Published in final edited form as:

Neurosci Biobehav Rev. 2009 April ; 33(4): 493–497. doi:10.1016/j.neubiorev.2009.01.006.

Risk factors for mental health: current approaches in translational neuroscience

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Mental disorders are increasingly recognized to be chronic and disabling, belonging to a group of serious medical illnesses including heart disease, cancer and diabetes (Insel and Scolnick, 2006; Mathers and Loncar, 2006). The Global Burden of Disease report has revealed that neuropsychiatric conditions account for a quarter of all disability-adjusted life years (Prince et al., 2007). Furthermore, the burden of mental disorders is likely to be underestimated because of inadequate appreciation of the link between mental illness and other health conditions. Several health conditions increase the risk for mental disorder and co-morbidity complicates help-seeking, diagnosis and treatment and can affect prognosis. An often underestimated risk factor for mental health has to do with exposure to maternal or nutritional perinatal conditions, as well as exposure to early stress.

For the most common major illnesses, we now have medical and psychosocial interventions of proven efficacy in randomized, controlled trials. Many patients with mood disorders will respond to treatment and some will recover completely. However, the available treatments appear still insufficient, thus urging a more effective bridge between basic research discoveries and the development of novel therapeutic strategies for the cure and prevention of mental illnesses. One the limiting factors for developing appropriate therapeutic strategies could derive from the notion that researchers have so far approached mental illnesses as fundamentally different from all other medical diseases (Insel and Scolnick, 2006).

These considerations have prompted us to deal with these issues by soliciting a number of contributions from researchers involved in basic research in mental health. The aim of this Special Issue of *Neuroscience and Biobehavioral Reviews* is to give an overview of how different approaches can be used in translational neuroscience in order to facilitate the identification of vulnerability factors, novel diagnostic markers as well as pharmacological targets to be exploited by the pharmaceutical industry for the development of innovative preventive approaches and treatment strategies.

Within this issue studies performed in humans (Gerra et al., 2007; Andersen and Teicher, 2008) provide a clear evidence that exposure to adverse events during the course of development predispose an individual to substance abuse. Understanding the role that development plays in the expression of these risk factors is often overlooked, but definitively

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needs more attention to fully understand the impact of early life events on the complex neurobiological derangement, including HPA axis and dopamine system dysfunctions, playing a crucial role in addictive and affective disorders - and possibly metabolic -susceptibility.

Despite the important information provided by human studies, these have a limited capacity to explain basic mechanisms of disease. In this issue we included a number of papers demonstrating how, in recent years, there has been a growing emphasis on developing complex models that incorporate a number of variables which can be manipulated by the experimenter thus providing new opportunities for translation from basic to clinical research. We will provide examples of studies performed with the common aim of understanding the role of environmental/nutritional factors in shaping brain development and functioning. While studies performed using rodents (Alleva and Francia, 2008; Andersen and Teicher, 2008; Cirulli et al., 2008) offer a great opportunity to ask questions that can be answered in a short-time scale and allow for the analysis of neurobiological substrates, (Coccurello et al., 2008; Laviola et al., 2008; Marco et al., 2008; Nag et al., 2008; Scattoni et al., 2008) those using non-human primates offer a great opportunity to ask questions that can be answered in a short-time scale and allow for the analysis of neurobiological substrates, those using non-human primates provide the closest match to humans in terms of genetic, behavioral, biological and social similarity (Cirulli et al., 2008). In addition, non-human primates' relatively long lifespan, extended infancy, and socio-affective behavior parallel many aspects of human development. The challenge that basic science needs to meet is to make use of a comparative approach to benefit the most from what each model, notwithstanding its constraints, can tell us about the mechanisms underlying an increased risk for mental health.

Developmental stress and substance abuse

Childhood adversity, stemming from abuse, parental loss, witnessing of domestic violence or household dysfunction is a major cause of poor mental and physical health (Heim and Nemeroff, 2001). One major consequence of early adversity is a markedly increased risk for substance use, abuse, and dependence (Dube et al., 2003). Childhood abuse produces a cascade of physiological and neuro-humoral events that alter trajectories of brain development and the neurobiological consequences of exposure to childhood abuse parallel the effects of exposure to developmental stress in preclinical studies (Teicher et al., 2004). The aim of the review by Anderson and Teicher (Andersen and Teicher, 2008) is to summarize some of the recently reported effects of early stress on brain development in animals and man, focusing on potential associations that may help to elucidate causal links between early adversity and subsequent abuse of alcohol, nicotine, and illicit drugs. A major emphasis of this paper is on developmental/temporal factors, recognizing that drug abuse is a "developmental disorder" in which there are windows of vulnerability when exposure to drugs of abuse are more likely to lead to abuse and dependence. To this framework the authors add new evidence for the existence of sensitive periods in which discrete brain regions are maximally susceptible to the effects of stress, and emphasize the substantial lag period that may intervene between time of exposure and manifestation of adverse consequences. On the same line of research, the paper by (Gerra et al., 2007) provides evidence in cocaine addicts that a history of childhood neglect and poor parent-child attachment may partially contribute to a complex neurobiological derangement including the neuroendocrine axis and dopamine system dysfunctions, playing a crucial role in addictive and affective disorders susceptibility. Indeed these authors present experimental evidence indicating the neurobiological changes underlying substance abuse susceptibility and their interaction with early adversity. Results indicate that a reduction of the dopamine metabolites, higher basal levels of stress hormones, and a significantly higher rate of psychiatric symptoms, characterizes subjects reporting early adverse family experiences, compared to those characterized by good parental bonding (Gerra et al., 2007).

Role of social variables in shaping brain function and vulnerability to psychopathology: recent evidence from animal models

While there is now clear evidence documenting the relationship between childhood abuse and neglect (or other early adverse events) with individual vulnerability to psychiatric diseases, such as anxiety and depression, or drug abuse, clinical studies cannot produce sufficient evidence on cause-effect relationships. Since human studies have unavoidable limitations in the assessment of pathophysiological mechanisms --beyond the level allowed by imaging techniques and limited neurochemical investigations -- preclinical studies that can guide clinical investigations are strongly needed and there is an increasing amount of translational research that is beginning to tie basic research to clinical outcomes of individuals exposed to abusive or inconsistent care-giving in early life (Cirulli, 2003a). A major goal of these studies is to define times in development and strategies for intervening to prevent or reverse the effects of adverse early life experiences. Although prevention is clearly the preferable route, some degree of reversal of psychopathology and pathophysiology caused by early life adversity appears to be an achievable goal.

The majority of the models that have been developed so far have relied on mimicking the effects of early trauma by means of disrupting the mother-infant bond (Levine, 1957). Indeed, human data and animal studies have suggested that the relationship between the quality of the early environment and emotional responding at adulthood appears to be mediated by parental/maternal influences on brain development (Schorre, 2000). Since Harlow's work on the effects of maternal deprivation on infant rhesus macaques there has been an extensive investigation of the effects of disruption of the mother-infant relationship on adult neurobiology and behaviour in primates and rodents (Harlow and Harlow, 1965; Liu et al., 1997). These models have been used to understand the mechanisms mediating the effects of early environmental adversity on risk of psychopathology in humans. Converging evidence suggests that there are profound maternal effects on offspring gene expression resulting in long-term consequences for stress responsivity and maternal behavior. However, the question that has emerged from this work involves the nature of the effects of maternal care on gene expression and the mechanisms mediating sustained alterations of the gene expression of offspring. This question has led researchers to explore the epigenetic mechanisms regulating gene transcription and the relationship between these mechanisms and mother-infant interactions. In their review Champagne and Curley (Champagne and Curley, 2008) explore the various animal models for studying maternal effects on adult neurobiology and behavior and the recent evidence implicating changes in DNA methylation in sustaining maternal effects on gene expression. Moreover, there is recent work implicating epigenetic modifications in the pathophysiology of human psychiatric populations and this work is reviewed and discussed within the context of findings from animal models of mental health.

Research in the neuroscience field has a major goal to achieve, that is to complement psychiatric genetic epidemiology by specifying the more proximal role of nervous system reactivity in the gene-environment interactions. Indeed, there are a number of still open questions that need to be addressed, including the quality and quantity of experience that can predispose an individual towards psychopathology and the specific neural substrates affected. Appropriate animal models, in which early environmental and experiential factors can be manipulated under controlled conditions, are needed to answer these questions. The review by Cirulli et al. (Cirulli et al., 2008) addresses this point reviewing animal models that have been generated targeting experiential factors with robust effects that are relatively consistent across species, such as maternal separation and deprivation in mammals both using rodents and non-human primates. While previous studies have all documented profound alterations in development as a result of early manipulations of mother and infants, the review addresses the question of the neurobiological substrates involved in these effects. In particular, data from rodents and non-

human primates are discussed pointing to neurotrophins such as Nerve Growth Factor (NGF) and Brain-derived neurotrophic factor (BDNF), which are known to play a major role in brain development and in the trophism of specific neuronal pathways, as molecular substrates involved in the response to stressful events and capable to modify brain plasticity, setting the stage for increased vulnerability for neurodegenerative diseases or psychopathology at adulthood. This topic is further explored in the review by Francia and Alleva (Alleva and Francia, 2008) showing how neurotrophins could mediate the effects of stressful experiences at adulthood on brain function and vulnerability to disease in animal models. These authors also present data in humans, showing that NGF levels are enhanced in psychological contexts mainly associated to anxiety and fear, such as the first skydiving experience as well as clinical data indicating a role for neurotrophins also in vulnerability and resilience to stress-related neuropsychiatric disorders. Overall, these findings strengthen the notion of a role of neurotrophins as factors mediating both short- and long-term experience effects on brain structure and function.

The paper by Marco et al. (Marco et al., 2008) provides further support to the notion that manipulations of the mother-infant relationship in rodents is a suitable animal model for the study of neuropsychiatric disorders that might become evident during adolescence. Given the increasing consumption of cannabis derivatives among the juvenile population and the reported comorbidity of neuropsychiatric symptoms with cannabis abuse, they also discuss their results indicating altered responses of maternally deprived adolescent animals to cannabinoid compounds.

Early social experiences are mainly of two kinds: mother-offspring and peer interaction. In rodents, the latter has been so far rarely studied. The review by Branchi (Branchi, 2008) indicates the communal nest (CN) as an innovative experimental strategy that favours an exhaustive investigation of the long-term effects not only of mother-offspring but also of peer interaction. CN is a rearing condition employed by up to 90% of mouse females in naturalistic settings and consists of a single nest where two or more mothers keep their pups together and share care-giving. Mice reared in a communal nest display relevant changes in brain function and behavior, including high levels of neural plasticity markers, such as BDNF, and elaborate adult social competencies. Overall, the data reviewed suggest that CN could be an interesting experimental strategy to exploit, both diverse and complementary to the ones currently used for studying how the early environment determines developmental trajectories.

Role of nutritional factors in shaping brain function

The review by Berger-Sweeney and colleagues (Nag et al., 2008) highlights the importance of nutritional factors in neurodevelopmental disorders focussing on the Rett syndrome, a severe neurodevelopmental disorder affecting primarily girls. Rett patients generally appear healthy until 6–18 months of age, when motor and cognitive skills regress. Stereotypical hand movements, limited language, severe autistic-like features, as well as potentially life-threatening seizures, respiratory dysfunction and severe kyphoscoliosis ensues. A mutation in the gene encoding methyl-CpG-binding protein 2 (MeCP2) causes up to 96% of classic Rett cases (Amir et al., 1999; Chahrour and Zoghbi, 2007); the MeCP2 gene encodes a protein that binds to methylated CpG pairs of DNA sequences and condenses chromatin structure, thus making DNA inaccessible to transcriptional machinery. MeCP2 Rett mouse models have been behaviorally characterised and recently also used to assess the role of selected nutritional factors on progression of the disease, at least in the animal models. Nag, Ward and Berger-Sweeney review the literature on the consequences of nutritional manipulation during critical periods of development on neuropathology and phenotype of different developmental disorders (Down Syndrome, Attention Deficit Hyperactivity disorder, and autism). To illustrate the potential role of experimental models, the authors report effects of a dietary supplementation

with choline, a precursor of the neurotransmitter acetylcholine (Meck and Williams, 2003), on the Rett phenotype. The increased availability of choline during the early phases of postnatal development results in task specific positive effects on behavior, primarily improving motor coordination. While the possible mechanisms through which choline may improve the behavioral phenotype in a Rett mouse model are far from clear (ranging from choline induced alteration in neuronal morphology, in cholinergic neurons function, or in DNA methylation) these studies elegantly candidate the mutant mouse models of neurodevelopmental disorders as a powerful tool to evaluate the role of different epigenetic factors on the onset and progression of the disease.

The effects of psychosocial stress throughout life on body weight and food intake regulations are evaluated in the review article by Coccorello, D'Amato and Moles (Coccorello et al., 2008). These authors illustrate the contribution of rodent experimental models in the study of the biological determinants of obesity, with special emphasis on i) the relationship between psychosocial stress and energy homeostasis and ii) mechanisms linking stress and reward systems. Indeed, even if rodent models of social stress are becoming increasingly popular for the study of several health related issues, the interaction between social stress and the so-called obesogenic environment has been so far poorly investigated. The authors also list the benefits that the human research on obesity would receive from the study of these models. Rodents models mimic more closely type, intensity and duration of the stress, including psychosocial stress. Furthermore, these models contribute to disclose the biological bases and functional explanations of individual differences in response to stressful environmental conditions. In addition, although there is a bulk of data arguing that stress can contribute to the pandemia of obesity in western societies, the only experimental models showing that stress causes increased calories ingestion and fat deposition is repeated exposure to an aggressive conspecific in male mice (Moles et al., 2006). Finally, rodent models allow identifying the role of stress to overeating and, in turn, to obesity, by increase of the salience of food-related stimuli. Ingestion of especially high palatable/high fat diet would relieve the negative emotional effect of stress (also reducing the activity of the HPA axis) thus representing a sort of self-medication; some form of obesity should then be regarded as a drug addiction like disease. As recently highlighted (Volkow and O'Brien, 2007), consideration of mental component of obesity should be a target in the treatment of this complex disorder to maximize the compliance and minimize the relapse.

Development of novel experimental tools: behavioral phenotyping in mouse models of neurodevelopmental disorders

The review by Scattoni, Crawley and Ricceri (Scattoni et al., 2008) deals with the importance of behavioral phenotyping in mouse models of neurodevelopmental disorders and underscores the importance and reliability of early developmental assessment of behavior and highlights the role of a detailed evaluation of the mouse ultrasonic vocalizations as a behavioral endpoint targeting the communicative competencies of this species. This appears extremely relevant for the construction of validated experimental models of developmental and psychiatric disorders which include communication deficits among the pathological signs, e.g autism spectrum disorders (Moy and Nadler, 2008). Indeed, whereas ultrasonic vocalizations have been studied extensively in a rodent ethological perspective in the last decades, only very recently they are systematically becoming a core feature in behavioral phenotyping of both adult and neonatal mutant mice modelling neurodevelopmental disorders. Interestingly, this review article also stress the point that not only the neonatal vocalization patterns, but also the adult ones may represent an innovative tool to evaluate communicative/social alterations in experimental models (Jamain et al., 2008).

A popular model of the respective role of genes and environment in behavioral disorders holds that the environment can either facilitate or mask an underlying genetic vulnerability ("double

hit” model). However, there is increasing evidence that this simple model is insufficient. In fact, an unexpected complexity of gene-environment interactions is emerging that cannot be accounted for by the classical “double hit” model: it is becoming clear that the fetal and neonatal environment contribute to permanent sculpting of neural circuits and to behavioral phenotypes to a much greater degree than previously thought. Epigenetic mechanisms that could permanently affect early gene expression and hence morphogenesis include transcription factors (e.g. CREB, MECP2), environment-induced variations of neurotransmitters/neuromodulators that influence neurogenesis and neuronal migration, and also variations of hormonal levels induced by different environment stimuli, including social interactions. Such phenomena may very well be particularly relevant during neurodevelopment.

The reeler mutant mouse has been extensively studied as a putative model of multifactorial neuropsychiatric disorders such as autism and schizophrenia. Among candidate molecules, reelin is a protein of the extracellular matrix playing a key role in the development of brain circuits and synaptic plasticity. The heterozygous reeler mouse thus represents a model for studying the role of reelin deficiency for the onset of these syndromes. Laviola and colleagues investigated early phases of neurobehavioral development in mutant mice, and whether the results of adverse infant experiences may validate the model (Laviola et al., 2008). Their results suggest that unusual stress episodes early in development have behavioral consequences in some, but not all, individuals depending on both gender and genetic background. The heterozygous reeler mice, when subjected to an accurate behavioral analysis, exhibited a complex psycho-pharmacological phenotype, and differential responsivity to ontogenetic adverse conditions. Further data also support a differential organization of major brain neurochemical systems in this genotype. The authors provide evidence that this mouse model offers the possibility to disentangle interactions between genetic vulnerability and environmental factors and that such approach may thus be helpful to investigate the pathogenesis of neurodevelopmental psychiatric diseases.

In summary, rather than being simply a positive or negative modulator of a genetically-driven program of morphogenesis, the environment (both external and internal) appears to make use of genetic and non-genetic mechanism to sculpt brain circuits. Some of the key research challenges for the years to come include: i) the identification of key morphogenetic signals that represent critical nodes for environmental effects on brain development; ii) the identification of environmental stimuli and contexts having the most profound effect in modulating these morphogenetic signals. Clarifying these questions will help, among other things, to build a solid neurobiological foundation for current behavioral therapies, and perhaps also to optimize these therapies.

It remains our final editorial duty to sincerely thank all of our colleagues who have contributed to bring this special edition to fruition: the authors of the articles, whose expertise and commitment made this small project possible, and all the referees who cooperated with us in the peer review process.

Acknowledgments

Supported by Bilateral Italy (ISS)-USA (NIH, Office for Rare Diseases) grant “X – linked or autosomal rare mental retardation syndromes: Phenotypic analysis in transgenic mouse models”; grant ISS-NIH to (Fasc. 5301); Italian Ministry of Health (Ricerca Finalizzata ex art. 12 – 2006) and “EuroRETT E-RARE Network”.

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