1 **Biocultural aspects of mental distress: Expanding the biomedical**
2 **model towards an integrative biopsychosocial understanding of**
3 **disorder**
4

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Abstract

Objective: To produce a theoretical approach about the relations between neuroscience and psychopathology that expands beyond the biomedical model to include a non-reductionist, enactive, and biocultural perspective. **Method:** An integrative review, drawing from the *biocultural approach* from Anthropology, is used to produce examples from epigenetics, neuroplasticity, and functional neuroanatomy. **Results and conclusion:** A biocultural approach points to a brain that is highly plastic, reinforcing a much more complex model in which biological vulnerabilities and the historical-cultural environment co-construct each other. The examples given seem to point to the pressing need for a critical expansion of reductionist models of psychopathology. Importantly, the cultural-historical environment to which we refer is not a set of neutral social relations to which individuals are homogeneously exposed, such that aspects that are usually studied under the social determinants of health and disease (poverty, discrimination, violence, and other factors that represent sources of control, production, and distribution of material resources, ideology, and power) need to be incorporated in adequate biopsychosocial models of mental distress.

Keywords: Biocultural psychopathology; Biological psychiatry; Brain disease models; Mental health; Social determinants of health and disease

1. The need to go beyond reductionism in biological psychiatry

The “biomedical model” currently dominant in the fields of psychopathology and psychotherapy of mental disorders starts from methodological reductionism, largely assumed by neuroscientists working in basic and preclinical research, and may result in ontological reductionism in the claims of biological psychiatry (Kirmayer & Gold, 2012). *Methodological* reductionism is the most frequent epistemological strategy in the neurosciences. It can be observed mainly in the idea that it is desirable to study mental and behavioral phenomena from the point of view of neuronal activity and, more recently, from molecular neurobiology (Aguar & Ortega, 2017). The methodological strategy consists mainly in using experimental and theoretical models that, although they may mimic important aspects of the disorders, do not reach higher level aspects, such as narrative constructs, rationalities, imaginations, or relational aspects (Choudhury & Kirmayer, 2009; Fuchs, 2018; Kirmayer & Gold, 2012; LeDoux & Hofmann, 2018b; Maximino & van der Staay, 2019).

Reductionism as a methodological strategy is valid. However, there is a strong tendency to confuse methodology and ontology and make statements such as “the (animal) model was used to study anxiety” (LeDoux & Hofmann, 2018b; Maximino & van der Staay, 2019; Pine & LeDoux, 2017) and study relatively simple, unidirectional causal relationships – “a change in neuroplasticity leads to symptoms of depression”, or “changes in levels of this neurotransmitter lead to schizophrenia” – even when we know that normal and pathological biobehavioral functions are best characterized as complex systems, with multiple feedback loops and multilateral interactions between levels (Bunge, 1977; Choudhury & Kirmayer, 2009; Kirmayer & Gold, 2012; Maturana & Varela, 1980). Thus, although methodological reductionism is an option that does not necessarily lead to a reductionist view of mental disorder, it is often treated from the assumption that clinical interventions can advance only if we treat higher level phenomena (symptoms and subjective experience) in terms of lower level processes (neurobiological processes)(Kirmayer & Gold, 2012). Ontological reductionism moves towards eliminativism, assuming that higher-level processes are constituted by lower-

level processes and their interactions, and that no other entity needs to be postulated to explain them; thus, every mental process is understood as a brain process, and eventually the terms used to describe mental processes (interpersonal relations, cognitive schemas, motivations, emotions) will be discarded (Churchland, 1998; Churchland & Churchland, 1992; Jong, 2002).

The relative success of methodological reductionism in discovering lower-level mechanisms has led to a hegemony of this epistemic stance in the field of biological psychiatry (Aguiar & Ortega, 2017), culminating in the movement toward Research Domain Criteria (RDoC) within the American National Institute of Mental Health. The central idea of the RDoC is very representative of a radical biological turn in psychiatry, and proposes that diagnoses of mental illness should be based on the following assumptions (Cuthbert, 2014; Insel et al., 2010; Jablensky & Waters, 2014):

- Diagnoses should be based on both symptoms (phenomenology) and underlying neurobiology
- Since mental disorders are instantiated in brain circuits, they *are* biological diseases
- Different levels of analysis must be considered when considering neurobiology, and these levels of analysis must cut across different dimensions of functioning – but the levels of analysis are restricted to biological or intra-psychic organization (genes, molecules, cells, circuits, physiology, behavior, and self-report); and the dimensions of functioning are intra-subjective (negative valence, positive valence, cognitive systems, regulatory or excitability systems, sensory-motor systems) or, at best, proximal social processes (interpersonal relationships).

If the RDoC are an extreme position in biological psychiatry, they are not very far from the Brazilian literature on the subject (cf. Aguiar & Ortega, 2017). This deeply reductionist strategy of the RDoC did not bear much fruit from the point of view of understanding mental disorders (Wholey, 2014), even though it has generated a great deal of research in Neuroscience and biological psychiatry. One possible reason for the lack of “translational/translational” success lies not only in the

78 difficulties of ontological reductionism, but also in the limitations of methodological reductionism
79 itself, since it is most successful when research on lower levels of organization is informed by what
80 we know about what we know about higher levels (Rosen, 1969).

81 This movement of epistemological and ontological reductionism in psychiatry and psy-
82 chopathology, in addition to professing great confidence that it would be somehow adequate to use
83 neurobiological mechanistic explanations to explain psychopathological phenomena, claims that it
84 is desirable to focus explanation on lower levels – cells and molecules, at best circuits. However,
85 the different levels of nervous system organization – from neurophysiology to interpersonal rela-
86 tionships – have emergent properties that exhibit their own rules and forms of organization (Bul-
87 lock, 2002; Choudhury & Kirmayer, 2009; LeDoux & Hofmann, 2018a; Maturana & Varela, 1997).

88 This strategy of biological psychiatry not only ignores the vast literature on psychosocial
89 phenomena, social determinants of health, and psychological vulnerabilities and resilience, but also
90 ignores more complex neurobiological models. Neo-humoral explanations (e.g., the monoaminergic
91 theory of depression) are still widely accepted in the field; these explanations, however, “skip lev-
92 els”, ignoring the complex interaction that neurotransmitters such as serotonin perform across di-
93 verse brain circuits (Lowry, 2002), with mechanisms of neural plasticity (Wilson et al., 1998), with
94 immune and inflammatory mediators (Berk et al., 2013), with circulating hormones (Lowry et al.,
95 2003; Smith et al., 2004), with a great diversity of receptors (Nichols & Nichols, 2008), and so on.
96 If, on the one hand, the models produced by neuroscience become increasingly complex, the ex-
97 planatory models of biological psychiatry remain simplistic and unidirectional (Choudhury & Kir-
98 mayer, 2009; Doane et al., 2017).

99 Although limited, there is some success in these simplistic approaches because some psy-
100 chopathological effects can be attributed to global changes at the level of neurotransmitters, or to
101 other cellular or biochemical processes. However, the ultimate expression of most developmental
102 pathways leading to mental disorders depends on the unique history of individuals in relation to

103 their social world (Beauchaine et al., 2018). Ignoring these factors is sometimes possible method-
104 ologically, because isolated changes in a single gene or in some crucial developmental stage can
105 produce persistent effects that lead to specific developmental trajectories that are stable in different
106 environmental contexts, so that they will be observed even across widely varying biocultural histo-
107 ries and social worlds (Beauchaine et al., 2018). However, confusing the relative (and small) trans-
108 lational success of methodologically reductionist strategies with the endorsement of an ontological
109 reductionism, or even with the generalization that methodological reductionism will always be suc-
110 cessful, is anti-scientific and has important consequences for treatment. As complex as emergentist
111 explanations may be, they call for a more parsimonious movement in understanding the complex
112 processes of interaction and co-construction between the biological, psychological, and social
113 worlds in the pathways of psychopathology.

114

115 **2. The promise of integrative approaches**

116 If the emergentist perspective is a good description of psychological processes, it follows
117 that integrative approaches - which use information from biological, psychological, and sociocul-
118 tural aspects to describe the networks of interactions and relationships that construct psychopatho-
119 logical phenomena – will be more powerful for their understanding and, ultimately, treatment. This
120 is the main statement of George Engel's call, in his seminal 1977 article in which he defines a
121 biopsychosocial model. There are different contributions to integrative approaches in psychopathol-
122 ogy, of which probably the most famous are *diathesis-stress* models (Zuckerman, 1999), that have
123 been proposed for different disorders. These models propose that disorders result from the interac-
124 tion between diatheses - constitutional dispositions or biological, cognitive, or social predispositions
125 that make a person more vulnerable to developing a mental disorder - and stressors - external fac-
126 tors (life events, minor daily events, and chronic stressful situations) that interfere with conditions
127 affecting the individual, with an adverse effect (Margis et al., 2003). Most diathesis-stress models

128 assume relatively linear relationships and look primarily to biological diathesis - genes or changes
129 in developmental pathways – but a subset of models incorporate psychological and social variables
130 (Hong, 2013).

131 As a rule, diathesis-stress models represent the variables not as *causes* in a reductionist
132 sense, but as risk factors – that is, as *causes* in a probabilistic rather than deterministic sense, or as
133 *mechanisms* (Thagard, 1999). In addition, many vulnerabilities and (protective factors) are *shared*
134 with a large set of disorders, making them nonspecific vulnerabilities and useful from the standpoint
135 of describing variance, but not in resolving diagnostic validity. The term stressor itself is often de-
136 scribed generically (“early stress” as a vulnerability shared by different disorders, including depres-
137 sion and posttraumatic stress disorder), in part because of the large number of life events that may
138 figure in longitudinal and developmental descriptions of psychopathology (Birk, 2020; Margis et
139 al., 2003). Thus, the presence of nonspecific vulnerabilities obscures the boundaries between disor-
140 ders, as well as the usefulness of these vulnerabilities beyond description.

141 Moreover, merely describing the presence of vulnerabilities and stressors does not generate
142 integrative models, since the *interaction* between these factors is fundamental (Belsky & Pluess,
143 2009; Ingram & Luxton, 2005; Zuckerman, 1999). This interaction can be *additive* and relatively
144 linear, *ipsative* and inverse (the greater the presence of one factor, the lesser the need for a second
145 factor in precipitating a disorder), and so on (Ingram & Luxton, 2005). Moreover, it is fundamental
146 to understand that this interaction is dynamic, and can change over time (Ingram & Luxton, 2005).
147 One example is the concept of kindling proposed by Post (1992) to describe the time course of mul-
148 tiple depressive episodes. The term “kindling” is taken from the field of epilepsy to describe the
149 sensitization of neural circuits following excessive electrical activity that leads to seizures. Post
150 (1992) Post proposed that a depressive episode produces neuronal changes that result in increased
151 sensitivity to stressors, so that less intense stressors will be needed in the future to "activate" the

152 processes that lead to a new depressive episode. This example illustrates ty that the interactions be-
153 tween vulnerabilities and stressors is not stable over time, and should be understood as dynamic.

154 An unsuspected source of integrative approaches to understanding psychological distress is
155 found in biocultural anthropology. Although the “the term biocultural can carry a range of meanings
156 and represent a variety of methods, research areas, and levels of analysis” (Hruchka et al., 2005, p.
157 4), a minimal definition of the field is the “a critical and productive dialogue between biological and
158 cultural theories and methods in answering key questions in anthropology” (Hruchka et al., 2005, p.
159 4). This application of the theoretical lenses of cultural anthropology and biological anthropology
160 can produce a embodied perspective on how psychic distress is located at different levels of analy-
161 sis without being reduced to a privileged level. This integrative perspective requires an important
162 focus on complex methods and openness to different and often competing theoretical paradigms. A
163 biocultural perspective on mental disorders starts from the distressed individuals and places them in
164 the context of how culture situates the suffering that results from the illness (Choudhury & Kir-
165 mayer, 2009; Worthman & Costello, 2009).

166 It is also important to situate the development of biocultural anthropology in a critical key.
167 If, on the one hand, approaches between cultural anthropology and biological anthropology focused
168 on an “adaptation paradigm” – which hypothesized that the social environment represents an adap-
169 tive challenge that is met by humans through genetic, developmental, physiological, and socio-cul-
170 tural adaptations (Goodman & Leatherman, 1998) –, on the other hand it is fundamental, for a criti-
171 cal perspective, to understand how macro- and micropolitics traverse these elements (Leatherman,
172 2005). It is critical to understand how local socio-cultural forms are part of a network of economic
173 and power relations within societies, in which the intersection between global processes and local
174 actors, stories, and systems must be examined (Goodman & Leatherman, 1998). These processes,
175 histories, and systems are fundamental sources of biological variation, and in many cases represent
176 the most important stressors associated with psychopathology.

177 Nikolas Rose and collaborators (2021) point to these local socio-cultural forms as an “eco-
178 logical niche”, defined as

179 a zone of living within a milieu that can be occupied by a particular organism with its mode of existence
180 [...]. But rather than thinking of a niche as occupied by a ‘species’, we focus on the diversity of niches –
181 the multiple habitats – of groups of humans differentiated by age, gender, ethnicity, economic resources,
182 housing situation and more which shape their forms of life as biosocial beings (p. 4)

183 Rose and collaborators (2021) point to the work of Greg Downey (2016) and his definition
184 of an ecological niche occupied by street children in São Paulo as a way to understand this defini-
185 tion and its implications for mental health: “the niche is both pre-shaped to them and also requires a
186 constant activity of recreation, encompassing” the displacements and journeys to and from favelas,
187 the search for empty spaces and abandoned buildings to sleep in, the evasion of police and private
188 security agents, etc. (Rose et al., 2021, p. 4). Thus, the patterns of interaction with the social and
189 material environment posed by these children's niche represent exposure to particular forms of hos-
190 tile interactions, violence, and accidental insults. However, niches also represent possibilities for
191 different activities, ways of life, and experiences. In this sense, Rose et al. (2021) propose to expand
192 this conception of niche, bringing it closer to the concept of *Umwelt*, inspired by the biologist Jakob
193 von Uexküll (1982), reflecting the idea that different human beings inhabit different worlds of expe-
194 rience.

195 Fuchs (2018) notes that many of the salient features of human *Umwelten* depend on culture,
196 history, and political and economic context. Understood as *Umwelten*, the niches occupied by indi-
197 viduals provide possibilities for different subjective experiences (emotions, feelings, cognitions),
198 but also provide different biological influences:

199 The niches inhabited by Brazilian street children are toxic, not just because of the daily struggle to
200 acquire the necessities of life against a pervasive threat of violence from other people, but because their
201 vitality is constantly under threat from exposures to the pathogens and parasites with which they share
202 their lives (Rose et al., 2021, p. 10).

227 crete, extracorporeal, and intersubjective world. The recursive interaction of the human brain with
228 the material and cultural artifacts of a cultural world with historical origins reorganizes the internal
229 and external worlds of human beings (Luria, 1981). From a developmental point of view, therefore,
230 the cultural dimension and the biological dimension of the mind assume a role of building on each
231 other at different points in development, so that neither the biological nor the cultural are static in-
232 teracting entities, but in fact have a dynamic character (Cagigas & Bilder, 2009).

233 This view presents important challenges for neuroimaging research (Cagigas & Bilder,
234 2009; Li, 2003). First, as Cagigas e Bilder (2009) point, the unit of analysis “comes to include the
235 cultural-historical modeling that a person's brain has undergone prior to participation in a particular
236 experimental task” (p. 25) – i.e., it is no longer possible to understand and interpret the results of a
237 neuroimaging experiment without understanding the cultural-historical context (ecological niche,
238 *sensu* Rose et al. (2021)) of the participants. Furthermore, the Lurian proposal of a triadic organiza-
239 tion of cortical areas (Luria, 1981) also presents points of divergence with traditional neuroimaging
240 research, an interesting outlet by which we can begin to explore the dynamics of nervous system
241 functioning within a (bio)cultural-historical context.

242 Classically, neuroimaging studies have been used to justify a hyper-modular functional neu-
243 roanatomy with one-dimensional and linear causal relations between brain activity and psychologi-
244 cal functions (and dysfunctions). In analogy to the “classical” genetics of mental disorders, one
245 could say that these studies deal with “areas for” certain functions (“the amygdala is the area for
246 fear”). A more contemporary view does not necessarily view the functional correlations between
247 brain activity and task performance from a fixed point of view, but rather that these brain processes
248 are dynamic and involve functional connectivity (Rogers et al., 2007). In particular, contemporary
249 functional neuroanatomy has focused on processes that reflect the engagement of dynamic networks
250 both in “resting states” and during cognitive challenges (Broyd et al., 2009; Deco et al., 2011; Ray
251 et al., 2017; Rogers et al., 2007).

252 The evaluation of brain activity during rest (i.e. when the individual is not performing any
253 task during the scan) is intriguing in this sense. In this context, a pattern of activations and deactiva-
254 tions is observed throughout the nervous system. One pattern in particular – the *default mode* – has
255 received considerable attention in the field of psychopathology (Broyd et al., 2009). In 2001, Mar-
256 cus Raichle coined the term “default-mode” to refer to a pattern of deactivations in brain regions
257 (which include the precuneus, posterior cingulate cortex, medial prefrontal cortex, and medial, lat-
258 eral, and inferior parietal cortices) that initiates when subjects engage in some cognitive task, but
259 which are active during rest with a high degree of functional connectivity between the regions
260 (Raichle et al., 2001). Raichle et al. (2001) have called this network the “default-mode network” to
261 denote a state in which the individual is awake and alert (which could be confused by the use of the
262 term “rest”), but not actively engaged in an attention-demanding or goal-directed task. There are
263 some findings that point to deactivations in this default mode network, changes in its internal con-
264 nectivity or in connectivity with circuits that are activated during cognitive tasks in individuals di-
265 agnosed with some disorders, including schizophrenia, depression, anxiety, and autism spectrum
266 disorders (Broyd et al., 2009). These findings are commonly interpreted through “reverse infer-
267 ence”, referring to excessive attentional orientation (self-focused introspective and exteropective
268 cognition in schizophrenic patients, self-focused rumination in patients with depression, etc.) as a
269 possible mechanism explaining these changes (Broyd et al., 2009).

270 What possible biocultural relationships can be drawn in this functional neuroanatomy of
271 psychopathology? Although studies are scarce, mainly assessing the default-mode network, there
272 are some interesting findings showing that functional connectivity is a locus of biocultural variabil-
273 ity relevant to psychopathology. For example, Sokołowski et al. (2020) assessed the relationship be-
274 tween early adversity, current stress, and functional connectivity during an emotional expression
275 perception task, and found that cumulative stress (i.e., interaction between early adversity and cur-
276 rent stress) produced a pattern of functional connectivity in the middle temporal gyrus, lateral oc-

277 capital cortex, precuneus, pre- and postcentral gyri, anterior cingulate and posterior cingulate gyri,
278 and Heschl's gyrus. Although this study assessed individuals without a diagnosis of mental disorder,
279 the expression of emotions can be considered an intermediate phenotype for several disorders, sug-
280 gesting a mechanism by which early adversity instantiates brain processes that are associated with
281 disorders. Duque-Alarcón and collaborators (2019) assessed resting functional connectivity in indi-
282 viduals diagnosed with borderline personality disorder and observed a correlation between history
283 of childhood sexual abuse and connectivity between the left medial prefrontal cortex and the nu-
284 cleus accumbens, caudate body, putamen, subcallosal cortex, and orbitofrontal cortex.

285 This “post-Lurian” functional neuroanatomy of psychopathology, supported by contempo-
286 rary findings of functional connectivity and default-mode networks (Rogers et al., 2007), seems to
287 have recovered the notion of plasticity but left aside how much of that plasticity is determined by a
288 cultural-historical context. However, reconciling the neurosciences with a biocultural psychopathol-
289 ogy will involve producing a dialogue between neuroimaging and Luria's meta-theory that necessar-
290 ily includes the cultural-historical world in which both psychopathology and the neurosciences are
291 embedded. The question that emerges, from this dialogue, is: how do genes (which will be dis-
292 cussed below) and the cultural-historical environment co-construct each other, producing outcomes
293 of psychological distress or potency? How is this co-construction crystallized in the functional sys-
294 tems of the human encephalon?

295

296 **3.2. Epigenetics of susceptibility and resilience**

297 The diathesis-stress model has become progressively more complex with biocultural read-
298 ings of genomics, blurring the reductionist boundaries of the field. If at first the focus of research in
299 the field was on finding gene-environment interactions that explained why the presence of suscepti-
300 bility genotypes did not produce sufficiently high risk ratios, this focus has been rapidly shifting to

301 understanding how exposure to susceptibility and resilience factors alter the expression of risk
302 genes.

303

304 3.2.1. *Gene X environment interactions: Genotype as a “differential plasticity factor” for psychoso-* 305 *cial stress*

306 Gene X environment interactions have been part of the field of genetics since the 1930s,
307 starting with the debate between Ronald Fisher and Lancelot Hogben about the origins of variation
308 observed in genetic research - while Fisher suggested eliminating gene X environment interactions
309 through statistical treatment, Hogben proposed that this interaction should not be eliminated, but
310 should be investigated for its own sake, since it could shed light on the cause of certain elements of
311 development (Tabery, 2008). In the field of psychopathology, this discussion is magnified empiri-
312 cally by the study of Caspi et al. (2003, 2010), which described the interaction between the *5HT-*
313 *TLPR* polymorphism, an important candidate that had already emerged in genetic research, and
314 stressful life events. The *5HTTLPR* polymorphism is a functional polymorphism of the promoter re-
315 gion of the gene encoding the serotonin transporter; although most researchers report two variations
316 in humans - the short form (“s”) and the long form (“l”) - there are other isoforms (Nakamura et al.,
317 2000). These isoforms generate functional differences in the transporter, with individuals homozy-
318 gous for the long isoform (*l/l* genotype) showing faster platelet serotonin reuptake (Greenberg et al.,
319 1999). Furthermore, allelic variants of this polymorphism are related to different "intermediate phe-
320 notypes" that represent risk factors for mental disorders, including personality traits (Schinka et al.,
321 2004; Sen et al., 2004), impulsivity (Stoltenberg et al., 2012a, 2012b), and responsiveness of brain
322 regions associated with emotional and social behavior, such as amygdaloid nuclei (Holmes, 2008).
323 In addition, allelic variants are also associated with functional connectivity of the default mode net-
324 work, with individuals homozygous for the short isoform (genotype *s/s*) showing weaker connectiv-
325 ity to the superior medial prefrontal cortex (Wiggins et al., 2012).

326 Caspi and collaborators have shown that *5HTTLPR* genotype moderates the impact of stress-
327 ful life events on depression symptoms, such that individuals homozygous for the short isoform (s/s
328 genotype) had a greater impact of the amount of stressful life events on depressive symptoms, while
329 individuals homozygous for the long isoform (l/l genotype) had less impact (Caspi et al., 2003). The
330 authors interpreted these results to suggest that variations in this promoter region modify the re-
331 sponses of organisms to environmental stress, leading to intermediate phenotypes for depression
332 and anxiety - namely, alterations in neural circuits for responses to stressors, challenges, and threats,
333 as well as differences in responses of the hypothalamic-pituitary-adrenal axis to stressors (Caspi et
334 al., 2010). It should be pointed out that these findings were not free of controversy, echoing the ar-
335 guments of the historical conflicts between Fisher and Hogben (Tabery, 2008, 2015). Regardless, as
336 Caspi et al. (2010) point, a large number of studies have been conducted in the search for these in-
337 termediate phenotypes, including studies in humans and animals. From this seminal finding by
338 Avshalom Caspi's team, several studies have been conducted seeking to understand the relationship
339 between different polymorphisms in candidate genes, stressful life events, and psychiatric disorders
340 or intermediate phenotypes, including the relationship between *MAOA* gene variants, childhood
341 maltreatment, and antisocial behavior (Caspi et al., 2002; Frazzetto et al., 2007; Kim-Cohen et al.,
342 2006); interactions between *COMT* variants, cannabis use, and psychotic symptoms (Caspi et al.,
343 2005; Collip et al., 2011; Henquet et al., 2006; van Os et al., 2010); and interactions between *DRD4*
344 polymorphisms, maternal stress, and attention deficit and hyperactivity disorder (Grizenko et al.,
345 2012; Zohsel et al., 2014).

346 These findings are commonly interpreted as pointing to a model, which I will call the "filter
347 hypothesis," in which genotypic variations function as "filters" for the effect of psychosocial stres-
348 sors. This "filter hypothesis" is an additive version of a diathesis-stress model in genetics. In this
349 model, psychosocial stress would be a kind of initiator of pathological processes, but these adverse
350 life events could only lead to a pathological effect from the correct variation of the genotype. For

351 example, in the case of *5HTTLPR* polymorphisms, homozygosity for the long variation "filters out"
352 the effects of psychosocial stress, so that the accumulation of adverse life events does not impact
353 (so much) the mental health of individuals. More complex models have been proposed; for exam-
354 ple, Belsky (1997; Belsky et al., 2009; Belsky & Pluess, 2009) suggested that, from an evolutionary
355 point of view, a given variant that represents a vulnerability if associated with psychosocial stres-
356 sors may have beneficial effects when the socio-cultural context is more positive, from a develop-
357 mental standpoint. Belsky suggests that it would be more interesting to speak of the *differential*
358 *plasticity* or differential susceptibility conferred by a given genetic variant, understood as the re-
359 sponsiveness of the phenotype produced by this variant to both positive and negative conditions
360 (Belsky et al., 2009). This approach incorporates not only additive and ipsative models of diathesis-
361 stress interaction (Ingram & Luxton, 2005), but also how variations in the environment channel de-
362 velopmental processes in opposite ways.

363

364 3.2.2. *Beyond polymorphisms, epigenetics*

365 Epigenetics has become, in a recent turn in part of the social sciences, a "revolutionary para-
366 digm" that reconnects the biological sciences with the human sciences (Landecker & Panofsky,
367 2013; Pickersgill et al., 2013; Warin et al., 2016). In large part, this results from the perception that
368 the field of epigenetics allows a departure from biological essentialism, because it considers plastic-
369 ity in gene expression, allowing not only quantitative (higher or lower expression of proteins lead-
370 ing to a "dimensionality" of characters associated with them) or qualitative (e.g., alternative splic-
371 ing) variations, but mainly their modulation by various environmental factors, including psychoso-
372 cial factors (Malabou, 2008, 2016). For example, philosopher Catherine Malabou (2008) com-
373 mented:

The interaction of these plastic modalities sketches an organization that does not at all correspond to traditional representations of the brain as a machine without autonomy, without suppleness, without becoming—representations that today have become true “epistemological obstacles.” (p. 29-30).

In summary, epigenetics is the study of the plastic interactions between environment and genome. Unlike mutations, epigenetic changes caused by environment and behavior are reversible, because they do not alter the DNA sequence; in fact, environmental events can alter the way a particular gene is expressed. DNA *methylation* typically blocks access to that gene sequence by proteins that induce its transcription, thus commonly preventing protein expression; *demethylation* causes the opposite process (Cedar & Bergman, 2009). These are examples of *histone modification*, in which chemical groups are added to or removed from histones – proteins that bind to DNA in a strong manner, inhibiting transcription – modifying the state of DNA binding to them (Cedar & Bergman, 2009); other forms of histone modification include phosphorylation, acetylation, ubiquitylation, and sumoylation, and again the main consequence is inhibiting or activating gene transcription. Finally, non-coding RNA also regulates protein expression (Mattick & Makunin, 2006). In addition, there is also evidence that these epigenetic mechanisms are also related to the regulation of alternative splicing (Luco et al., 2011), the process of selecting different combinations of splice sites in messenger RNA precursors, producing different proteins from the same DNA sequence.

The "epigenetic turn" in neuroscience, more recently, has been proposed as a "bridge" between biological and socio-cultural effects on psychopathology (Freitas-Silva & Ortega, 2016, 2014; Junior et al., 2018):

The recent introduction of the notion of epigenetics in the psychiatric field seems to exercise the strategic function of resignifying the limitation of the results found, redescribing the importance of each causal factor in the pathological constitution chain and contributing to the emergence of a new etiological model of mental disorders [...]. [A] etiological hypothesis emerging in the psychiatric field is less deterministic and more probabilistic than imagined by the researchers themselves or than promised by early neuroscientific research. Thus, the explanation of the processes of disorder formation seems increasingly distant from the

simplest reductionist model and closer to the variations between vulnerability and resilience that characterize the logic of risk (Freitas-Silva & Ortega, 2014, pp. 778–780, transl. from Portuguese by the author).

Thus, this "epigenetic turn" removes the focus of neurogenetics from a necessarily linear or unidirectional model (the "gene-for" paradigm), bringing it closer to more complex notions of epidemiology (Castiel, 1999; Freitas-Silva & Ortega, 2016, 2014). This "epigenetic turn" has led to a number of researches on changes in gene expression and/or DNA methylation as mediators of psychosocial effects on mental health (Gottschalk et al., 2020). The bulk of these studies focus on currently present effects, as it is difficult to study longer-term effects on DNA methylation or gene expression. These studies do, however, point to a complexification of the filter and differential susceptibility hypotheses. Duman and colleagues studied not only the interaction between early adversity (insecure attachment, abuse and neglect, exposure to violence, family economic hardship) and the *5HTTLPR* polymorphism, but also the association of chronic stress experiences, gene expression, and cortisol responses to an acute experimental psychosocial stressor (Triers Social Stress Test). Thus, compared to s/s and s/l subjects, l/l subjects who experienced greater early adversity and chronic stress showed greater increases in serotonin transporter expression in peripheral blood after the Triers Social Stress Test, as well as greater methylation of *SLC6A4*, the gene for the serotonin transporter (Duman & Canli, 2015). Similarly, in a cohort of nurses from low and high work stress environments, less methylation of the same region of the *SLC6A4* gene was observed in the cohort from the high-stress work environment (Alasaari et al., 2012); in addition, higher methylation levels were associated with higher burnout levels in these cohorts (Alasaari et al., 2012). Methylation levels in this region of the *SLC6A4* gene were associated with the incidence of major depressive disorder (Zhao et al., 2013), suggesting that it may represent a very dynamic methylation site responsive to recent chronic daily stressors (Gottschalk et al., 2020). Indeed, Gottschalk et al. (2020) hypothesize that the hypo-methylation of the *SLC6A4* gene promoter region may reflect a kind of genotype-independent adaptive mechanism in response to (occupational) stress. This mechanism has a physi-

425 ological function in minimizing stress exposure and preserving psychological functioning, but may
426 result in long-term pathological and dysfunctional consequences, including maladaptive coping
427 strategies and depressed mood (Gottschalk et al., 2020). This is in agreement with the idea that the
428 *SLC6A4* gene is a *plasticity* gene (Shattuck, 2019)

429 An interesting finding concerning epigenetics relates to the relationships with socioeco-
430 nomic status. One of the most stable associations that is observed in the sociology of mental disor-
431 ders is the inverse relationship between socioeconomic status (SES) and mental disorders (Yu &
432 Williams, 1999). SES is strongly associated with a number of important social and environmental
433 conditions that contribute to chronic stress burden, including high-density housing, urban violence,
434 noise pollution, discrimination, and other chronic risks or stressors (Baum et al., 1999). There are
435 important effects of SES on the methylation status of specific age-associated DNA sites (i.e., whose
436 methylation status changes with age; Bocklandt et al., 2011) when comparing individuals with low
437 SES to individuals with medium to high SES (Fiorito et al., 2017). Importantly, SES-associated
438 DNA methylation changes were already present at birth and partially persist through early child-
439 hood (Laubach et al., 2019; McDade et al., 2019; Santos et al., 2019), affecting biological processes
440 that regulate immune and neurodevelopmental functions (Bush et al., 2018). For example, an ex-
441 ploratory study in trauma-exposed individuals and individuals diagnosed with post-traumatic stress
442 disorder suggested that interactions between methylation and socioeconomic status occur mainly in
443 genes related to central nervous system functions (Uddin et al., 2013).

444 Interesting examples of the relationship between epigenetics, SES, and mental disorders can
445 be seen by turning again to the *SLC6A4* gene. In a study investigating the relationship between SES,
446 attachment styles, and *SLC6A4* promoter methylation, individuals with “unresolved” forms of at-
447 tachment show an association between promoter methylation and low SES – unlike individuals with
448 a secure attachment style, where no such association is observed (Jones-Mason et al., 2016). Taken
449 together with the findings about the *SLC6A4* gene discussed earlier (Alasaari et al., 2012; Duman &

Canli, 2015; Zhao et al., 2013), these results suggest that attachment security may act as a protective effect against the effects of low SES on *SLC6A4* gene promoter methylation. Thus, epigenetic impacts on the *SLC6A4* gene may represent a biocultural mechanism by which psychosocial stressors that are important and represent differential plasticity for mental disorders may produce neurobiological and behavioral maladaptive effects.

4. Towards a critical neuroscience of psychopathology

The examples of functional neuroanatomy and epigenetics seem to point to the pressing need for a critical expansion of reductionist models of psychopathology. Above all, these examples point to the need to take seriously the Lurian thesis in which biological vulnerabilities and the historical-cultural environment co-construct each other. Importantly, the cultural-historical environment to which we refer is not a set of neutral social relations to which individuals are homogeneously exposed. This perspective is fundamental “(b)ecause human biologies are affected by and reciprocally influence such factors as the control, production, and distribution of material resources, ideology, and power” (Goodman & Leatherman, 1998, p. 19). The most important predictors of mental disorders – low socioeconomic status, early adversity (emotional abuse, severe family conflict, domestic violence, bullying), occupational stress – are unevenly distributed across social class, race, gender, and sexual orientation.

The notion that “social factors” or “environmental insults” drive mental health problems is not necessarily new; in fact, several researchers have proposed ways in which insufficient parental care, stress, trauma, environmental insults, or malnutrition produce effects on specific biological “pathways” – neuroendocrine stress mediators, inflammation, the microbiome, and their correlations with epigenetics and neuroplasticity (Rose et al., 2021). Of course, most of these proposals derive from findings in a laboratory context, drawn primarily from work with non-human model organisms, which limits their extrapolation (Ramsden, 2012). Merely referring to these factors as

475 “psychosocial stressors” glosses over the fact that the concepts of stress and stressors are variable
476 and unstable by definition (Manning, 2019; Margis et al., 2003), and that the social aspects to which
477 the term refers are poorly articulated: “psychosocial analyses accord less attention, theoretically and
478 empirically, to who and what generated psychosocial insults and buffers” (Krieger, 2011, p. 198).

479 I began this essay with a provocation about the ontological reductionism dominant in most
480 psychopathology and “psych” clinical sciences. The argument that an expanded perspective is
481 needed does not mean a return to the psychosocial alone, nor a neurocentricity, but a perspective
482 that takes into account all the biocultural and psychosocial mechanisms relevant to the understand-
483 ing of psychological suffering – and, as a consequence, to its treatment. An important point here is
484 that mechanisms “are not merely aggregates of factors, or elements of scaffolds, but that they cap-
485 ture ‘emergent’ properties that are organised in very specific ways” (Manning, 2019, p. 17). Captur-
486 ing the relevant biocultural and psychosocial mechanisms implies using methodological strategies
487 beyond reductionism. This is not to completely abandon animal models or laboratory studies on hu-
488 mans, but to understand the limitations of extrapolation from these studies and, above all, to assume
489 the need for *methodological pluralism* in studies that seek to understand these variables. The appeal
490 to qualitative methods in the social sciences, such as ethnography and participant-research, will be
491 fundamental to unveil these relationships (Manning, 2019; Rose et al., 2021; Shattuck, 2019). For
492 that to happen, it is necessary that psychopathology and its allied fields move away from epistemic
493 positions consolidated around a certain neurocentric discourse, opening themselves to the critique
494 and to the richness of the social sciences. This will be a small but hard step towards a truly integral
495 mental health.

496

497 **Conflict of interests statement**

498 The author declares no conflict of interests

499

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