings to guide reasoning about scientific research and

its clinical implications. She describes the resources that are drawn upon to fill these gaps as "analytical categories" in the sense that they are theories and models that people may have only very limited knowledge of – environmental- or epigenetic-based arguments in the case of her research – but which they draw upon because they serve to make essential cognitive links in their day to day lives, clinical practices, and research (Gibbon 2018: 761-2, 776-7). Thus, despite MGSS researchers' relatively superficial understandings of these classic theories[7], some of which may only have been confronted in classes on the history of neurosciences or in the introductions to research articles, the effects of these theories on their reasoning are substantial: concretely contributing to the interpretation of new data, the formation of new knowledge, and the development of new research questions.

Furthermore, as specialists grapple with findings from the level of the cell to that of the person, there is slippage between concepts such as homeostasis to homeorhesis. As an example, if we return to the MGSS geneticist's discussion of the responses of two hypothetical people to a traumatic circumstance. He argued that in the two cases, homeostasis is restored at a molecular level but with different effects on the life trajectories of the two people. In the first case, the traumatic experience would lead the person to attempt to avoid similar situations (active coping), but would result in no change to their stress response at the level of the cell. In the second case, the person would shift their cellular response to the stressful environment, with the effect of better being able to endure such situations (desensitization). Both people would continue their lives situated on different trajectories. In these models, MGSS researchers posit possible responses to a fundamental "double character" of biological explanations, as described by Jacob: "In the study of any biological system, at any level of complexity, two kinds of questions can be asked: 'How does it work [*quel en est le fonctionnement*]?' and 'How did it come about [*quel en est l'origine*]?'" (Jacob 1920: 31 cited in Méthot 2020: 269[8]) Through these forms of reasoning, MGSS research has contributed to the understanding of adaptations to ELA as incurring the cost of crossing thresholds in the epigenetic landscape and the stabilization of a different state of molecular homeostasis that is read as corresponding to a newly stable developmental trajectory (homeorhesis).

To return to the epigraph citing Jacob, reasoning about living beings requires thinking across systems and scales and continual hypothesizing about how different levels of organization function together to contribute to how organisms take shape. According to Jacob, "Each period is characterized by a range of possibilities defined not only by current theories or beliefs, but also by the very nature of the objects accessible to investigation, the equipment available for studying them and the way of observing and discussing them." (Jacob 1970: 11 cited in Méthot 2020, 253) As reflected in the words of the geneticist and in the MGSS models overall, theories of homeostasis and homeorhesis – and slippage between the two – pervade the attitude that informs contemporary explanations of how people come to be on specific trajectories and constrain the possible interpretations of emerging data. In current explanations, people's responses to adversity, as described by the geneticist and both adaptive in their own ways, straddle the zone of adaptive and pathological. People are perceived as closing off certain developmental trajectories and possible futures, and as a result, find themselves in an increasingly deeply canalized molecular and personality or psychopathological profile.

[7] By "superficial" we mean that they may not be familiar with the original texts of the people who proposed these classic theories or the experimental systems in which they grounded their research.

[8] We have included part of the original French text as the translation shifted the meaning to some extent.

Critical periods, latent causes, and the logic of life trajectories

Physiologists have long studied the body's reaction to the environment, yet the effects of trauma have historically been considered a category apart, particularly in the case of trauma encountered during youth. The MGSS postdoctoral fellow cited in the epigraph noted in a separate conversation that certain components of the epigenetic machinery are "more plastic or more active during development", referring notably to CH methylation. According to the epigenetic landscape analogy, experiences that affect CH methylation during this period may be considered to have a disproportionate effect on canalization compared with later life experiences. Yet he observed that the plasticity associated with one neural change has to be situated within the context of multiple processes occurring throughout the brain that, although studied individually, all influence a person's trajectory in which one might see correlations with depression or suicide. It is the combined results of these interactions that overall underlie the phenotypic perturbations that are retrospectively assessed postmortem. As an illustration, MGSS research suggests that ELA may reprogram cells at a molecular, epigenetic level that manifest at a variety of scales, such as histological features (e.g., myelination).

This perspective destabilizes what appears to be all-too-easy assumptions in scientific and policy literature that epigenetic mechanisms have an exceptional or specific role in mediating the impact of ELA. Instead, the postdoctoral fellow argued for a more modest attribution of an exceptional role to genes and their epigenetic profiles in the lifelong chain of events linking ELA to psychopathology, even if, for instance, specific processes are believed to be particularly active early in life. In other words, critical processes established in early life – beyond the possibility of circular reasoning which continually reorients attention to the early years – can only be understood as isolated contributions to a dynamic system that may or may not exhibit homeorhesis within the context of other biological processes and life experiences.

The neuroanatomy researcher cited earlier in the article concurred with assertions that negative environments in early life might be expected to induce neurologically durable responses to, describing childhood as "such a vulnerable period." He believed this is the case because it is a phase of highly active brain maturation and if people have "suffered during that period of intense myelination, it's likely that you'll be able to detect something going wrong at the cellular and molecular level on this tract." Based on these understandings of neural development, while certain forms of neural changes occur throughout the lifespan, the way they are potentially modulated when they first come into play during normal development have potentially lifelong effects. These neuroanatomical profiles are believed to interact with additional neural processes in such a way that the cumulative impact of life experiences on the brain affect subsequent neural development and personal trajectories.

Extrapolating from molecular processes and developmental pathways to clinical profiles, the molecular biologist cited earlier, who is also a psychiatrist, drew on his clinical and research experience to argue for a relationship between brain-wide changes following the experience of early abuse and subsequent personality traits:

> This hypothesis makes a lot of sense clinically because a lot of the people who have been severely abused early on in life have a hard time regulating their emotions and behaviour. A lot of the problems that they present in the hospital and all the interpersonal problems that they tend to have are strongly related to this difficulty. ...Obviously I am generalizing, but they tend to have a lot of interpersonal difficulties and not have stable relationships and are,

> in general, difficult people to deal with, because they are hostile, or more aggressive, impulsive.

Thus, the stability of these biological and personality traits is seen as the counterpoint of molecular changes occurring in early life and the exposure to negative environments during that time: these people find themselves on a new temperamental trajectory thought to correspond to micro-reorganizations of valleys and hills of the epigenetic landscape that ultimately lead to deep-set canalization. This understanding of the body and the lifespan "capture the oxymoronic state of the fixation of malleability" in which terms such as "stable change" and "heritable modification" are invoked to explain how things that are "fixed in the midst of plasticity" become sites of "latent causation." (Lappé and Landecker, 2015) This and similar emerging models posit the construction of new temporalities and material bases of disease – and in this case self-destruction – in which early experiences during critical periods act as "latent causes" of a series of events later in life.

This is the logic reflected in and emerging through molecular models of mental health trajectories as MGSS researchers attempt to navigate what one doctoral student described as "endless interactions" that could be conceived of within their research findings. By identifying correlations between early life events and depression and suicide, they seek to understand not only when, why, or how things change, but also why they might be conserved, and with what effects on homeostasis or homeorhesis across multiscalar processes. With respect to DNA methylation, the geneticist suggested that while gene expression is "unbelievably dynamic", there will also be "things that are stable for their own reasons". His reasoning was based on the role of neurons in shaping identity and biography:

> I would imagine neurons are privileged [in terms of stability]… There's a reason the neuron cells don't turn over, you know? I suspect that's because the neuroarchitecture is fundamental to you being able to have this conversation and find your way back home today… I think if cell assembly theory is true, that your memories are locked within the connections between cells and networks, if you either kill neurons or make changes in that network, it might affect how you remember. I'm sure there's a lot of insurance in the brain, too, where it's like, [a person would not be affected by] one cell gone – there's probably lots of redundancies built in…

In other words, he suggests that some forms of stability might be beneficial or necessary to ensure biographical continuity and to provide a coherent means of interacting with our environment. This statement reflects Waddington's concept of homeorhesis, enrolled here to reason through why a personality becomes resistant to change over time. Thus, a person's life is seen as marked by the multiscalar consequences of experiences that occurred during periods of plasticity that later "come to light", to quote the postdoctoral fellow, and manifest as a function of other events (e.g., proximal risk factors for suicide[9]).

The fact that MGSS researchers currently have limited insights into these processes means that it is difficult to identify with certainty the temporal character of the neurobiological traits and their relationship with specific environments. For instance, studies suggest that pharmaco- and psychotherapies, which notably contribute to the most mortem epigenetic images captured postmortem by the MGSS, may have epigenetic impacts (see Jiménez et al., 2018 for review). In

[9] Similar notions, which are often grouped under the rubric of meta-plasticity, are currently being formulated, tested, and to some extent documented in experimental settings (Baker-Andresen et al., 2013)

the opinion of the molecular biologist and clinician, these types of questions point to a problem in their approach:

> You can only have access to the brain after people die... So... these individuals were abused, a lot of things happened after they were abused in childhood, and they died many years later. We don't know if what we are looking at is directly related to the abuse or is a consequence of everything that happened after, or a combination of both. We don't know.

Therefore, the biomarkers that MGSS researchers study might be understood as having been stable since youth, effectively insulated from time and biological processes that might otherwise change them. In this case, they might be seen as deeply set forms of canalization that remain stable (e.g., stable and untouched, protected from active methylation or demethylation), persistently shaping a person's life trajectory. This is a classic understanding of homeorhesis in which the developmental path set by an early environment is maintained by a new baseline for the *milieu intérieur* at a cellular level that provides lifelong biographical integrity, straddling the adaptive and pathological. It is seen as resistant to subsequent environmental factors. Alternatively, and equally possible, the biomarkers hypothesized to be produced by early adversity might be dynamic. They may be transitory molecular states – whether associated with homeostasis or allostasis – that do not have, in and of themselves, perceptible effects on a person's life trajectory. As another alternative, the molecular traits could contribute to a shallow form of canalization that does not exhibit homeorhesis, in the sense that they may still be modulated by later life experiences.

We noted earlier in the text that the lives of many of the people whose tissues are studied at the MGSS experienced not only early adversity, but also life-long problems with mental health and addiction, alongside interpersonal difficulties. This being the case, one might also interpret the molecular findings as being constantly reinforced by the person's life experiences. This perspective could be seen as the opposite of homeorhesis in the sense that the trajectory is not unmoved by later perturbations in the environment but instead the depth of the trajectory's canalization could be seen as increasing, or potentially decreasing, over time. The state of research described above by the molecular biologist is, in the end, as compatible with one explanation as the other. Yet each of these understandings has significantly different implications for how we envision lives and the extent to which, and how, life trajectories might shift.

MGSS researchers' work constantly demands that they attempt to situate discrete findings within the context of other findings at different scales but also in terms of their potential functional outcomes. As noted by Jacob 50 years ago, these objects or findings are situated within a nested set of systems that continually interact to produce outcomes that cannot be deduced by their own analysis. In such a context, attitudes and objects interact to inform the logic of life that is inferred from specific findings. Thus, the limitations imposed by the state of molecular research noted by the molecular biologist underscore that conclusions currently being reached in models of at-risk life trajectories are far from the obvious or only interpretations possible. In effect, early adversity, later life challenges, specific biomarkers, and suicide are believed to be associated, but the nature of their relationships remains unclear: it is not yet understood which gene(s), neuroanatomical trait(s), environment(s), or combinations thereof may be most closely associated with the life trajectories thought to result from early trauma. Yet depending on the understanding of these relationships that becomes stabilized, the environment – whether conceived of as congenital traits, early life experiences, the rest of life, or all these factors – considered relevant for study and interventions may differ significantly.

Rethinking trajectories and models of canalization between homeostasis and homeorhesis

What sets someone on a life trajectory? How do you reason between vastly different scales of evidence – from phenotypic to molecular – to model at-risk trajectories? These questions have been driving forces in physiological and psychological research for more than a century as researchers have attempted to identify the effects of life experiences on people's bodies and minds at a variety of scales. These inquiries have focused on the processes and mechanisms that regulate people's reactions to traumatic events and their potentially durable consequences. From Erichsen's clinical observations of the effects of physical trauma on his patients to Freud's musings about the effects of the breaching of protective shields, studies of development at the intersection of genomes and environments, and recent model-organism-based studies of the effects of maternal behaviour on long-term stress responses of offspring, researchers and clinicians have sought to understand how people's life experiences affect their life trajectories.

Over time, an image of the effects of adversity has been stabilized in which extreme early events have come to be associated with durable negative effects on the psyche. This perspective is reflected in MGSS research, in which the biomarkers associated with ELA are considered to set affected individuals on what the team's neuroanatomical researcher called a "bleak" trajectory. Yet, like his colleagues, he also believes there are "cumulative effects of living with these [molecular] traits". In other words, while early adversity is still thought to play a key etiological role in these processes, it is thought to be only part of a broader set of constantly interacting mechanisms that structure the epigenetic landscape. Moreover, epigenetics research elsewhere suggests that seemingly stable traits can be destabilized and, additionally, operate within and against a larger backdrop of aging, later life experiences, and psychopathology (Horvath and Raj, 2018; Kebir et al., 2018). Such effects also operate over successive generations and on evolutionary time scales. Finally, though often studied individually for their potential effects, genetic traits function together within an organism, and any interpretation of findings must consider the possibility that the individual molecular traits may produce different effects and outcomes when combined. Across both phylogenetic and ontogenetic timescales, therefore, it appears difficult to ascribe specific epigenetic profiles to particular life experiences of a given individual and, more broadly, to clearly define boundaries between concepts of epigenetic stability or plasticity, and their respective molecular underpinnings.

In effect, contemporary efforts to understand phenotypic plasticity and stability have yielded multiscalar findings that support the conclusions of Paillard and others: organisms' phenotypic plasticity and stability – or their tendency to move onto, stay in, or move off of a trajectory – can result from passive or active processes, continuous or discontinuous changes, and adaptive or nonadaptive responses to environments that may or may not be reversible (see Morange, 2009: 495; see also Lawson-Boyd and Meloni, 2021). In other words, plasticity at a discrete level among scales of biological organization (e.g. molecular epigenetic changes) may represent the mechanism responsible for stability at higher levels (such as personality traits and psychopathology), urging for refined and careful use of these malleable concepts. Researchers are beginning to trace the molecular details of presumed responses to trauma and associated life trajectories. However, beyond the identification of a series of discrete epigenetic and neuroanatomical traits, they lack the methodological tools and evidence to arbitrate among models to propose a definitive understanding of who responds to trauma in what way, under what circumstances, for how long, and with what effects.

The objects of research considered associated with these processes have changed substantially in the last 100 years, but the attitude toward them today reflects many of the theories developed over this time period. Concepts such as plasticity, stability, homeostasis, and homeorhesis, which are broadly used across many other research fields in biology, help researchers to make conceptual links and bring with them a substantial "baggage," as noted by the MGSS postdoctoral fellow and they *do* a lot, producing specific narrative choreographies (Müller and Kenney 2021) that permit researchers to connect the dots between discrete findings. This enables the construction of conceptually coherent, but transitory, models about the effects of molecular traits believed to be the result of traumatic experiences, which will then be challenged and revised as new theories, experimental approaches and data are produced.

Following the work of sociologist Ruth Müller and feminist science studies scholar Martha Kenney, we argue that the models that result from these narrative choreographies are not inevitable (Müller and Kenney 2021: 1245), but instead reflect researchers' efforts to interpret their empirical research. Due to their training and shared knowledge, their interpretations are influenced by authoritative models of neurodevelopmental psychopathology that have been produced over the course of more than a century. Moreover, situating their findings within these models demonstrates the relevance of their research, by offering molecular data that has the potential to empirically ground long-standing clinical observations and early neuroscientific theorizing. Overall, these studies have collectively – historically and into the present – resulted in standardized tools, experimental systems (e.g. behavioural models in rodents, or modelling brain and neuronal maturation using cells in a dish), and shared knowledge that emerging research draws on for legitimacy and continuity. The shared background knowledge and assumptions shape the questions that scientists ask and the studies they conduct. This shared body of knowledge allows interdisciplinary researchers to work on the same object that at once "doesn't mean anything" (postdoctoral fellow), yet still guides the ways in which they each approach their own empirically 'doable' research (Fujimura, 1992). Here lies the cognitive trap raised by Paillard (2008[1976]) and elaborated on in this text.

In such a light it is not surprising that the most widely embraced message of behavioural neuroepigenetics is of specific trajectory-based thinking despite the fact that the bulk of the research in neuroepigenetics falls short of comprehensively demonstrating the underlying molecular kinetics, while also documenting multiscalar effects of numerous experimental and subject-specific variables that obscure interpretations of these correlations. A certain unity (Bachelard, 2002: 26) coalesces in the logic of life that researchers (and society) infer from epigenetics and other forms of research (Yehuda et al., 2016), even though this unity is not demonstrated by their own laboratory results. This permits understandings of lives grounded in beliefs about homeostasis and homeorhesis – at the level of molecular and phenotypic traits – in which singular life events are thought to indelibly shape lives. This mode of thinking has led to limited consideration of the uncertainty about the stability of epigenetic traits – in other words, about whether the apparently stable and supposedly rapid effects of early trauma are in fact the result of this singular experience or the progressive and "slow" result of repeated negative life experiences, which often characterize the life trajectories of many people affected by ELA (see Lloyd and Larivée, 2021).

There are consequences of interpreting lives of mental illness and deaths by suicide as the result of one marked experience as opposed to a lifetime of difficulties. At the very least, the former may lure us collectively into the possibility of producing time-limited interventions that are conceived of as preventing or reversing these changes. Both types of experiences are

associated with suicidal behaviour, and the latter is similarly documented by epidemiological and clinical studies also conducted by the MGSS. The severe abuse studied at the MGSS easily falls into the categories of trauma and violence that have historically been of interest. Recognition of the effects of the protracted harm of early negative experiences raises issues of accountability that have led to various forms of surveillance and intervention. Similar moves have been made to draw attention to the effects of environmental disasters on the later lives of people affected. However, in some cases, these adverse environmental circumstances may be punctuated by extreme events but are also associated with ongoing toxicity whose effects are more difficult to measure (Ahmann, 2018: 15).

These protracted experiences reflect the "sluggish temporalities of suffering" (Ahmann, 2018: 144), which have been described as "slow violence." Environmental humanities scholar Rob Nixon argues that

> violence is customarily conceived as an event that is immediate in time, explosive and spectacular in space, and as erupting into instant sensational visibility. We need, I believe, to engage a different kind of violence… incremental and accretive, its calamitous repercussions playing out across a range of temporal scales. (Nixon, 2011: 4)

Social scientists studying different forms of slow violence have called not only for the recognition of the effects of these forms of violence but also for a "*moral punctuation*: an explicit marking of time that condenses protracted suffering and demands an ethical response". Such a call demands a rethinking, or even a "deliberate manipulation", of time (Ahmann, 2018: 144). In the case of phenotypic stability, this requires a reconsideration of the micro processes and environments that lead to the stability and instability of traits.

To what extent is it possible to expand behavioural neuroepigenetic models of the effects of trauma to include not only explosive but also slow forms of violence to underscore the importance of temporality? Psychological models and bodies of research make extreme trauma something that seems tangible and reliably measurable: these experiences are signposted by trips to the emergency department or the intervention of child services, and understood as experiences that warrant psychological or psychiatric attention. Neglect, abandonment, and disappointment, by comparison, often seem to pass unnoticed. Nixon suggests that "in the long arc between the emergence of slow violence and its delayed effects, both the causes and the memory of the catastrophe readily fade from view." (Nixon, 2011: 8-9) Their relative invisibility limits the possibility of investigations into the dynamic processes that may be associated with them and further obscures understandings of plasticity already underscored by Paillard. Drawing on Nixon's work and her own research on activists attempting to draw attention to the toxic effects of industrial landscapes, anthropologist Chloe Ahmann notes that it is hard to make "eventfulness …out of nothing" (Ahmann, 2018: 149). Both Nixon and Ahmann call on social scientists to document and thereby bear witness to these unseen experiences of slow violence. Ahmann, furthermore, argues for a consideration of the politics of temporality, transforming time into "the object, not merely the context, of human behavior" (2018: 153).

In behavioural neuroepigenetics, this provocation calls attention to the ways in which specific attitudes inform the logic of life – among a wide range of other possible interpretations – that has become influential in the neurosciences and beyond. Bringing a different attitude to bear on the objects of fundamental research might unsettle conceptualizations of homeorhesis and turn attention toward whether people stay on life trajectories despite external perturbations or because of them. This type of reconsideration could lead to a new politics of temporality. Tracking these temporalities could mark a new path for the future of epigenetic research and

constitute what Gaston Bachelard calls "dynamic ways of thinking that escape from certainty and unity, and for which homogeneous systems present obstacles rather than imparting momentum." (Bachelard, 2002: 27) In a Bachelardian style, Jacob proposed that to fundamentally understand the objects of biological research, "It requires analysis of the nature of these objects, and of the attitude of the investigators, their methods of observation, and the obstacles raised by their cultural background." (Jacob 1970: 11 cited in Méthot 2020: 258). Such an imperative raises conceptual, ethical, and methodological challenges as much for the social sciences as for laboratory sciences and clinical care.

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