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A New Look at the Neural Diathesis–Stress Model of Schizophrenia: The Primacy of Social-Evaluative and Uncontrollable Situations

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The neural diathesis–stress model of schizophrenia proposes that stress, through its effects on cortisol production, acts upon a preexisting vulnerability to trigger and/or worsen the symptoms of schizophrenia. In line with its focus on the neurobiology of stress response in schizophrenia, this model treats stressors as a homogeneous category. Recent research has shown that, in healthy individuals, cortisol is most strongly produced in response to stressors that result from perceived uncontrollable threats to important goals and/or social-evaluative threats. We hypothesize that it is specifically these stressors that trigger and/or worsen the symptoms of schizophrenia in those with a preexisting vulnerability. This hypothesis may provide a way of making sense of contradictory findings on the relations between stress and schizophrenia. We propose some empirical tests of this hypothesis and explore implications for the treatment and management of the disorder.

Key words: cortisol/psychosis/stressors/vulnerability

The diathesis–stress model of schizophrenia[1] has become established as a framework for explaining how environmental factors interact with preexisting vulnerability in the etiology and course of the disorder.[2] In their version of the model, Walker and Diforio[3] propose specific neurobiological mechanisms through which environmental stress may be harmful to those with a genetic predisposition to schizophrenia and may actually trigger the initial illness episode.[4] The neural diathesis–stress model of Walker and Diforio holds that the constitutional diathesis for schizophrenia is an abnormality in dopamine (DA) neurotransmission. The expression of this diathesis depends on neuroendocrine pathways through which stress exposure, specifically cortisol release mediated by the hypothalamic-pituitary-adrenal (HPA) axis, influences DA transmission. Stress-related increases in cortisol levels exacerbate the abnormality in DA neurotransmission that underlies vulnerability to schizophrenia, resulting in the onset of the illness.

The review of Walker and Diforio[3] of the role of cortisol in schizophrenia begins by noting that the majority of studies have found higher baseline levels of cortisol in schizophrenia patients compared with healthy controls. In addition, cortisol levels in patients have been reported to be related to ratings of symptom severity.[5] To counter the possible objection that high cortisol levels are a consequence of the stress of experiencing psychotic symptoms rather than a cause of them, Walker and Diforio cite findings[6] that cortisol levels are significantly higher immediately before psychotic episodes than in periods of recovery. This supports the notion that elevated cortisol levels precipitate symptom exacerbation rather than being a consequence of it.

Walker and Diforio go on to review findings that drugs that raise cortisol levels worsen the symptoms of schizophrenia, that neuroleptics significantly blunt HPA activity and decrease cortisol levels, and that cortisol levels are higher in those with schizotypal personality disorder than normal controls. Their claim for an involvement of cortisol in the biology of schizophrenic symptoms is bolstered by evidence suggesting that schizophrenia patients have damage to the hippocampus,[7] which plays a pivotal role in the HPA-axis.[8] However, raised cortisol levels are found in other disorders, such as depression and Cushing's disease, and are hence not specific to schizophrenia.[9] If HPA-axis abnormalities are present in all these disorders, they must be mediated by different neural mechanisms. Walker and Diforio[3] propose that the HPA-axis plays its role in schizophrenia through having knockon effects on other neural systems, specifically the DA neurotransmission system.

Having established a causal role for cortisol in schizophrenia, Walker and Diforio cite a number of studies that have found cortisol release to be heightened in response to stressful experiences.[10,11] This allows them to conclude that the mechanism through which psychosocial stress has its effects in schizophrenia is through its cortisol-releasing consequences. Walker et al[12] offer two roles for psychosocial stressors in schizophrenia. They propose firstly that, through the action of the HPA-axis,

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psychosocial stress may play a role in "triggering the initial expression of clinical symptoms"[p475] and secondly that symptoms of schizophrenia may be worsened by psychosocial stress.

An examination[13] of the research literature in this area since the review of Walker and Diforio[3] supports their conclusion that an HPA-axis dysfunction exists in patients with schizophrenia. Basal cortisol levels have been found to be higher than controls in individuals with schizotypal personality disorder[14] and schizophrenia,[15] as well as being positively related to the positive, but not negative, symptoms of schizophrenia.[16] Other studies have found no elevation of basal cortisol levels in schizophrenia[17] or in those at ultrahigh risk of psychosis.[18] One way to explain such contradictory findings is through the confounding effects of antipsychotic medication. Drug-naive, first-episode patients have been found to have higher basal cortisol levels than controls,[19] whereas studies with medicated patients, using shorter sampling times and lower frequencies,[19] have failed to find such a difference.[20] In terms of HPA-axis reactivity, evidence for reduced hippocampal and pituitary volumes in patients,[21,22] which is probably "a consequence of repeated episodes of HPA-axis hyperactivity,"[13(p309)] is consistent with evidence of a blunted cortisol response to stressors in medicated patients,[23–25] which one would expect after HPA-axis hyperactivation due to repeated or chronic exposure to stress.[26,27]

The model of Walker and Diforio aims to explain how particular neurobiological consequences of stress interact with a biological diathesis to shape the expression of psychiatric symptoms. It is not concerned specifically to explore the psychological conditions under which such a stress response might arise. One obstacle, therefore, to applying this model in explaining psychosocial influences on the genesis and maintenance of schizophrenic symptoms is the assumption that psychosocial stressors, a notoriously subjective concept,[28] form a homogeneous category with similar physiological effects. For example, Walker and Diforio[3(p669)] claim that "cortisol release is linked with acute exposure to stressors across the life span," without exploring how such stressors might differ in their ability to alter cortisol levels.

Acknowledgment that only certain types of stressor trigger increased levels of cortisol was a driving force behind a recent meta-analysis by Dickerson and Kemeny[29] on the effects of different types of stressor on cortisol activation. This built on work[30] highlighting that while some studies have found psychological stressors to activate a cortisol response,[31] others have not.[32] Dickerson and Kemeny suggest that this variability exists because stressors differ in their effectiveness in triggering cortisol changes. They propose a multidimensional conceptualization of stress, suggesting that cortisol is primarily released in response to particular types of stressor. Specifically, they propose that uncontrollable threats to the goal of maintaining the "social self" will trigger reliable substantial cortisol changes. This proposal is predicated on the existence of a "social self-preservation system," which operates through the HPA-axis. Whereas the HPA-axis is known to be activated when physical threats are identified in the environment, enabling one to protect oneself from physical danger, Dickerson and Kemeny suggest that it may also be activated when threats to one's social esteem and status are detected.

Their meta-analysis was based on the effect size of cortisol reaction to stressor tasks as reported in 208 studies (the effect size being a measure of the difference between pre- and post-stressor cortisol levels). Stressor tasks included cognitive tasks (eg, Stroop tests), public-speaking/verbal interaction tasks, negative emotion induction procedures, noise exposure tasks, and public-speaking/cognitive task combinations (delivering a speech and completing a cognitive task consecutively). These studies were rated by the authors on Likert-like scales for social-evaluative threat and uncontrollability. A study was said to exhibit uncontrollable conditions if it had elements that informed participants that they were failing or could not avoid negative consequences. Examples of uncontrollable conditions included impossible tasks and the presence of loud noise without the possibility of a behavioral response. A social-evaluative threat was defined as occurring when an aspect of the self (eg, valued trait or ability) was or could have been negatively judged by others. For example, tasks were coded as involving social-evaluative threats if there was the presence of an evaluative audience during the task, if there was the presence of a negative self-comparison (eg, being outperformed by a confederate), or if there was permanent recording of the performance.

The meta-analysis of Dickerson and Kemeny found that cortisol responses to stressor tasks associated with social-evaluative threats had an effect size of $d = 0.67$, compared with an effect size of $d = 0.21$ for tasks without a social-evaluative component. In addition, uncontrollability was found to be a significant predictor of cortisol response, associated with an effect size of $d = 0.52$, as compared with controllable tasks ($d = 0.16$). However, to elicit the cortisol change, uncontrollability had to occur in the context of a motivated performance task, defined as "active performance situations that require or demand immediate overt or cognitive responses,"[p361] eg, performing mental arithmetic. These tasks are hence goal-directed and have the potential for evaluation along a self-relevant domain. The authors conclude that "being in a situation in which an important goal is threatened, where the desired outcome is not contingent on the organism's behavior, appears to trigger cortisol activation."[p378]

The largest effect sizes (differences between pre- and post-stressor cortisol levels) described by Dickerson and Kemeny ($d = 0.92$) arose for situations where

social-evaluative threats co-occurred with uncontrollable outcomes, such as in uncontrollable, motivated task performances in a social-evaluative context (eg, public speaking and mental arithmetic with time constraints, all performed before an evaluative audience). In contrast, when participants performed motivated tasks without an uncontrollable, social-evaluative context, significant cortisol activation did not occur. Noting that social-evaluative situations are not limited to performance contexts and can also involve negative interpersonal evaluations, Dickerson and Kemeny cite the finding of Stroud et al[33] that significant cortisol activation may be generated through participants being ignored and ostracized. They also suggest that relationships that are critical, rejecting, or harassing may create an uncontrollable evaluative context that might activate the HPA system and hence affect cortisol release.

One limitation of the meta-analysis of Dickerson and Kemeny is that it only utilizes studies involving first-time exposure to laboratory stressors, raising the question whether these results might generalize to real-life stress conditions.[30] While, to our knowledge, no naturalistic studies have looked specifically at the effects of uncontrollable, social-evaluative situations on cortisol levels, methodologies that have been devised to measure naturalistically the effects of general stress on cortisol production have found significant results.[34] Furthermore, the effects found in the laboratory are likely to be measured conservatively because, as Dickerson and Kemeny note, participants' freedom to withdraw entails that laboratory conditions are never completely uncontrollable. Additionally, social-evaluative situations contrived in the laboratory are likely to lead to less intense effects than real-world social encounters, where social-evaluative episodes might be expected to have greater and longer term consequences. At present, extensions of such studies to naturalistic environments remain to be conducted.

With these caveats in mind, the generalization of the findings of Dickerson and Kemeny to real-life settings and their integration with the neural diathesis–stress model of Walker and Diforio lead to a number of testable hypotheses. Specifically, we hypothesize that it is perceiving situations to involve social-evaluative threats combined with uncontrollable outcomes that trigger schizophrenic symptoms (where a vulnerability exists) or worsen existing symptoms. Furthermore (although leading to weaker effects), perceiving situations to have either of these elements, ie, to be social-evaluative or to involve uncontrollable threats to important goals (including the goal of maintaining the social self), will also be able to either trigger schizophrenic symptoms (where a vulnerability exists) or worsen existing symptoms. Conversely, stressors not of these types would be predicted not to trigger or exacerbate the symptoms of schizophrenia. We now examine whether this hypothesis finds support from existing research findings.

Stress and Schizophrenia

The exclusive focus on healthy participants in the meta-analysis of Dickerson and Kemeny means that it remains to be determined whether patients with schizophrenia also show their largest cortisol responses to stressors that present uncontrollable, social-evaluative threats to the self. To our knowledge, only 2 studies have been performed, with similar results, into the cortisol response of schizophrenia patients to psychosocial stressors[23,24] and none into the specific effects of uncontrollable, social-evaluative stressors. In one study,[23] healthy controls and schizophrenia patients were asked to give a 10-minute talk in front of a mirrored wall, which participants were told had a jury of 3 professionals behind. Salivary cortisol was measured immediately after this task, and heart rate was continually monitored. Heart rates of both participant groups increased during the psychosocial stressor, taken to indicate that the public-speaking task was equally physiologically stressful to both participant groups. In line with the findings of Dickerson and Kemeny, healthy controls were found to have increased levels of salivary cortisol after the public-speaking task. Contrastingly, patients with schizophrenia showed a smaller cortisol increase.

Several features of the Jansen et al[23] study limit its value as a test of the hypothesis under consideration. Firstly, the stressor was not designed to be social-evaluative. In the meta-analysis of Dickerson and Kemeny, elements of an experiment that indicated a social-evaluative stressor were that the threat involved: (*a*) permanent recording of the performance, (*b*) presence of an evaluative audience during the task (at least one other person present besides the experimenter), and (*c*) presence of a negative social comparison, such as real or potential outperformance by another. The only social-evaluative elements in the study of Jansen and colleagues were permanent recording (via videotape) and a suggested, although not actual, evaluative audience. Because no control task was used, increased heart rates cannot be attributed to the spurious evaluative audience. This experiment did not meet any of the criteria of Dickerson and Kemeny for uncontrollability, and no subjective reports of the stressfulness of the task situation were elicited. Indeed, the blunting of the cortisol response in schizophrenia patients could be interpreted as reflecting a disorder-related cognitive dysfunction, such as misinterpretation of the situation or the stress stimulus.[35] A further issue is that the patients had been receiving stable doses of neuroleptics for at least 3 months, suggesting that the confounding effects of medication on cortisol reactivity cannot be ruled out. Indeed, although no comparison of patients' and controls' basal cortisol levels was made, graphical representations of these data suggest no difference between the groups, in contrast to the pattern that would be expected in unmedicated samples.[19] The fact that

none of the participants were first-episode patients suggests a further potential confound resulting from previous HPA-axis hyperactivity (see above). We therefore conclude that there is, as yet, no direct evidence that it is specifically stressors perceived as presenting an uncontrollable and social-evaluative threat to the self that are important for triggering a preexisting vulnerability to schizophrenia. We return later to what a suitable experimental test of our hypothesis would involve.

Indirect evidence for our hypothesis comes from studies that show uncontrollable and social-evaluative threats to the self that are important in the etiology of schizophrenia. For example, examinations of the effects of "intrusive life events" (events in which individuals experience others attempting to exert control over them) have found them to be associated with the onset of psychotic episodes.[36] Unfortunately, much of the research on the impact of life events on schizophrenia has not attempted to separate out different dimensions along which events can be stressful. For example, Hultman et al[37] found that relapsed patients experienced more stressful independent life events (ie, events independent of the patient's disturbed behavior) 3 weeks before relapse than nonrelapsing patients. They did not, however, distinguish between life events in terms of their uncontrollability and social-evaluative nature. Another difficulty with the existing literature is the presence of apparently contradictory findings on the relations between stress and schizophrenia. For example, Horan et al[38] note that some studies have found greater numbers of negative life events in schizophrenia patients,[39,40] consistent with the notion that such individuals have stress-prone lifestyles. However, they also note that other studies have either failed to replicate this[41] or found the direction of effect to be reversed.[42] Similarly, Norman and Malla[43] note that some studies[44] found evidence of antecedent stress associated with onset, while other studies did not.[40] We suggest that at least some of these contradictory findings result from the conceptualization of stress as a unitary phenomenon. If stress is considered as a multidimensional construct, with social-evaluative and uncontrollability comprising 2 dimensions, then these contradictions may turn out to result from previous studies' failure to distinguish among different varieties of stress.

Studies that have directly addressed perceived uncontrollability have provided evidence that it is specifically such situations that trigger the symptoms of schizophrenia in those with a constitutional vulnerability. For example, Frenkel et al[45] found that having an attributional style with an external locus of control (the tendency to attribute negative events to external, uncontrollable causes) in adolescence confers an increased risk of schizophrenia in later life. Other researchers have also implicated perceptions of control in the development of psychosis.[46] For example, early trauma, which has been shown to increase the risk of psychosis,[47] has been proposed to operate through the mediating mechanism of perception of control.[48] Studies such as that by Mirowsky and Ross[49] have shown that powerlessness and the threat of victimization and exploitation can lead to symptoms of schizophrenia, in this case paranoid delusions. Furthermore, Mirowsky and Ross[49] note the observation of Fisher[50] that the factors that produce powerlessness "are varied but largely reduce to the actual lack of power, such as being black or poor."[p170] The present hypothesis therefore receives indirect support from evidence that certain long-standing environmental conditions (such as poverty, immigrant status, and social marginalization) act as risk factors for schizophrenia.

Empirical Tests and Implications for Therapy

Our hypothesis about the specific psychological conditions that interact with a preexisting diathesis to trigger schizophrenic episodes lends itself to a range of possible empirical tests. We begin by noting that judging situations as involving an uncontrollable, social-evaluative threat to the self is a subjective process,[51] which is likely to be affected by the disorder itself. Specifically, a situation that a normal individual finds innocuous may very possibly be interpreted as uncontrollable and/or social-evaluative by an affected individual. Patients with delusions of reference, eg, are particularly likely to perceive such features in neutral events (eg, a glance from the mailman) or even positive events (being smiled at by the mailman). Attentional biases may further complicate this picture.[52,53] Thus, laboratory paradigms designed to introduce uncontrollable or social-evaluative situations may not have the intended effects on participants with schizophrenia. One possible solution might be to ask individuals to give subjective ratings of situations on these dimensions. The methodological issues around achieving such ratings would of course need careful consideration.

Other potential confounds include the influences of age and gender on HPA activation. While the effects of age on HPA-axis reactivity are still unclear, response of the HPA-axis to psychosocial stressors appears to differ between the sexes, with women between puberty and the menopause usually showing lower HPA-axis reactivity than men in the same age range.[54] Such conclusions may shed light on the documented greater prevalence of schizophrenia in males than females.[55] Furthermore, recent failures to find a difference in HPA-axis activity between the genders[56] may be due to different types of stressors having differential effects on male and female stress responses. Although research has not yet determined whether male and females have different HPA-axis activation in response to stressors that are specifically uncontrollable or social-evaluative, Stroud et al[57] have found that women have a greater magnitude of cortisol response than men in relation to social rejection,

whereas men have greater cortisol responses in relation to achievement-oriented tasks (such as verbal and math tests).

The first potential test of our hypothesis would be to examine cortisol changes in first-episode, drug-free patients with schizophrenia, in response to both naturalistic and laboratory stressors that they have subjectively rated as presenting uncontrollable, social-evaluative threats to the self, and which also meet all the criteria of Dickerson and Kemeny for such a stressor. Our hypothesis would predict that cortisol responses should be elevated in patients in such situations. In contrast, stressors not rated as presenting uncontrollable, social-evaluative threats should not cause significant cortisol responses. Although the ethical implications of such investigations would need to be considered carefully, any such stress-related cortisol increases should further relate to the exacerbation of specific symptoms of schizophrenia (eg, auditory verbal hallucinations, persecutory delusions) in such situations.

A further test of our hypothesis would be to investigate the efficacy of specific coping strategies aimed at dealing with social-evaluative threats with uncontrollable outcomes. Existing stress-reduction programs shown to have beneficial effects on symptoms[58] have aimed at managing stress conceptualized as a homogeneous category. In the terms of the present hypothesis, cognitive behavioral therapy aimed at allowing patients to gain control of situations and to reduce the negative perceptions of others in social-evaluative situations would be postulated to be more effective at reducing symptoms than teaching them how to cope with other life events or difficult environmental conditions. Existing research on the effectiveness of coping styles for managing stressors can help make these recommendations more specific. Coping strategies have been divided by Lazarus and Folman[59] into 2 types, problem-focused strategies and emotion-focused strategies. Problem-focused strategies involve confronting and seeking solutions to the problem, while emotion-focused strategies involve focusing not on the event but on how the level of distress can be reduced. Roth and Cohen[60] have suggested that, in response to stress created by uncontrollable situations, problem-focused strategies are likely to have negative effects, whereas emotion-focused strategies should be more adaptive. A recent study[61] has tested this prediction in relation to an uncontrollable situation created by women's failed attempts at in vitro fertilization. Emotion-focused strategies were associated with better adjustment, possibly because some emotion-focused strategies (escape-avoidance) have been found to reduce an individual's cortisol response to a stressor[24]. Future studies might investigate whether extensions of these types of coping strategies to schizophrenia, particularly while adopting present proposals for considering stress as multidimensional, are similarly beneficial in reducing symptoms.

Another potential test of our hypothesis could be implemented by the study of monozygotic twins discordant for schizophrenia. Assuming an equivalent biological diathesis in each case, we would hypothesize that the triggering of the diathesis in the twin with schizophrenia would result in part from a greater lifetime exposure to perceived uncontrollable and social-evaluative situations that would be reflected in higher subjective ratings on these variables. Potential confounds in assessing such exposure would include autobiographical memory deficits associated with schizophrenia[62] and the attentional deficits and overvalued ideas discussed above. An alternative approach would be to identify an at-risk population such as young adults with at least 2 first- or second-degree relatives with schizophrenia. We would hypothesize that subjective ratings of exposure to events perceived as social-evaluative or those involving uncontrollable threats to important goals, and particularly ratings of exposure to combinations of both, would prospectively predict the probability of developing schizophrenia. However, the temporally limited nature of cortisol reactivity means that one would expect the high-risk group to show an elevated risk of onset for a limited period, rather than a raised lifetime risk of schizophrenia.

Conclusion

It has been argued that the neural diathesis–stress model of schizophrenia can usefully be expanded to account for the heterogeneity of effects of psychological stressors. Evidence has been presented that it is specifically the situations perceived as social-evaluative and those involving uncontrollable threats to important goals that raise cortisol levels in healthy individuals. We have hypothesized that this pattern will be reflected in first-episode, drug-free patients with schizophrenia and will be responsible for both triggering and exacerbating the symptoms of schizophrenia. However, as noted above, it is yet to be demonstrated that such cortisol reactivity patterns are similar between healthy individuals and schizophrenia patients. If supported, such a hypothesis leads to clear implications for treatment and management of schizophrenia. In considering future research, it is clear that more research is needed into the relation of stress to the etiology and course of schizophrenia, and that a multidimensional model of stress will be valuable in this effort.

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