Homeostasis, homeorhesis, and the "logic of life": Envisaging plasticity and stability in molecular research on trauma and its effects

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Abstract [150-250 words]

How does a trait develop, and what makes it persist? This question is at the heart of studies of 21st-century neurosciences that attempt to identify how people develop specific personality traits and how these may become permanently anchored in their neurobiological profiles and temperaments. Such studies have documented the neuromolecular effects of early life adversity and have contributed to an understanding of subsequent life trajectories as being disproportionately affected by early negative experiences. This view has arisen despite little evidence of the stability of the presumably early-developed molecular traits and their potential effects on phenotypes Moreover, the overall understanding of these trajectories raises questions as to the origin of the potential stability of molecular traits: namely, whether they simply persist or whether they are actively maintained, and potentially augmented by, ongoing life adversity. These two perspectives have potentially significant implications for the understanding of the malleability of life trajectories and commitments to support people in shaping their trajectories. Through an analysis of historical and contemporary scientific literature and ethnographic research with neuroscientists, we consider how trauma came to be associated with specific psychological and neurobiological effects grounded in understandings of homeostasis and homeorhesis (trajectories). We then consider the ways in which neuroscientific researchers conceptualize the relationships between early adversity and elevated suicide risk later in life. We conclude with a consideration of the conceptual, ontological, and ethical implications of framing persistent life traits as the result of the persistence of long-embodied biological traits, persistent life environments, or both.

Keywords [4 to 6]

neuroscience, plasticity; homeorhesis, behavioural epigenetics, early life adversity, trauma

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> 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[1])

How does a trait develop, and what makes it persist? This question sits at the intersection of evolutionary and lifespan studies in neurobiology as well as individual and population-level profiles. Within this vast field, our interests centre on the theorization of trait development and stabilization in 21st-century neurosciences. Specifically, we are interested in theories about how people develop certain personality traits and how these may become permanently anchored in their neurobiological profiles and temperaments. Studies of the neuromolecular effects of early life experiences, particularly negative ones, have contributed to an understanding of subsequent life trajectories being disproportionately affected by early life adversity (ELA). This view has arisen despite little evidence of the stability of the presumably early-developed molecular traits and in the face of evidence that the role of molecular traits and their potential effects on phenotypes must be considered within multiscalar and multiple temporal perspectives. Moreover, ongoing negative experiences of "slow violence" (e.g., Ahmann, 2018) in the life trajectories of people who previously experienced ELA raises questions as to the origin of the potential stability of molecular traits, namely whether they simply persist or whether they are actively maintained, and potentially augmented by, ongoing life adversity. These two perspectives have potentially significant implications for the understanding of the malleability of life trajectories and commitments to support people in shaping their trajectories.

Trait development and persistence 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). At the intersection of environmental epigenetics and neuroscience is behavioural neuroepigenetics, 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 neurobiological characteristics (e.g., myelination and connectivity of different regions of the brain and their relationship with personality traits and psychopathology), 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.

The body's plastic and stable processes have long been of interest to molecular researchers, who express both hope and ambivalence about the utility of broad notions such as plasticity. As the

philosopher and historian of science Antonine Nicoglou (2015) notes, the scope of these debates covers not only the concept of plasticity in the context of molecular biology but also the limits and diversity of its definitions and models (see also Suárez-Díaz and García-Deister, 2015). She observes that when one looks at the historical uses of the term *plasticity* throughout the different disciplines of biology, even in 1980 the meaning of the term was not yet fixed in biology. Instead, it remained a malleable notion that was variously deployed and defined and, in the process, drew on understandings of a wide range of dynamic phenomena including homeostasis and canalization (Nicoglou, 2015: 72).

In 1976 the neurophysiologist Jacques Paillard argued that the concept of plasticity has the effect of obscuring many of the potentially dynamic processes underlying plasticity and stability. He argued that the apparent morphological invariance of systems are, for example, maintained by a vast number of micro-reorganizations at various subsystem levels. Conversely, a micro change "may have no effect at the functional level because a vicarious process contributes to maintain functional invariance… 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). Yet describing this "logic of life" (see Jacob, 1970) remains a challenge (Etxeberria and Wolfe, 2018; Talcott, 2014). Paillard raised several concerns about the use of the concept of plasticity to describe evolutionary, developmental, and genetic processes and asked, "In its present form, is the term one of those generalizations condemned by Bachelard?" (Paillard, 2008[1976]:9), promoting over determined thinking rather than grounded, scientific reasoning. Moving beyond these generalizations to provide multiscalar characterizations of the plastic and stable biological processes underlying morphological invariance (or variance) or similarly identifiable aspects of a person's phenotype or neuropsychiatric profile is the goal of many contemporary studies in behavioural neuroepigenetics. Yet within this research, plasticity remains "a big umbrella" term (PI1, MGSS neuroanatomy researcher), continuing to gloss processes both known and unknown.

We suggest that the use of generalized terms such as *plasticity* and *stability* affect the interpretation and translation of contemporary findings in molecular research. Each finding, often associated with different neural processes, is 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 characteristics may produce opposite rather than cumulative effects. Moreover, the dynamics of these stable and unstable processes and their effects remain little understood. The result is two different and contradictory logics of life. We argue that, in addition to the inherent risk of producing deterministic explanations, reductionist approaches – grounded in trajectory-based thinking – bear the weight of a century of psychological and physiological research and theorizing on the effects of trauma and stress. A consequence of this historically influenced reasoning is that findings which could begin to unpack the molecular processes associated with plasticity and stability serve instead to reinforce existing models of the singular effects of trauma on people's life trajectories.

In this article, 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. 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 adversity 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). To identify whether they 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, forthcoming).

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 argue that their models explain all instances of these states or behaviours (which they see as complex states or behaviours with many contributory 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.

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 effect, 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. 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 produce specific processes and outcomes.

This article begins with a historical examination of the ways in which trauma came to be associated with specific psychological and neurobiological effects. We then consider the ways in which a group of behavioural neuroepigenetics and neuroscience researchers conceptualize 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 persistent life traits as the result of the persistence of long-embodied biological traits, persistent life environments, or both.

Theorizing the neurobiological and psychological legacy of trauma

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. 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). In addition, researchers' and clinicians' attention "gradually shifted from [physical injury of] the spine and the brain to the mind as the key pathological site." (Lerner and Micale, 2001: 12) As a result of these changing interests and understandings of the mind and brain, research agendas came to focus on the relationship between subjective experiences and regulatory processes associated with the nervous system, and the mechanisms through which these processes were thought to be dysregulated.

Extreme fright and its effects on homeostatic states

Mid-nineteenth-century observations of emotional instability following the experience of extreme or abnormal events prompted efforts to understand the physiological mechanisms associated with such instability. 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).

Physiologist Claude Bernard described the physiological processes that were thought to be mobilized in the face of negative external environments in terms of the maintenance of an internal environment as 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, italic in original)

Building on the work of physiologist Charles Richet, one of the critical features of Cannon's conception of homeostasis is attention to instability (Arminjon et al., 2010: 273), which he saw, following Richet, as "an 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). In contrast, physiologist Ivan Pavlov considered that recurrent trauma altered regulatory processes such that, beyond the effects during exposures, between exposures organisms would have 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)

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)

Thus, though researchers displayed interest in plasticity, most experimental psychology research remained oriented toward the circumstances that led to pathological outcomes and characterizing those outcomes.

Mid-20th-century understandings of the consequences of negative experiences, and the long-term effect of chronic stress on regulatory processes (e.g., Selye, 1950), then, were increasingly influenced by conceptualizations of pathology as a "disease of adaptation" (Young, 1995: 40).

Organisms and their environments

During the last decades of the nineteenth century, researchers and clinicians increasingly conducted controlled studies of the relationship between individual phenotypes and environmental inputs. Some 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). Experimental psychologists began to address

"psychological questions about the evolution of individuality, consciousness, and agency in the living world." (Schloegel and Schmidgen, 2002: 617) By the late 1890s, psychologist Alfred Binet had extended the implications of his studies of protozoa to the elaboration 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), along with enhancing "the capability of resistance" to diseases (Jennings, 1917: 30). 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 experimental model organisms influenced not only behaviourism, but also child psychology and psychoanalysis. (2006: 177) Among the most striking examples are Sigmund Freud's speculations based on psychophysiological 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 organisms' regulatory processes and instead oriented attention to, first, how organisms orient themselves to specific environments, and second, the effects of negative or traumatic environments. Freud and other researchers constructed a conceptual link between physiological models of development and specific psychological states and tensions, both shaped by the environment. Freud promoted an understanding of the psyche as an organ subject to permanent modifications or wounds as a result of traumatic shocks (Malabou, 2007). Once breached, he believed it would be impossible for the psyche to prevent itself from being flooded with large amounts of stimulus, resulting in a large-scale disturbance of the organisms' functioning (Freud, 1920, 1961: 23-24).

These forms of thinking about stimulation, adaptation, stability, and trauma provided the foundation for the increasing preoccupation with the regulation of the central nervous system, changes in neural networks during traumatic experiences, and resulting psychopathology. These processes became the object of experimental study in the first half of the twentieth century, as

researchers attempted to characterize the relationship between physiology, psychology, and behaviour (Ohayon, 2012).

Diatheses and development

In parallel with 19th- and 20th-century interests in the development of psychopathology, other researchers and clinicians attempted to identify why certain people seemed more susceptible to mental illness or to be on trajectories associated with mental illness. Neurologist Jean-Martin Charcot's research on the physical and psychological effects of trauma was based on his view that psychological problems resulted from situations of sudden, extreme terror or frightening experiences that interacted with innate traits of his patients (Charcot, 1889, in Micale, 2001: 123). In his studies and clinical observations on hysteria, Charcot hypothesized that the disorder could be traced "to a physical defect of the nervous system, such as a brain tumor or spinal lesion, that resulted either from direct physical injury or defective neuropathic heredity" that awaited activation by appropriate circumstances (Micale, 1990: 382, 1993: 503). The precipitating circumstances in Charcot's case studies ranged from life-threatening railway and work-related accidents to "a trifling cut" or burn, excessive exposure to chemicals, assault on the street, wartime experiences, and fright from thunderstorms and lightning (Micale, 1990: 386, 2001: 121-122). Charcot and others hypothesized that such congenital predispositions may be passed through generations, albeit unpredictably (e.g., the defect might skip generations or take different forms in successive generations). These early considerations of vulnerability to traumatic experiences were not concerned with when during a person's life trauma occurred, but rather the identification of a vulnerable subpopulation and the effect of the latent trait in specific circumstances.

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 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 deleterious environmental influences or events on early brain development, ranging from prenatal exposure to radiation to mercury poisoning, fetal alcohol exposure, and maternal smoking (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]

Attention to the effects of traumatic experiences on youth developed 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 but during which Mendelian understandings of evolution held sway, Waddington observed that genes tended to interact non-randomly with one another to produce developmental trajectories, leading 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.

> 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 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 mutation affects an organism under the pressure of the environment and developmental constraints overall (Cox, 2013: 381). As such, Waddington believed that development had to be studied through the optic of self-regulation (Baedke, 2019: 312). 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 ways in which organisms and environments resulted in the apparent stability of certain developmental *pathways* or *trajectories*.

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 linkages in which organisms are "set up to detect certain stimuli within certain ranges and thus view different parts of 'the environment'" (Cox, 2013: 381). This perspective provided a framework and metaphor allowing individual trajectories to be seen as emerging from the intersection of personal characteristics and environmental factors.

The burgeoning literature on diatheses and the developmental effects of trauma preceding and following Waddington's work attempted to identify the predisposition and type of perturbation that might durably affect life trajectories and what might make people react differently to trauma. Cannon, Crile, and Freud proposed models of the effects of extreme environments on people, Charcot had convincingly argued for the role of congenital vulnerabilities to partially explain differential reactions to negative experiences, and the work of Waddington and others definitively brought these theories together to explain how these factors affected people over time through the lens of trajectories and homeorhesis. 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 to identify the mechanisms and processes that might enable similar experiences to 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 neurological traits and dysfunctions among abused children (Green et al., 1981: 130). In the late 1980s and early 1990s, research on childhood sexual abuse associated the experience with long-term, diverse, negative 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." (Herman, 1992: 379; see also Lloyd and Larivée, 2020)

Diathesis-stress models, first developed by 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). From this perspective, elevated stress responses in adulthood are seen as a part of broader developmental processes.

A growing number of researchers concluded that pathogenic stress responses could 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 (see, for example, Post et al., 1992 on the kindling effect, which has since been applied to experiences and conditions ranging from child abuse to the development of depression or alcoholism) and the effects of traumatic experiences on homeostasis and homeorhesis. 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 the development of a phenotypic trait and its persistence.

The logic of plasticity and stability in behavioural neuroepigenetics research

In the past decade, the rapidly expanding body of research on the molecular effects of early trauma has drawn attention to the manifold ways in which lived experiences affect the brain. At the MGSS, this research both builds on and departs from longstanding studies of vulnerabilities associated with genetic variation. MGSS research suggests a "massive dynamism" in the brains of the people they study, according to PI2, a geneticist. Yet despite this dynamism, epigenetic changes associated with ELA are hypothesized to be potentially stable over the lifespan. Other researchers

suggest that these changes may be passed down to subsequent generations in some cases, though this is a controversial claim. Among the range of neural 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 the expression of a gene or its biochemical reactivity. We also examine how these processes are considered to affect neuroanatomical processes affected by ELA, including myelination (the insulation of neuronal cell axons, enabling fast conduction of their electric impulses).

Since the 1980s, epigenetic processes have been primarily investigated for their role in determining 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 every functional property of multicellular organisms, including the adaptation to environmental challenges and 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). Heritability determines whether epigenetic traits are understood as stable or unstable. As a result of this research focus, 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 active DNA demethylation occurs were not identified until just over a decade ago (Tahiliani et al., 2009). It is now clear 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. Research further suggests that postmitotic neuronal cells, which live for decades have, over evolutionary time, developed atypical forms of epigenetic plasticity. 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 occurs cumulatively 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). Strikingly, CH methylation has recently been shown (Zhang et al., 2020) to be specifically associated with different cortical layers and regions in the brain as well as the structures to which neurons send axonal projections. Through these processes, CH methylation appears to determine or reflect cell fate and neuroanatomical development at high resolution.

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, acknowledging the limitations of retrospective post mortem investigations, 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) (Lutz et al., 2018; Lutz et al., 2021).

Yet epigenetic profiles captured in experimental settings represent only a snapshot of epigenetic dynamics throughout the lifespan. These snapshots likely reflect the results of cumulative molecular imprints of all previous life experiences, including ELA, as well as more recent stressors, psychopathological episodes, and their respective epigenetic embedding, which might include DNA methylation changes in opposite directions. Given current methodologies and knowledge, the postulate that some epigenetic changes associated with ELA may persist until adulthood is a reflection of the inherent impossibility of detecting*transient* effects of ELA in such human retrospective studies, rather than of an empirically founded observation.

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 primate brain) likely 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 traits 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): although they 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, they nevertheless re-emerge at each generation (as a result of inherent self-organizing properties whose mechanisms are not yet understood), and may retain some degree of plasticity as a function of environmental conditions. These traits, while not consistent with the strict molecular definition of epigenetics, nevertheless fit with the concept of homeorhesis, as conceived of by Waddington, in the sense of shaping individuals' development and life trajectories.

Back to ontogeny, a recent set of experimental results further supports widening the definition of behavioural epigenetics, with evidence for functional adaptations that are not transmittable but are dependent on changes in the DNA sequence rather than on *epi*-processes. These results relate to somatic mosaicism and to the increasing recognition (largely due to recent technological developments allowing the sequencing of individual cells) that cells within an organism may have different genetic sequences. This mosaicism may be more abundant in the brain than in other tissue

types (Breuss et al., 2020), possibly reflecting yet another functional specialization of this organ toward adaptability to environmental changes. It notably relies on genetic elements, known as retrotransposons, that have the capacity to change their location in the genome – that is, in essence, to affect the linear DNA sequence. In 2018, neuroscientist Tracy Bedrosian and colleagues found that the activity of retrotransposons increased in mouse pups raised under conditions of low maternal care. These results suggest that early care – and perhaps other environmental factors – may influence the rate of retrotransposition and therefore modify not only the way the DNA code is functionally interpreted (through epigenetic modifications), but also the code itself. In other words, these results represent the extreme example of a substrate, DNA, that is both stable (over successive generations of a given species) and unstable (in neurons), and suggest that there may not be any absolute chemical or physical representation of biological stability. This possibility urges caution and modesty when considering current definitions and concepts of structure-function relationships in relation to the biological embedding of life experiences, and their implications within behavioural neuroepigenetics as well as the interpretations of this research in socio-economic, political, and policy-making settings.

Thus, researchers are only beginning to characterize the nature and dynamics of plastic processes and their potentially durable effects: "instability as a condition of stability," in Paillard's words, or vice versa. The logic of life driving models of the psychological and biological effects of ELA nonetheless builds on long-standing psychological and physiological models that suggest that experiences during critical moments of development can lead to the persistence of embodied traits due to both plastic and stable processes in the form of acquired biological characteristics. Significant connections are thus conceived of between instances of ELA and negative mental health outcomes later in life (e.g., personality disorders, depression, suicide), with neurobiological traits as the correlating factor in the developmental processes that lead from one to the other (Barnett Burns et al., 2018).

Theorizing specific neurobiological and psychological effects of trauma

Brain studies conducted by the MGSS are producing the kinds of data that neuropsychiatric researchers have sought for over a century. Yet gaining such detailed insights forces scientists to grapple with the question of which elements of these data are significant in terms of personal traits or life trajectories. 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. This isolated trait is only one among innumerable molecular processes that might be related to the behavioural outcomes of the experience of trauma (Barnett Burns et al., 2018). Moreover, their analyses are based on limited snapshots of the final moment of people's lives and different moments of their life trajectories gathered in interviews with the kin of the deceased (Lloyd and Larivée, forthcoming). In addition, 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. As an illustration, recent technologies enable statistical comparison of groups of individuals with or without a history of ELA at > 25 million methylation sites in the genome. Even if purely

randomly distributed, data at such a massive scale generate "chance" findings (i.e., false positives). Accounting and correcting for artifacts represents a research field unto itself. 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 phenotypes and document how they emerge at the intersection of biological, social, or psychological domains while remaining vigilant for confounding factors, artifacts of the research process, factors such as pleiotropy (in which a gene might affect two or more seemingly unrelated cellular processes or phenotypic traits in the body), and the necessity to refrain from causal inferences. In this section of the paper, we turn to the words of MGSS researchers as they draw on the historical and contemporary understandings of development and responses to trauma to consider the implications of experimental findings.

Homeostasis, allostasis, homeorhesis, and understandings of the pathophysiological effects of traumatic events and negative environments

When researchers at the MGSS recount the effects of adversity, they describe processes that span the neurobiological (DNA methylation, myelination) and psychological (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, fundamental research in animal models, and theories of how the body is believed to respond to trauma. PI2 drew on these sources to describe how he sees these processes occurring generally and, potentially, specific to an individual. 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 end 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 adversity to particular contexts to avoid being overwhelmed by stressful circumstances. These people would make up a subpopulation showing few discernible consequences of their stress responses following the experience of trauma. This interpretation of plastic processes corresponds with PI3's belief that some people are more "elastic" than others. In line with this, PI2 continued, 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 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. As PI2 explained, this means that people's experiences to 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. His explanation of the relationship between the body and the environment echoes arguments advanced in the mid-twentieth century by physician and philosopher of science Georges Canguilhem, who described the relationship between the being and its milieu as functional, as much between intracellular elements and the cell as between the organism and its milieu: all of these relationships contribute to the individuality of the organism (Canguilhem, 2008: 111). This multiscalar reasoning and extrapolation between micro processes and effects on the organism 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)

In effect, PI2's words reflect this understanding that the consequences of trauma lead to the loss of a previous state of homeostasis, with enduring effects on a person's clinical and subjective phenotype. Reasoning from the level of the cell to that of the person, PI2 depicts a situation in which homeostasis is restored at a molecular level but with different effects on the life trajectories of

the two hypothetical people he describes. 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. In the second case, the person would shift their response to the stressful environment, with the effect of better being able to endure such situations (desensitization). These responses involve, respectively, a return to homeostasis at the level of the cell and an allostatic response, which is to say the establishment of a new homeostasis at the level of the cell. Both people continue to move through their lives, but they are differently situated vis à vis the environment in anticipation of future experiences and personal needs. Implicit in this reasoning is the logic found in Waddington's models of developmental biology, in which people's genetic constitutions and environments interact to produce different life trajectories, or homeorhesis. As a result of these canalization processes, different organisms would not be expected to respond in similar ways to the same environment. In other words, people react differently to environmental stimuli.

Molecular and psychological research is beginning to document these processes and to offer rudimentary explanations to the provocation posed by Canguilhem over half a century ago:

> The milieu of behavior proper to the living (*Umwelt*) is an ensemble of excitations, which have the value and signification of signals. To act on a living being, a physical excitation has not only to occur but also to be noticed. Consequently, insofar as the excitation acts on the living being, it presupposes the orientation of the living being's interest; the excitation comes not from the object but from the living. In order for the excitation to be effective, it must be anticipated by an attitude of the subject. If the living is not looking, it will not receive anything. A living being is not a machine, which responds to excitations with movements, it is a machinist, who responds to signals with operations. Naturally, this is not to contest that it happens through reflexes whose mechanism is physicochemical. That is not where the question lies for the biologist. Rather, the question lies in the fact that out of the abundance of the physical milieu, which produces a theoretically unlimited number of excitations, the animal retains only some signals (*Merkmale*). (Canguilhem, 2008: 111-112)

The MGSS research has played a central role in describing the molecular processes thought to underlie the ways in which an organism comes to orient itself to signals in different ways as well as the development of new physiological baselines and their "costs". This research has contributed to the understanding of adaptations to ELA as incurring the cost of crossing subtle thresholds in the epigenetic landscape (without necessarily major changes in cellular identity) and the stabilization of a different state of homeostasis that corresponds with a new developmental trajectory (homeorhesis) as a result of stable epigenetic effects of trauma. These molecular findings are now being drawn upon to advance an explanation of how people come to be on specific trajectories in which they either avoid or prepare to endure stressful or traumatic circumstances. In these explanations, people's responses as described by PI2 – both adaptive in their own ways – straddle the zone of adaptive and pathological, as people start to close off certain developmental trajectories and possible futures, and as a result, find themselves in an increasingly stable molecular and personality profile.

Critical periods, latent causes, and the origins of vulnerability

Physiologists have long studied the body's reaction to the environment, yet the effects of trauma have been considered a category apart, particularly during youth. The 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 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 an epigenetic trajectory in which one might see correlations with depression or suicide. All these interactions produce responses to perturbations that are phenotypically visible. As an illustration, MGSS research suggests that ELA may reprogram cellular processes at a molecular, epigenetic level that manifest at a variety of scales, such as myelination. This perspective destabilizes what appear 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 causality to genes and their epigenetic profiles in the lifelong chain of events linking ELA to psychopathology, even if specific processes are believed to be particularly active early in life.

PI1 concurred about the neurologically durable responses to negative environments in early life, describing childhood as "such a vulnerable period.". He argued that because the brain is maturing, 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 plastic and stable processes occur throughout the lifespan, certain neuroanatomical changes that occur as a part of 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, PI3 drew on clinical experience and research that tend to support the relationship between brain-wide changes thought to follow 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 plasticity 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. 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.

The logic of plasticity and stability

What logic of life is reflected in and emerges through models of the processes involved in plasticity and stability? How do these molecular scientists draw on neuroscientific and physiological theories to provide explanations that bridge the known and unknown processes that contribute to these two states? How do theories and data shape MGSS researchers' efforts to navigate what one doctoral student described as "endless interactions"? 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, PI2 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, PI2 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 environments. This perspective recalls Canguilhem's argument that organisms orient themselves to the environment in meaningful ways. Viewing them through the lens of Waddington's theorizing on canalization, or homeorhesis, one might say that the continual interactions between organism and environment, over time, stabilize people on certain trajectories. Thus, a person's life could be 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[5]).

These intuitions were echoed in a conversation with an epigenetics researcher who is not affiliated with the MGSS. She suggested that "it probably wouldn't be good to leave the [neuroplasticity] window open when we're older because… I wouldn't be having a discussion with you. I'd be listening to the furnace going on or off… We narrow our perceptual field according to our experience." In other words, through development we learn to know what is important in our environments. She added that an American colleague who works in epigenetics believes that the failure of these windows to close could be implicated in schizophrenia. From this perspective, the stabilization of neural traits and identity formation is essential for 'normal' development.

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 have epigenetic impacts: see Jiménez et al., 2018 for review). In the opinion of PI3, 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.

Given the limitations posed by molecular research, reasoning about the stability of biomarkers associated with ELA and identified after death and when the markers 'got there' and why they stayed explicitly draws on or is implicitly guided by long-standing models of neurodevelopment.

Consequently, 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 potential persistence of molecular effects of 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. 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 passively remaining stable (e.g., simply stable and untouched, protected from active methylation or demethylation), persistently exerting their influence on a person's life trajectory. This is an understanding of homeorhesis in which the modified developmental path set by an early environment is maintained by a new baseline for the *milieu intérieur* that provides lifelong biographical integrity, again straddling the adaptive and pathological. Alternatively, and equally likely, the biomarkers might be seen as dynamic, in the sense that there is no reason to believe that they should be persistent throughout life, but they might be actively maintained by a person's external environment or the perpetuation of their internal psychological and physiological states. In this understanding of canalization, a person's life might be understood as constantly reinforcing the developmental path, making deviation less likely as the depth of the trajectory's canalization increases over time. Each of these understandings has significantly different implications for how we envision lives and the extent to which, and how, life trajectories might shift.

Conclusion: Querying environments

What makes a trait develop and persist? This question has been a driving force 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 are shaped by their environments.

Historically, research guided by pathophysiology and psychopathology has often envisioned the apparently stable effects of trauma as allostatic shifts, the crossing of a developmental threshold, or a shift in homeorhesis. Short-term, potentially adaptive responses to trauma have been framed as lessening energetic costs of subsequent negative experiences, blunting people's future responses to the same stimuli or leading them to avoid similar stimuli. Yet the costs of trauma and its sequelae have also been conceived of in the longer term, when allostasis would occur and people would be effectively readied for future negative experiences. Return to a pre-trauma state was considered difficult because of the long-term stability required to avoid ruptures in biographic integrity. An organism was seen as vulnerable to stress from birth or as adapting early to extreme environments, with limited possibilities for neural plasticity thereafter.

In MGSS research, the biomarkers associated with ELA are considered to be potentially stable (actively or passively). Affected individuals may be seen as on what PI1 called a "bleak" trajectory. Yet, like his colleagues, he also believes there are "cumulative effects of living with these [molecular] traits". 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 processes 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 may 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.

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 can be underscored by 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). Researchers are beginning to trace the molecular details of this plasticity, but, beyond the identification of a series of epigenetic traits, they lack the methodological tools and evidence to arbitrate among models and speculations of researchers operating a century ago, or to progress toward a definitive understanding of who responds in what way, under what circumstances, for how long, and with what effects. So, while plasticity as a concept helps researchers to make conceptual links, it does not, as the MGSS postdoctoral fellow notes, provide solid understandings of people's life trajectories. However, the "baggage" associated with narratives of plasticity and stability nonetheless *does* a lot.

It is curious, then, but perhaps not surprising, that the most widely embraced message of behavioural neuroepigenetics is that of early plasticity in response to trauma and the apparently

passive stability of people's biological and biographical trajectories thereafter. On the one hand, scientists have demonstrated correlations between certain early life experiences – often among people with long-term experiences of mental illness and negative life experiences – and post-mortem traits and suicidal behaviour. On the other, the bulk of the research in neuroepigenetics and even in the research group that identified these correlations has documented the unstable, fluctuating, multiscalar effects of numerous experimental and subject-specific variables that obscure interpretations of these correlations. In other words, 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. From where, then, does the emphasis on stability emerge? How has trauma, particularly trauma early in life, come to be seen as an experience with indelible molecular effects? How did this view come to be a widely accepted logic of life, eclipsing the uncertain, diverse, and contradictory processes described by Paillard in the 1970s, which seem more compatible with behavioural neuroepigenetic research findings?

As sociologist Maurizio Meloni observes, understandings of plasticity and stability of trajectories occur at the interface of "various branches of the life-sciences." (Meloni, 2018: 4). If fundamental studies have documented many forms of plasticity and stability, they have nonetheless focused on the most readily observable biological responses to significant or extreme experiences. Likewise, while clinical and epidemiological studies have documented the indeterminacy of personal life trajectories, they have nevertheless historically problematized the effects of marked and traumatic experiences on individuals and populations, particularly during the early years of life. These studies have resulted in standardized tools that emerging research draws on for legitimacy and continuity. 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", yet still guides the ways in which they each approach their own empirically 'doable' research (Fujimura, 1992). Here lies the trap of the concepts of plasticity and stability (Paillard, 2008[1976]).

These vague yet weighty understandings of plasticity and stability permit understandings of trajectories 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, forthcoming).

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. Both types of experiences are associated with suicidal behaviour, and both are documented in MGSS research. 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 logics of life – attributing particular weight to significant events early in life – have become influential in the neurosciences and beyond. Greater attention to the ongoing findings in these areas of fundamental research might unsettle conceptualizations of how homeorhesis occurs, and lead to consideration of the development of shallow and deep-set canals in response to multiple forms of experiences as a result of multiscalar environments, and across a variety of temporalities. Tracking these unknowns is the future of epigenetic research, and their consideration is a form of 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) Such questions raise conceptual, ethical, and methodological challenges as much for the social sciences as for laboratory sciences and clinical care.

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[1] While we draw on and cite specific publications of the MGSS (i.e., MGSS researchers, students, and trainees are listed as authors), researchers quoted in the article are identified only by their role in the group, such as "postdoctoral fellow". Principal investigators (PIs), are identified by number based on the order in which they appear in the text.

[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.

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

[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).

[5] 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).