An evolutionary perspective for contemporary psychiatric research

La ricerca psichiatrica in una prospettiva evolutiva

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SUMMARY. Behaviour represents the ultimate output of the brain and is characterized by a high level of inter-individual variability. On the one hand, taking into account evolutionary history and adaptive significance of behavioural responses allows to design experimental protocols that improve both data quality and interpretation. On the other hand, a multilevel approach, which analyses factors ranging from the genetic set up to the socioeconomic status, leads to a more comprehensive and effective investigation of mechanisms underlying brain function. Exploitation of this approach in clinical studies may provide new strategies to more precisely investigate psychiatric disorders.

KEY WORDS: behaviour, evolutionary perspective, psychiatry.

RIASSUNTO. Il comportamento rappresenta il risultato finale dell'attività cerebrale ed è caratterizzato da un'elevata variabilità interindividuale. Al fine di fare fronte a tale variabilità, un'attenta valutazione della storia evolutiva e del significato adattativo delle risposte comportamentali permette di disegnare protocolli sperimentali in grado di migliorare sia la qualità dei dati raccolti sia l'interpretazione degli stessi. Inoltre, un approccio a più livelli, che tenga in considerazione fattori che vanno dai geni allo stato socio-economico del paziente, permette una più esauriente ed efficace analisi dei meccanismi alla base della funzione cerebrale. L'applicazione di questi approcci alla clinica ha la potenzialità di migliorare le strategie utilizzate nello studio dei disordini psichiatrici.

PAROLE CHIAVE: comportamento, evoluzione, psichiatria.

INTRODUZIONE

The history of psychiatry follows a rather interesting trajectory: a long initial phase in which "lunatic asylums" described in the frontispiece to the third american edition of the book by J. C. Bucknill and D. H. Tuke, titled *A Manual of Psychological Medicine* (1874) led to a second more contemporary phase which started with Diagnostic and Statistical Manual of Mental Disorders (DSM) I (1952) and culminated with the number of classification of DSM-IV. After this period, we entered third millennial era in which clinicians, dealing with the mental suffering with a rapidly increasing number of patients (at least, in Western countries), have to face the emerging realities of neurosciences laboratories. In the latter, presently, genomic-, molecular-, cellular-, tissutal- and organ- level studies characterized a variety of genotypic and phenotypic factors which epigenetically results in individual patients. Most of the present debate is in fact somehow obscured by the difficulty encountered by scientist working at different levels of analysis and the erroneous or courageous way in which statements are produced about the genetic bases of several psychiatric conditions (1).

Therefore, the present research in behavioral neuroscience is focused on the epigenetic pathways making neurons, brains and the whole nervous system of a single mammalian individual responsible for its behavioral phenotype, molded, shaped, sometimes sculptured by the early experiences encountered in the first postnatal phases (2,3).

Even in altricial rodents, the early social conditions experienced in the infantile, pre-adolescent phase exert

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remarkable repercussion in the adult phase, or in terms of neurotrophin expression and as social coping styles of territorial adult males. We also found that in macaque monkeys BDNF and NGF act as neuroendocrine markers underlying differential responses to maternal deprivation in males and females. In particular, the selective changes in BDNF levels in females could help explain the greater vulnerability to mood disorders of this gender reported in humans (4). In all these studies, neurotrophic proteins (NGF and BDNF) appear to play a key regulatory role (5).

A DARWINIAN PERSPECTIVE

Another important consideration resides in the excessive regulatory and integrative role sometimes attributed by clinicians to the brain misinterpreted as "the organ of thought". A more Darwinian, evolutionary-grounded perspective, looks and attempts to interpret the organism as the entire body, as an unitary entity: according to it, the rostro-caudal net envelops the rest of organs and tissues, and one *apical* inflated ganglion (the brain, or the CNS) is actively and incessantly tuned by a second inflated ganglion, expectedly situated in the opposite *caudal* position, the adrenals. Both inflated ganglia possess proportionally large cortices and the interplay between these two maximally distant integrative centers have preferred avenues such as highly sensitive hippocampal neurons incessantly exchanging information via adrenal products.

The relevance of the hypothalamic-pituitary-adrenal axis is often overstated. In fact, it includes only some, though important, nodes of the net. Actually, the system involves many other players: neuroendocrine and neuroimmune net constitutes a complex network, homeostatically regulated, controlling the organism reaction to the environmental challenges (2,6,7). *Brain, Behavior and Immunity* and *Psychoneuroendocrinology* are good evidences of scientific journals led by editors paying special attention to papers aimed at disentangling the integrated responding of individual organism to environmental stimulus sets and vice versa.

Coming to depression, we use as a kind of "manifesto" that is rather simple. Yet oxymoron considerations, by the brilliant primatologist and neuroscientist Robert M. Sapolsky when asked to comment on the role of neurogenesis in depression in the very days when Eero Castren hypothesis on the role exerted by neural stem cells in "repairing" or reshaping CNS circuitries affected by a depressive condition started to be rather popular (8,9).

Another critical issue that should be considered is the amount of time spent studying evolutionary biology, both as general "natural " mechanisms and processes (and, more dangerously) selective survival of individuals or kin in terms of individuals possessing nervous networks (for the 2 inflated ganglia network, see above). In Italian medical faculties, zoology and basic physiology were compulsory and unavoidable courses until a few decades ago: nowadays, there is a risk of an inappropriate training in these fields and of an overlooking of a Darwinian perspective towards brain and behavior pathophysiology. The potential dangerous consequence may concern the misinterpretation of "biological factors" as almost exclusively genetically grounded and directly inducing a variety of ineluctably and irremediable pathological conditions. Soon after the term neuroscience emerged in basic and applied biology, it was clear that neural cells constituting neural circuitries and network, particularly those constituting CNS assemblies, possess a remarkable plasticity. Therefore, if plasticity is the most magnificent characteristic of synapse sprouting by neural cells, the old-fashioned idea that fixed factors, as genetic ones, may definitely dictate the fate of a single abnormal patient is more and more weak.

Neuroscientist Ruggero Pierantoni in his book published in 1981 (10) proposed that all known vital functions escape the fate of having "ups and downs"; cyclic cell activity, sinusoidal life trajectories are the normality, non-linear phenomena appear if not very rarely in all living organisms of functions. Ontogeny and senescence are simply the beginning and the end of the inverted U shaped of the bell curve. A renewed perspective on developmental neuropsychiatry and senescence neuropsychiatry should be therefore aimed at understanding the similarities about these two groups of processes: on the one hand, the neonate, infant and the adolescent according to sex dependent trajectories appear to acquire adult-like performances. On the other hand, aging leads to highly diverse senescent individuals in which the natural "decay" due to increasing age affects performances mostly on a non-ameliorative trend. Behavioral neuroscience is attempting to compare those two opposite cases of human or more generally vertebrate condition. Sir Patrick Bateson's speculations addressed to clinicians underline that a caterpillar is not an incomplete or incompetent version of a butterfly, making those not well trained in comparative psychology aware of the fact that different ontogenetic stages are shaped by often very different ecological niches in which they evolved (11). The environment in which a tadpole spends its life is definitely aquatic, but this is not the case for its adult version, the toad (12).

Recently, a new sub-discipline has appeared: Biological Psychiatry. It consists in an approach to psychiatry aimed at understanding mental disorder in terms of the biological function of the nervous system. It has an interdisciplinary approach, drawing in fields such as basic and applied neuroscience, psychopharmacology, biochemistry, genetics and physiology to investigate the biological bases of behavior and psychopathology. A society highly committed to pioneering and promoting the highest levels of education and dissemination within this field is the World Federation of Societies of Biological Psychiatry (WFSBP). In the framework of the last WFSBP meeting (Paris, France, 2009), we organized the symposium titled "Identifying biomarkers of depression: new insights from animal models".

In the former century, psychopharmacology, at its beginning, and behavioral pharmacology, at its end, were the common ground where basic behavioral scientists and clinicians used to exchange ideas about psychopathological conditions and their relative drug treatments methods to cope with mental suffering of Western patients. More recently, a potentially dangerous transition from animal models of classical lab-based psychopharmacology to a variety of novel methods occurred. Such transition, in some cases, led to a disappearance of (time consuming) yet sound ways of measuring and more importantly interpreting mammalian behavior in general. Laboratory cultural anthropology in the lab community, especially in Italy, has been progressively dictating new rules in which skilled, well-trained, creative and tenured technicians disappeared from the institutional environment, more and more often replaced by Ph.D. and post-doc for which the "publish or perish" imperative was a survival dogma. When molecular biology met behavior, the economical constraints inhibited more detailed andtime-consuming testing strategies while ultrashort time methods, e.g. the Porsolt test, started to be the more stringent way of evaluating rodent depression (13).

VALIDITIES

The Construct validity is the extent to which a procedure appears to measure a higher order, inferred theoretical construct, or trait in contrast to measuring a more limited dimension. In the case of the biological psychiatry field and the work on animal models, it refers to investigating general valid assumptions about the cause of the psychopathology, taking also in account the eco-ethological perspective, and not just specific symptoms having an apparent similarity between the model and the phenomenon to be modeled.

One of the present effort of our group is to re-unify two different scientific groups. From one hand, behavioral neuroscientist, more and more exploit a very reduced number of species, among which laboratory mammals, particularly strains derived from the House mouse (*Mus musculus* vel *domesticus*) are progressively becoming the standard model for the human patients also due for the feasibility of the transgene techniques in this small size, therefore, very economic species; for the 1950 scenario see (14). In 2010, mouse facial expressions were eventually described. On the other side, field ethologists reported of grief symptoms in a variety of wild or zoo mammals, such as elephants (15,16), monkeys, apes (17). Only very recently, "emphatic bonds" were evident also in laboratory mice (18,19). The accurate characterization of those typical human pre-morbid conditions needs to be completed for laboratory species such as, e.g. marmoset monkeys and rodents.

It seems important for psychiatrist, particularly in Italy, to be well conscious of the history of the finding concerning early biochemical characterization of seminal neurotrophin, a proteic molecule, described in the early 1960s by Rita Levi-Montalcini. Her Nobel lecture (20) together with a few historical considerations, well explains how this new synthesis about the trophic (and/or anti-apoptotic), tropic and differentiative effects of NGF were believed to affect only peripheral targets, when NGF was eventually found to exert a strong developmental influence on CNS cholinergic neurons (21-24). Much more recently the role of NGF as regulator of social behavior in laboratory rodents has been identified (2,25-27). When social coping is unbalanced by passionate love which recognizably leads to suicidal attempts, the peculiar biological characteristics of NGF, when confronted with other neurotrophins BDNF, NT-3, NT-4, make clear that the former is the most pathophysiologically relevant regulator of social bond: its role in the nosography of depression is still a matter of debate (28,29).

REFERENCES

1. Lewontin RC, Rose S, Kamin LJ. Not in our genes: biology, ideology, and human nature. New York: Pantheon, 1984.
2. Alleva E, Francia N. Psychiatric vulnerability: suggestions from animal models and role of neurotrophins. Neurosci Biobehav Rev 2009; 33: 525-36.
3. Cirulli F, Alleva E. The NGF saga: from animal models of psychosocial stress to stress-related psychopathology. Front Neuroendocrinol 2009; 30: 379-95.
4. Cirulli F, Francia N, Branchi I, et al. Changes in plasma levels of BDNF and NGF reveal a gender-selective vulnerability to early

adversity in rhesus macaques. Psychoneuroendocrinology 2009; 34: 172-80.
5. Levi-Montalcini R, Alleva E, Aloe L. A role for Nerve Growth Factor in nervous, endocrine and immune systems. Prog Neuroendocrinimmun 1990; 3: 1-9.
6. Columba-Cabezas S, Iaffaldano G, Chiarotti F, Alleva E, Cirulli F. Early handling increases susceptibility to experimental autoimmune encephalomyelitis (EAE) in C57BL/6 male mice. J Neuroimmunol 2009; 212: 10-6.
7. De Simone R, Alleva E, Tirassa P, Aloe L. Nerve growth factor released into the bloodstream following intraspecific fighting induces mast cell degranulation in adult male mice. Brain Behav Immun 1990; 4: 74-81.
8. Castren E. Is mood chemistry? Nat Rev Neurosci 2005; 6: 241-6.
9. Sapolsky RM. Is impaired neurogenesis relevant to the affective symptoms of depression? Biol Psychiatry 2004; 56: 137-9.
10. Pierantoni R. L'occhio e l'idea: fisiologia e storia della visione. Torino: Bollati Boringhieri, 1981.
11. Bateson P. Biological approaches to the study of behavioural development. Int J Behav Dev 1987; 10: 1-22.
12. Alleva E, Lega I, Bonsignore LT, Picardi A. Stress e migrazione: punti di vista etologico, psicobiologico e psichiatrico. Milano: Franco Angeli, in press.
13. Branchi I, D'Andrea I, Cirulli F, Lipp HP, Alleva E. Shaping brain development: mouse communal nesting blunts adult neuroendocrine and behavioral response to social stress and modifies chronic antidepressant treatment outcome. Psychoneuroendocrinology 2010; 35: 743-51.
14. Beach FA. The snark was a boojum. Am Psychologist 1950; 5: 115-24.
15. Masson MJ, McCarthy S. When elephants weep: the emotional life of animals. New York: Delta, 1995.
16. Moss C. Elephant memories: thirteen years in the life of an elephant family. Chicago: The University of Chicago Press, 2000.
17. Godall J. In the shadow of man. Boston: Houghton Mifflin, 1988.
18. Gioiosa L, Chiarotti F, Alleva E, Laviola G. A trouble shared is a trouble halved: social context and status affect pain in mouse dyads. PLoS One 2009; 4:e4143.
19. Langford DJ, Crager SE, Shehzad Z, et al. Social modulation of pain as evidence for empathy in mice. Science 2006; 312: 1967-70.
20. Levi-Montalcini R. The nerve growth factor: thirty-five years later. Embo J 1987; 6: 1145-54.
21. Alleva E, De Castro P, Taranto M. CuriosaMente. Roma: Istituto Superiore di Sanità, 2009.
22. Aloe L, Alleva E, Bohm A, Levi-Montalcini R. Aggressive behavior induces release of nerve growth factor from mouse salivary gland into the bloodstream. Proc Natl Acad Sci U S A 1986; 83: 6184-7.
23. Aloe L, Bracci-Laudiero L, Alleva E, Lambiase A, Micera A, Tirassa P. Emotional stress induced by parachute jumping enhances blood nerve growth factor levels and the distribution of nerve growth factor receptors in lymphocytes. Proc Natl Acad Sci U S A 1994; 91: 10440-4.
24. Aloe L, Tuveri MA, Guerra G, et al. Changes in human plasma nerve growth factor level after chronic alcohol consumption and withdrawal. Alcohol Clin Exp Res 1996; 20: 462-5.
25. Alleva E, Aloe L. Physiological roles of nerve growth factor in adult rodents: a biobehavioral perspective. Int J Comp Psychol 1989; 2: 147-63.
26. Alleva E, Santucci D. Psychosocial vs. "physical" stress situations in rodents and humans: role of neurotrophins. Physiol Behav 2001; 73: 313-20.
27. Alleva E, Branchi I. NGF: a social molecule. Psychoneuroendocrinology 2006; 31: 295-6; author reply 297-298.
28. Branchi I, D'Andrea I, Fiore M, Di Fausto V, Aloe L, Alleva E. Early social enrichment shapes social behavior and nerve growth factor and brain-derived neurotrophic factor levels in the adult mouse brain. Biol Psychiatry 2006; 60: 690-6.
29. Hellweg R, Ziegenhorn A, Heuser I, Deuschle M. Serum concentrations of nerve growth factor and brain-derived neurotrophic factor in depressed patients before and after antidepressant treatment. Pharmacopsychiatry 2008; 41: 66-71.