6

How Should Resilience Factors Be Incorporated in Treatment Development?

Peter B. Jones

Abstract

This chapter reviews the definitions of resilience with respect to psychological disorder and to schizophrenia, in particular. Alternative meanings of resilience emphasize innate characteristics and the steeling effect of experiences; these are not mutually exclusive and both could be harnessed in terms of treatments for the disorder. The implications of resilience are already well known in the sphere of psychosocial interventions and recent developments in cognitive therapies. The notion of building structural or physical resilience of the brain to prevent the onset of schizophrenia is not new: Kraepelin discussed such an approach in the conclusion of his most definitive description of dementia praecox a century ago. To do this successfully, however, remains a challenge, but much could be done if studies on risk modifiers and causes were reformulated toward public health intervention. Finally, new domains for inquiry into developmental resilience are explored, with a focus on neural connectivity and healthy brain growth.

Definitions of Resilience

> What does not kill us makes us *stronger*...—Friedrich Nietzsche (1887, in Bittner 2003:188)

Like many seemingly precise terms, resilience can mean substantially different things to different people and in different contexts. In the physical sciences, resilience refers to a characteristic of materials and summarizes the extent to which they return to their prior form following some form of deformation. This meaning does not infer that something is rigid and unaffected by stress, but measures the extent to which it returns to the status quo. Such resilience is an innate characteristic but, even so, may be subject to environmental influences; for instance, rubber may be more or less resilient at different temperatures.

This meaning is readily translated into psychology as an individual's tendency or ability to recover from the effects of adverse events is well known to lead to disorder. Thus, it captures a degree of adaptability that may arise from innate as well as acquired factors: the ability to bounce back. Resilience is something revealed only in the face of adversity (Rutter 1985) and is distinct from the concept of a protective (or risk) factor.

Resilience can have another related meaning and involve cases where adversity has no effect, whatsoever, on an individual: resilience so strong that no deformation occurs, and physical or psychological adversity has no effect. This is relevant to schizophrenia and other psychiatric research, especially in the realm of risk research. Risk factors are simply measurable features that are statistically associated with an outcome when groups which present these features are compared to groups that do not. Such risk factors can usefully be distinguished between those that, themselves, modify the probability of disorder (i.e., risk modifiers) and risk indicators that are simply pointers toward the former.

Genetic risk for schizophrenia, manifest as family history, is conventionally accepted as a risk modifier, indicating the presence of disease-related genetic factors and a manyfold increase in risk of the disorder (Cardno et al. 1999). The situation is, however, much more complicated, as we now appreciate that the transmitted risk is not only for schizophrenia but also for other severe mental illnesses (Gottesman et al. 2010), including autism (Sullivan et al. 2012b). There may be common mechanisms involving genes for proteins important for neurodevelopment and synaptic functioning (Guilmatre et al. 2009). The converse of this lack of specificity is the fact that this genetic risk may remain unexpressed. Even in monozygotic (MZ) twins discordant for schizophrenia, one twin may remain mentally healthy (Gottesman and Bertelsen 1989) even though endophenotypic characteristics may be present (Gottesman and Gould 2003). It is unclear whether the discordance involves an additional resilience factor(s) in the unaffected twin or whether some component of the complete causal constellation is missing.

Although familiar, these findings emphasize the bias in schizophrenia research to search for causes and mechanisms of the disorder rather than resilience and protection. Manfred Bleuler made careful observations on "the offspring of schizophrenics" (Bleuler 1972, 1974) who lived with parents that were resident patients in his asylum, sometimes within nonpatient families accommodated at the asylum. His clinical interests were quickened by the fact that, as Gottesman and Bertelsen showed for MZ twins, many of the offspring of affected parents remained in good mental health throughout much or all of the period of risk of psychosis. His summary has an optimistic air (Garmezy 1977) and presages our current interest in gene–environment interactions. He also alluded to yet a third definition of resilience, namely that of "steeling" or environmental inoculation. This is a particular example of where environment can change resilience not in a moment-by-moment instance, but in the long term and in subsequent, different environments. Bleuler wrote (1974:106):

> …despite the miserable childhoods described above, and despite their presumably "tainted" genes, most offspring of schizophrenics manage to lead normal productive lives. Indeed, after studying a number of family histories, one is left with the impression that pain and suffering can have a steeling—a hardening—effect on some children, rendering them capable of mastering life with all its obstacles, just to spite their inherent disadvantages. Perhaps it would be instructive for future investigators to keep as careful watch on the favorable development of the majority of these children as on the progressive deterioration of the sick minority.

This idea of steeling or hardening can be traced back to the mental hygiene movement in the early twentieth century and the roots of child psychiatry (Rutter 1985). It is inherent in developmental views of normal and psychopathological states in childhood and beyond, such as attachment theory and the importance of family and parent–child relationships (Bowlby 1969, 1973, 1980). In the context of adult psychiatry, attachment has gained ground in terms of understanding the emergence of personality disorder, but the long-term steeling effects of early experiences, rather than any deleterious effects, have been more controversial. That said, there have been trials of inoculation or "resilience training" to prevent disorders, such as adjustment reactions and posttraumatic stress, particularly in special groups such as emergency workers (Varker and Devilly 2012).

Thus, the concept of resilience has a long history and has been incorporated into early discussions of schizophrenia. Let us now consider the place of resilience in current thinking about treatments for the disorder.

Incorporating Resilience into Treatment Development in Schizophrenia

Nietzsche was wrong. Well, he would have been wrong had his view that adversity can lead to personal resilience, encapsulated in the opening quote, been applied to schizophrenia. Untreated psychosis leads to a deterioration of outcome (Marshall et al. 2005b) and, following first remission, each relapse leads to an accumulation of residual symptoms and a worsening of functional outcome (Robinson et al. 1999, 2004; Wiersma et al. 1998). Nevertheless, long-term studies indicate that over 20–30 years, a significant proportion of people with the diagnosis can function independently and without medication in normative social roles (Silverstein and Bellack 2008). Short-term studies of psychiatric rehabilitation interventions also indicate that cognitive, interpersonal, and community functioning can be improved through interventions that develop skills (e.g., Silverstein 2000). This is consistent with the focus on recovery of role functioning and identity that is independent of having a mental disorder (e.g., Roe 2001).

Such an approach builds upon the first definition of resilience, where it is viewed as a property that facilitates recovery or prior form or function. Nursing and clinical psychological formulations of schizophrenia routinely incorporate an assessment of an individual's strengths and resources from a psychological and social point of view (Jones and Marder 2008). These resilience factors are woven into a psychosocial treatment package, conventionally used in tandem with antipsychotic drugs. Individuals are encouraged to recognize and develop those factors which, together with knowledge about their condition, can considerably enhance their ability to manage the illness, so as to improve general functioning, maximize benefit from therapies, minimize unwanted effects, identify triggers for relapse, and reduce the risk of such events. This use of strengths and personal resilience in the management of schizophrenia is not specific to the illness. Rather, it is merely an adaptation of modern principles underpinning the effective management of long-term conditions (Goodwin et al. 2010). Resilience factors are naturally incorporated into the multidisciplinary management of schizophrenia as a long-term, complex condition.

There is, as yet, less to say about individual resilience and its interaction with drug treatments or biological approaches. Pharmacogenetic studies, whether of prescribed or illicit drugs, are always couched in terms of risk. No one would encourage a person with schizophrenia to continue taking cannabis on the basis of their genotype; however, most clinicians would doubly stress the importance of abstinence in the face of a putative risk allele, if one could be convincingly identified (Decoster et al. 2012).

Global intellectual ability and performance in individual cognitive domains are known to be positively associated with functional outcome in schizophrenia. Good performance can be considered as resilience. Cognition has become a key aspect of clinical assessment and a target for drug development (Nuechterlein et al. 2008; Kern et al. 2008). However, to date there is no convincing evidence that any particular cognitive profile can be considered a marker of resilience to guide drug therapy, nor that there are useful cognitive enhancers; few trials are adequately designed to even demonstrate useful effects (Kane et al. 2010b; Keefe et al. 2013).

Nondrug approaches to cognition, such as cognitive remediation therapy (CRT), show promise in schizophrenia (Jones and Marder 2008; Wykes et al. 2011; Keefe et al. 2012). There is some evidence that patient ratings of the therapeutic alliance make a difference to outcome of cognitive remediation (Huddy et al. 2012), but this cannot really be considered as, or related to, a resilience factor. Of the few investigations into modification of the effect of psychological therapy by genotype, Greenwood and colleagues (2011) discovered that there was absolutely no association between the catechol-O-methyltransferase val158met polymorphism and cognitive improvement following CRT in schizophrenia.

As markers of resilience, higher IQ or cognitive reserve and age have been examined as modifiers of the effect of CRT. Kontis and colleagues (2012)

demonstrated that the effects of CRT were limited in older people with schizophrenia and that cognitive reserve did not influence the relationship of age with CRT efficacy. Higher premorbid IQ was associated with increased practice effects on working memory in younger but not in older individuals. Just as in drug therapy, it is not straightforward to see how cognition can be construed as a marker of resilience to be incorporated into the development of psychological therapies for schizophrenia and to guide their use. However, cognitive ability remains a logical target for such treatments.

Incorporating Resilience into the Prevention of Schizophrenia

Resilience is not a property that will aid recovery or enhance the efficacy of treatments. It is something that will prevent parts of a causal complex, such as stressful events, drug use, or even genetic risk, from adding up to an inevitable pathway to illness. Thus, incorporating resilience into the prevention of schizophrenia seems to be an area that warrants consideration.

Recent epidemiological studies of psychosis have revealed the higher than expected prevalence of psychotic experiences in the general population (Kelleher et al. 2012b), with figures of over ten percent depending on age. Very few of these people go on, however, to develop a clinically relevant psychotic syndrome or illness, even among those who seek help (Morrison et al. 2012). The majority of people who have psychotic experiences could be said to be resilient to their evolution into illness and a diagnosis of schizophrenia. The fact that so many people can be untroubled by hallucinations or delusional beliefs is troubling for psychiatry but less so for clinical psychology. Just as clinical psychology builds resilience into its management, it also incorporates a spectrum of systematization and impact of symptoms, and recognizes that some symptoms can lead to others in a dynamic and even multifaceted way. Anxiety, depression, and psychotic symptoms can form a self-perpetuating cascade of psychopathology in some people, but not in others. Psychiatric epidemiology is only recently beginning to grapple with this level of complexity (Kessler et al. 2012).

Individual differences, including age and developmental stage, may foster resilience (for further discussion, see C. Morgan et al., this volume). General cognitive ability or IQ constitutes, however, a crucial factor. Population-based studies have consistently shown that IQ is lower in children who subsequently go on to develop schizophrenia, and that protection or resilience is also attributable to higher IQ or cognitive reserve (Barnett et al. 2006). A recent systematic review and meta-analysis of the epidemiological studies of this phenomenon (Khandaker et al. 2011) confirms the dose-response relationship between premorbid IQ and schizophrenia, such that there was a 3.7% decrease in risk with every one point increase in childhood IQ. This relationship between early life IQ and psychopathology appears for individual symptoms as well as diagnoses

and is relatively marked for psychotic experiences compared with depression and anxiety (Barnett et al. 2012). There is some evidence that this relationship breaks down at very high levels of IQ (Karksson 1970; Isohanni et al. 1999), but the relationship pertains for the vast majority of the population.

The relationships between schizophrenia, IQ in childhood, and early motor development—inefficient in those destined for schizophrenia as adults—are of interest. They may all be manifestations of the effectiveness of neural connectivity, something that allows a parsimonious explanation of their association (Jones et al. 1994; Isohanni et al. 2001; Ridler et al. 2006; Vértes et al. 2012; Alexander-Bloch et al. 2012). Simply put, this suggests that a resilient brain is a well-connected brain, one in which there is an economic balance between the costs of maintaining long-range connections and the efficiency of links between brain regions that share similar inputs (Vértes et al. 2012).

What makes a healthy, effectively connected, well-grown, and resilient brain? This is clearly a question with a complex answer. Genetic and environmental influences are going to be involved, operating from conception through intrauterine life and beyond, to account for the risk for schizophrenia. By environment, I refer both to the physical milieu of nutrients, toxins, and other physiologically important factors as well as electrical activity and experience—things that shape neural structures as well as depend upon them.

There are myriad epidemiological risk factors for schizophrenia. Some are likely to be risk modifiers, ranging from prenatal paternal death (Huttunen and Niskanen 1978) and infection (Khandaker et al. 2012a, b), to excess or lack of vitamin D (McGrath et al. 2010). Like these diverse examples, most risk factors operate in early life, prior to the completion of brain growth in the late twenties. In short, anything which jeopardizes healthy brain growth decreases resilience to schizophrenia. By extension, the promotion of healthy brain growth will increase resilience to schizophrenia, as well as an infinite number of other benefits.

As with so much to do with schizophrenia, Kraepelin addressed resilience and contemplated public health approaches to prevention through its promotion. In his textbook on *Dementia Praecox and Paraphrenia* (1919/1971:253) he addressed prophylaxis when considering children at genetic or behavioral risk for the disorder:

> In children of such characteristics as we so very frequently find in the previous history of dementia praecox, one might think of an attempt at prophylaxis especially if the malady had been already observed in the parents or brother and sisters. Whether it is possible in such circumstances to ward-off the outbreak of the threatening disease, we do not know. But in any case it will be advisable to promote to the utmost of one's power general bodily development and to avoid one-sided training in brain work, as it may well be assumed that a vigorous body grown up under natural conditions will be in a better position to overcome the danger than a child exposed to the influences of effeminacy, of poverty, and of exact routine, and especially of city education. Childhood spent in the country

> with plenty of open air, bodily exercise, escalation beginning later without ambitious aims, simple food, would be the principal points to keep in view. Meyer... hopes by all these measures to be able to prevent the development of the malady.

This line of argument regarding connectivity echoes Khan's (this volume) view of schizophrenia as a cognitive disorder. I would argue that the lifelong cognitive aspects of schizophrenia share a common cause with other psychopathology and phenomena seen in the disorder, including developmental and motoric aspects; cognitive aspects occur in parallel with these, but do not underlie them. All are due to a disorder (or variant) of connectivity development, which will have genetic as well as environmental components. It may lead to self-perpetuating and perhaps a catastrophic discrepancy in normal functioning. It will also be sensitive to the developmental stages of the brain throughout the first three decades of life. Most importantly, connectivity development disorders mirror the risk of schizophrenia over the life course of an individual. Kraepelin proposed that healthy development and the growth of a well-connected and resilient brain are well placed to buffer, create, and interact with its environment.

Conclusions

Given our present state of knowledge, which has not progressed much since Kraepelin, resilience to schizophrenia and its prevention can perhaps best be achieved by promoting health in all spheres of life: physical, psychological, and social. Obviously, this would require a massive effort, yet the benefits would be far-reaching, extending well beyond schizophrenia. All of society—whether at political, societal, professional, or individual levels—bear a responsibility for this effort, which can be targeted at the general population (primary prevention) as well as those at risk (secondary prevention). Resilience factors developed in such a way could, by design, be incorporated into the development of psychological treatments at all stages of the disorder: premorbid, prodromal, and thereafter. Even if drug treatments can be tailored to individuals through genetic or other biomarkers, their emphasis is still likely to be on risk, in terms of nonresponse or side effects, rather than on resilience. Biological psychiatry is capable of focusing on individuals at risk, but has yet to add resilience to its therapeutic palette.