Schizotaxia Revisited

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• A conjectured neural integrative defect (schizotaxia), due to a dominant schizogene completely penetrant for a parametric aberration in synaptic signal selectivity (hypokrisia), gives rise under ordinary social learning regimes to schizotypy, a personality showing ambivalence, aversive drift, dereism, autism, and cognitive slippage. Given unfavorable polygenic potentiators (eg, introversion, hypohedonia, and anxiety) and adverse life experiences (eg, childhood trauma or adult misfortune), around 10% develop schizophrenia. That schizophrenia is basically a neurologic disorder does not contradict whatever is known about its psychodynamics, nor preclude efficacy for psychotherapy or other psychosocial interventions. Research should concentrate on soft neurology and psychophysiology as indicators, being closer in the causal chain to the schizogene than psychometric, social, or high-level cognitive processes. Taxometric statistics are appropriate to testing a major locus model not simplistically formulated.

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Over a quarter century ago, in my presidential address to the American Psychological Association, I began by pointing out that the only nonsympomtom, nonpsychometric fact you can know about a person that gives you better than an even chance in a wager that the person will develop schizophrenia is that his or her monozygotic twin is schizophrenic. I concluded that lecture by predicting that when suitable indicators with appropriate taxonomic statistics were applied, it would become clear that schizophrenia is a neurologic disorder of genetic origin. By the term schizotaxia, a neologism in the title of the lecture, I designated a neural integrative defect that I conjectured to be the basic pathophysiology of the disorder, upon which, by the usual processes of social learning, there develops a personality structure I called, following Rado and Rado and Daniels, the schizotype. I also conjectured, again following Rado, that only a minority of schizotypal individuals decompensate into a clinical schizophrenia. These views were heretical among psychiatrists and, probably even more, among clinical psychologists in 1962, but are increasingly accepted today by informed scholars and practitioners. Radical environmentalism was ubiquitous in those days, and the somatic phenomena of schizophrenia, known since the classic works of Kraepelin and Bleuler, were either ignored or presumed to be psychosomatic in origin. It is to the merit of Fish to have revived these issues in her important developmental studies. The excellent book by Dollard and Miller on personality and psychotherapy, in which they offered a Hullian reconstruction of psychoanalytic concepts about mental disorder and treatment, does not contain a single index reference to the terms gene, constitution, or heredity, and these able authors were writing in harmony with the then-dominant theoretical tradition. In the decade following World War II, the only probable deviator from the received psychodynamic, family pattern, schizophrenogenic mother theory would have been the medical director of a state hospital in the Midwest, of an older generation. Such a psychiatrist (I knew several) would consider schizophrenia in some sense “organic,” although I do not recall any going so far as to call it “neurologic.” Since I turn out to have been a fairly good minority report prophet, I am pleased at the invitation of Dr Freedman to offer a brief statement of my current views, and I shall in the course of so doing permit myself to be somewhat personal, referring to influences on me as a scientist and clinical practitioner, again at Dr Freedman’s urging.

I cannot say exactly when I began to adopt a strong genetic view as to the specific etiology of schizophrenia, but it must have been around the end of World War II. I recall heated debates as a first-year graduate student (1941-1942) with a fellow teaching assistant, Lloyd George Everest, in which I took a psychodynamic and social learning view of the etiology of schizophrenia and he argued for an organic interpretation. He told me of a study showing that tadpoles die swimming in schizophrenic blood plasma, and he referred me to the twin studies by psychiatrist Rosanoff and colleagues on the genetics of manic depression and schizophrenia. Lecture notes of students who took my beginning clinical psychology course in 1946 indicate that while I said that the etiology of schizophrenia was unknown, I did tell them about some of the soft neurologic signs, the Worcester group’s data on vestibular nystagmus, the reduction in the specific dynamic action of protein, and the vascular and muscular differences between the schizophrenic subtypes found post mortem, trends presumably related to Sheldon’s distinction between the “mesomorphic toughness” of paranoid and the ectomorphic “hebephrenic jettisoning.” I do not know when I first read Kallmann’s classic 1946 twin study, but my colleague Lloyd Sines, PhD, says that in the fall of 1952, he was exposed, he is certain by me, to the idea that “insanity is in the blood.” I am confident that by the early 1950s I had adopted a strong genetic and neurologic theory about schizophrenia, approximately a decade before my American Psychological Association speech.

While I came into psychology from reading Menninger’s The Human Mind and hence with a strong Freudian orientation, the Minnesota department was
definitely not psychoanalytic. My doctoral adviser, Starke Hathaway, PhD, was strongly anti-Freudian. Animal psychologist William T. Heron did early work on the inheritance of maze learning ability and activity level in the rat. My undergraduate adviser, Donald G. Paterson, emphasized the hereditary factors in intel-
ligence in his class on individual differences. As to the “soft neurology” of schizophrenia,21 I recall vividly a case conference when the psychiatry department head, J. Charnley McKinley, MD, PhD, an old-style “neuro-
psychiatrist” who always did at least a basic neu-
rologic examination on psychiatric patients, elicited a fairly striking dysdiadochokinesia with no other signs of neurologic disease in a patient who was clinically and psycho-metrically an obvious schizophrenic. Mc-
Kinley warned the medical students that they should be careful not to jump to the conclusion, when some body had a plus/minus dysdiadochokinesia, or past pointing, or even a positive Romberg sign, that there was neurologic disease in the cerebellum or dorsal columns. He said that for some unknown reason, a sizable minority of schizophrenes showed these kinds of phenomena. I recall, when I was giving colloquia around the country in the late 1940s about the Minne-
sota Multiphasic Personality Inventory (MMPI), being asked how I explained the eight neurologic items on the Sc scale, which I had some trouble doing. I simply pointed out that the test was developed empirically, and if a theory of schizophrenia did not explain the fact, then there was something wrong with the theory. (One must remember that Bleuler’s 1911 book was for some strange reason not published in English until 1950!) In the middle 1950s, my analyst and subse-
quent analytic supervisor, Bernard C. Glueck, Jr, MD, who was trained under Rado at the Columbia Psycho-
analytic Clinic, led me while still his analysand to read Rado, and the classic article by Hoch and Polatin25 on pseudo-neurotic schizophrenia (which was followed some years later by an outcome study26). In Rado I came across the theory that the basis for schizotypy was a hereditary combination of kinesiologic diathesis and hedonic defect. In terms of Rado’s concept of the action self and the formation of the ego as a getter of pleasure, this interactive combination of a proprio-
cceptive and pleasure impairment was an interesting theory and one that even now I do not consider can be rejected without merit.

Meanwhile, I was engaging in psychotherapy and had occasion to contrast the behavior of my schizo-
typal and neurotic patients. I treated my first patient in 1942 with a combination of cognitive therapy and behavior modification, and looking back I believe that he was a schizotype, although at the time I diagnosed him as severely obsessive-compulsive. Due to intel-
lectual influences mentioned, my experience as a practitioner did not lead me to emphasize family dynamics or the schizophrenogenic mother. On the contrary, the more I worked with these patients the more I became convinced that there was something radically wrong with their central nervous systems (CNSs). I am reminded that Carl Rogers, despite his antinosologic bent (which even considered making a diagnosis to be counterproductive for the psychological help), told me in the early 1960s that his work with schizophrenes at the University of Wisconsin led him to suspect that “these people have something wrong with their brains.” Therapeutic experience did not lead me to throw out what we know about the psychodynamics of schizophrenia, although it seemed quite clear to me that Freud was wrong in saying that

THEORETICAL AND METHODOLOGIC STRATEGY

I will not go into the respects in which I think my 1962 position erred and why, because I am preparing a longer article for another place, and will here simply set out today’s version. In constructing a conjectured general theory of schizophrenia, the first thing to do is try looking at the phenomena as though they were not so familiar to us. Both psychiatrists and psychologists tend to have read and heard about the syndrome before they become theorists and practitioners, many of us already as sophomores in a general psychology class, which leads us to take for granted the going-together of some things that, looked at freshly and naively, do not seem to have any reason to appear together. In this respect, schizophrenia differs from the effective dis-
orders, for what a Peterman could probably give a pretty good description of being “up” or “down” without ever having seen a diagnosable case. This qualitative diversity of the symptomatology gives the theoretical tip-off, namely, if there is something a little bit haywire about almost every level and sector of the patient’s functioning, a sensible theoretical strategy is to conjecture that there is something wrong with the CNS throughout. So my conjecture about the neural integrative defect of schizotaxia is that it is ubiquitous, that it is something wrong with every single nerve cell at all levels from the sacral cord to the frontal lobes.

The usual theoretical strategy proceeds differently by selecting some clinically striking or socially impor-
tant aspect of the syndrome and identifying it with a particular psychological function or brain region or biochemistry, which is then considered the specific pathology. The obvious problem with this approach comes when the theorist has to deal with the other facets of the syndrome. He has to do some fancy foot-
work, complicated ad hoeing, and procrustean forcing to get an explanation of these noncental items, as a result of which other theorists do not find his effort persuasive. The family dynamics view that was prev-
alent around World War II seemed to do a somewhat better job of this because the clinical focus was on the interpersonal abnormalities. However, it did not do a good job with the grave cognitive defects, and in effect ignored the soft neurology and psychophysiol-
ogy. To stay away from contemporary theories, I give a couple of examples from the 1940s, when I was a

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psychology intern at the University of Minnesota Hospitals. Starting with the alleged efficacy of insulin treatment and the fact that the brain cells cannot use anything but carbohydrates, and maybe some such anecdotal observations as that many schizophrenes like to gobble sweets (Hitler!), it was conjectured that the specific pathology of schizophrenia was something aberrant in the carbohydrate metabolism. Or again, the “reticular activating system” having first been discovered in the late 1930s, looking at catatonic raptus or the withdrawn mute catatonic and the low activity level of late-stage chronic schizophrenias, it seemed reasonable to think that there was something wrong with the reticular activating system. However, that did not do much for us by way of understanding the social aversiveness, the cognitive slippage, and the like.

Since my theoretical strategy starts by postulating a ubiquitous malfunction, it has the opposite problem from these other theories, namely, it has to explain why different functions are not equally impaired. But this is a theoretical advantage methodologically, as we do not have nearly as much necessity for ad hoc and procrustean forcing. Why? Because we already know from the classical psychometric model of group factors and specifics, and from the well-established fact of individual differences in many domains outside of pathology, that the presence of a general factor should not lead us to expect it to operate equally in all domains. For example, the general intelligence factor permeates all the subtests of an omnibus intelligence test, but nobody expects that factor to have equal factor loadings on the subtests, and we find that it does not. So the situation with regard to ad hoc assumptions and procrustean forcing is much better with my kind of theory because one does not have to invent aresnith the kinds of theoretical influences that lead to some levels or sectors being relatively more aberrant than others. It should also be remembered that we have no clear-cut metric for degree of impairment in different behavior sectors unless all functions studied are quantified in standard score units. Lacking this, it is natural for practitioners to perceive that the grossest impairment in schizophrenia is in interpersonal relations, and it is of course the most important from the standpoint of other persons (family, coworkers, and the larger society). After all, nobody cares very much whether a person has trouble visually tracking the larger society. After all, nobody cares very much whether a person has trouble visually tracking the sinusoidal target, and nobody but a neurologist will notice if one has a marginal dysdiadochokinesia.

There are some general considerations, based on a neural integrative defect theory treated in the way we do classic psychometrics, that give plausible leads as to which kinds of functions one might reasonably expect to be more deviant, and I have explained them elsewhere.27

Another piece of strategic advice is that one ought not to be afraid of mixing explanatory levels. The phenomena of catatonic negativism cannot be “explained” in a nonpsychological way, that is, by some kind of simple neurologizing of opposed movements in the musculature, because as Bleuler pointed out 70 years ago, there is a molar, purposive aspect to catatonic negativism; as, for instance, such superficially opposite things as mutism and echolalia, or negativism and command automatism, have the common characteristic to minimize the psychological stress of dealing with the social environment’s demands. However, it would be equally foolish to try to explain past pointing or dysdiadochokinesia on social or psycho-

day, most clinicians do not fully accept the thesis that the mind is the brain in action, so that the schizotaxic defect may be expected to manifest itself quite directly in influencing, say, something like post-rotatory nystagmus or the P50 evoked potential anomal-

It is also essential to my approach that taxonic models are causally and statistically different in important respects from nontaxonic (dimensional, factorial) models. For example, in classic psychometrics, we want the indicators of a latent factor to be highly correlated, whereas the ideal situation in taxometric detection of a categorical entity is that there should be negligible “nuisance correlation,” so that the observed manifest relationship between two fallible indicators of the same latent taxon will be almost wholly due to their taxonic validity and not to the influence of quantitative factors.28,29 A particularly useful taxometric result is that the statistical patterns of only moderately valid fallible indicators permit estimates of higher validity for another indicator, the extreme case of this “bootstrapping” being one in which the weak signs enable one to detect that a new sign is infallible, the Super-Bootstrap Theorem.27,30,33

It is odd that some psychologists dislike my kind of theory as being identified with the “medical model” (clearly my intention), whereas both psychiatrists and psychologists, whether favorable or unfavorable toward DSM-III, usually view the latter as an implementa-

tion of the medical model. I think this is a con-
ceptual mistake. The authors of DSM-III tried hard to be descriptive-phenomenological (because the com-
mittees were attempting to avoid using the term “psychiatric diagnosis” to pathology or etiology), so the resulting nosologic rubrics bear more resemblance to a pre-Virchow list-
ing of “kinds of fevers”34 than they do to the list of kinds of “anemia” found in a chapter of Harrison’s Internal Medicine. The modern medical model identi-
ifies entities by the joint criteria of their pathology and etiology, not by their syndromic clustering. I am not faulting the constructors of DSM-III or opposing the use of it as an instrument in descriptive psychiatry; that is definitely not my position. I am merely pointing out that to identify these phenomenological rubrics as closely analogous to the disease entities of other branches of medicine is methodologically misleading. The literal “operational definition” of a disease entity by the conjunctive and disjunctive criteria of DSM-III is forced on us in the absence of satisfactory agree-
ment about pathology and etiology, and is at this time the best we can do if we want to make reliable dia-
gnoises in psychopathology. However, it ignores the latent-manifest distinction, and the fact that in the life sciences, the connection between the latent state of affairs and the manifest indicators is almost always stochastic. There are few diagnostic signs even in
organic medicine that are two-way pathognomonic, presenting no false-positives and no false-negatives (in the language of the epidemiologist, perfect sensitivity and perfect specificity). The latent-manifest distinction is not something peculiar to psycho-dynamics of the kind that many younger psychiatrists view with skepticism. It is also clearly set out in such more scientifically accepted fields as genetics, the classical psychometric model of factor analysis, and the theories of latent learning in experimental psychology and animal behavior. I sometimes think that we psychologists have brainwashed our psychiatric brethren into an obsession with reliability, without sophisticating them sufficiently about the relationship between reliability and net attenuated construct validity. The reliability coefficient does set an upper bound on validity, but in the first place, it is the square root that is the bound; and in the second place, in the behavioral sciences and much of the biological sciences, that upper bound is so far above the validity coefficient that one cannot infer mathematically whether revising an indicator, or substituting one indicator for another with lower reliability, will raise or lower the validity. Dr Hathaway, codeveloper with Dr McKinley of the MMPI and certainly no muddle-headed accep tor of unreliable clinical observations and inferences, emphasized this simple point by an example from nonpsychiatric medicine. Whatever a patient’s presenting complaint, the physician regularly takes the patient’s blood pressure, and a physician who performed a physical examination without taking blood pressure could surely be faulted. Yet the reliability of blood pressure readings, both because of diurnal variability and inter-judge differences in procedure, is rather poor. I have seen reliability coefficients as low as \( r = 0.65 \) for blood pressure determinations. The width of the wrist can be measured by anthropometric instruments with a reliability in the high .90 range. Why then does a physician regularly measure blood pressure and never (unless thinking about acromegaly...) measure the wrist width? The answer of course is that blood pressure is such an intrinsically valid sign of important medical conditions that we insist on measuring it, even if unreliable, whereas the diagnostic validity of wrist width is negligible. For example, I like to include blood pressure measurement as a core feature of all psychiatric interviews, but one does not find it in DSM-III or the Schedule for Affective Disorders and Schizophrenia, mainly, I suspect, because it cannot be reliably assessed in brief, nontherapeutic study of the patient.

THE SCHIZOTAXIA THEORY

I have been asked why we need two different words, schizotaxia and schizotopy, if all the persons who have one have the other. What I said in 1962 was that all schizotaxics become schizotopyal on all actual reinforcement schedules, and that latter was not empty phraseology. My point was that the schizotaxic parameters of the brain lead, in the ordinary range of social reinforcement schedules (provided by the primary care-iver and subsequently by siblings, peers, teachers, etc), to development of a schizotypal personality organization. However, one should leave open the possibility that a sufficiently well-managed prophylaxis, given diagnosis of an infant as schizotaxic, might prevent at least portions of this organization from developing. One wants to leave such things open as empirical questions and not prejudge them definitionally. Furthermore, a one-to-one correlation over individuals between two things does not mean that the two things are conceptually identical. To use logician Willard Van Orman Quine’s favorite example, all ani-mals with a heart have a kidney, but that does not show that the words heart and kidney designate the same concept!

Of course, schizotaxia defined simply as an integrative neural deficit is a pretty vague notion, so I tell our clinical students that if they want to think in a sophisticated way about this kind of theorizing they should read philosopher Arthur Pap on open concepts. On the other hand, it is not completely vague. One specifies, for example, that it is a defect not of input, or storage, or retrieval, as in a memory defect or mental deficiency; and it is not among the integrative defects producing dyslexia, tone deafness, the hereditary spelling defect, or garden variety poor motor skills; but it is an integrative deficit predisposing to schizophrenia, and of genetic origin. Such an open concept is defined contextually (or “im-plicitly,” as the logicians would have it). Its meaning is given mainly by its role in the network of antecedents, eg, in my theory a dominant gene, and in its consequences, eg, the psychophysiology, soft neurol-ogy, semantic aberrations, other forms of cognitive slippage, and the like. If you fill in the intrinsic content you have to talk in neurologic terms rather than in terms of the molar-defined causal network.

One may accept the concept of schizotaxia as an integrative deficit defined contextually but may be unwilling to accept the more specific filling-in that I offer with the concept hypokrisia. One does not solve scientific problems by making up words, but it is necessary to have a word to refer to a concept if another is not available. The conjectured hypokrisia (from the Greek words meaning an insufficient differentiation or discrimination) I take today, as I did in my 1962 lecture, to refer to a slight quantitative aberration in the synaptic control over the spiking of a neuron. Neglecting non-spike transmission, which we did not know about in 1962, the conjecture is as follows: considering all of the terminal buttons over a cell’s synaptic scale and coordinating each one with an axis (thus defining the synaptic signal space), a given spatiotemporal pattern of arrivals of presynaptic impulses (spiking) defines a point in the synaptic scale space, if the arrival times from an arbitrary zero point are associated with each of the coordinates. Associated with this point is, for a resting condition of the cell not in refractory phase, a certain Lorente de No optional transmission probability of spiking. The hypersurface of these probabilities represents the likelihood that any given spatiotemporal pattern of stimulation will produce a spike. The hypokrisia conjecture says that this hypersurface is (1) elevated and (2) dedifferentiated, ie, has a flattening of its hills and valleys in the schizotaxic brain when compared with the orthotaxic. From this simple ubiquitous defect I attempt to derive not all (that would be absurd) but most of the important phenomena of schizotaxia and its personality resultant, schizotopy.

If pressed further as to the defect, one might conjecture either an anomalous distribution microana-tomically over the synaptic scale, or, as I prefer, a deficient biochemical substance \( x \) whose specific func-tion in the normal brain is to retard the spread of regions of depolarization under each synaptic knob, or to facilitate repolarization, thereby lowering the odds that a given pattern of inputs will be over spike
threshold. On this basis I conjecture that there will be parametric alterations in the control functions linking one Hebbian cell assembly\(^{42}\) or, as today we would say, one module or system of modules to another. How much impact this kind of quantitative aberration will have on various functions will involve parametric relations in structural features that it is premature to speculate about, given our generally imperfect knowledge of how the brain works, except in the rough kind of relation mentioned above as to which broad classes of functions might be expected to be more aberrated.

An alternative neurophysiology theory of what underlies molar schizotaxia\(^a\) postulates a generalized quantitative deficiency of CNS inhibitory function. This interpretation of the integrative defect is the one preferred by Freedman and his colleagues\(^b\) and it does seem a natural interpretation of the P50 anomaly, that being a failure in schizophrenics to prevent or dampen the second cortical evoked response, as normally occurs. The phenomenology of early schizophrenia, which often includes complaints of “stimulus overload,” distractibility, difficulty in maintaining focus, exaggerated startle, etc., is also consistent with a deficient inhibition concept.\(^c\) On the other side, some impairments described so well by Bleuler could look like excessive inhibition, as does full-blown catatonic withdrawal. The interpretive problem here is, again, our relative ignorance of normal CNS integrative processes, especially as to the parameters of their convergence and feedback features. (One thinks of the paradoxical benefits of methylphenidate hydrochloride on the hyperactive child.) In our relative ignorance of details about cerebral systems in their hierarchical and convergent control relations, we are rather like someone considering a nonlinear, multiple-output Rube Goldberg machine, wondering whether its quantitatively aberrant outputs can best be explained by more or less friction (“play” or “binding”) at each link between moving parts. So while I am tentatively pushing hypokrisia as the core defect, the inhibitory deficiency alternative is surely an option worth testing. Whenever we find domain variations in intensity or direction of effects, there is of course a considerable explanatory symmetry between “overexcitation” and “underinhibition,” difficult to resolve without more knowledge of how the whole system works as a kind of functional system. So while I am tentatively sizing by psychodynamic and family theorists. But what gets this social process rolling initially is the combination of affective scrambling, aversive drift, and cognitive slippage as parametric features of the molar acquisition functions, and these arise from the schizotaxic defect.

In Rado’s terminology, the schizotypal is not a different category from the schizophrenic. The schizophrenic is a schizotype who is decompensated, either within the pseudoneurotic range, or different category from the schizophrene. The schizotypal is represented by the word compensation by analogy to the extent to which the patient with kidney disease or cardiac disease is clinically compensated. As we think of symptomatic neuroses as always built on character neurosis in psychoanalysis, similarly we think of schizophrenic, whether of the psychotic or pseudoneurotic (“borderline”) variety, as built on the schizotypal personality structure. And the schizotypal personality structure has evolved by social learning processes when the schizotypic CNS is subjected to the kind of stochastic schedule (variable and double sign) of rewards and punishment that care-givers, peers, and life generally provide all of us.

I conjecture that hypokrisia is an endophenotype (inner state in the causal chain between the DNA and the exophenotype, the overt behavioral dispositions) for which a dominant schizogene is completely penetrant. I am aware that the major locus idea is an
unpopular one among behavior geneticists and that some, such as my friend and former colleague Irving I. Gottesman, PhD, consider it to have been refuted.44-48 This is not the place to go into details of that, and I am not competent as a behavior geneticist. I content myself with saying that the alleged refutations do not deal with the type of complicated causal model that I postulate. In designing empirical tests of a theory, one must be sure to “give the theory its head” without being circular, sometimes a thorny problem. I am skeptical as to how adequately we can test a major locus theory with polygenic potentiators by employing formal diagnosis analyzed by conventional methods. Consider the following factors, an incomplete list that surely underestimates the true causal complexity: in studying families, we must either exclude with near certainty, or somehow “correct for,” genophenocopies like the SHAITU syndrome described below, meanwhile keeping in mind that its components operate as polygenic and environmental potentiators for true schizophrenia. The analysis must take account of the sex difference in impact of schizotypy on fertility, and these numerical values cannot be safely extrapolated from the data on full-blown schizophrenia. There may be positive or negative assortative mating for the schizogene taken over the whole range of clinical compensation, despite its negligible amount for formal diagnosis. There will almost certainly be assortative mating for the polygenic potentiators, and some of these correlations could be negative (eg, dominance). The potentiators are not likely to have equal impact on fertility for the sexes, partly on their own, but partly because of different potentiating effects for decompensation and, hence, fertility. The parental “side-concentration” of polygenes must be included in one’s statistics, because a proband (who has been reared as or else would not have been ascertained) is more likely to have received his or her potentiating polygenes from both sides than from the schizotypal parent, since if the latter carried a heavy loading of them, he or she would have been less likely to mate. This side-concentration effect is also probably different for the sexes. Psychodynamically, one would expect differences in the potentiating effect of identification with the schizotypal parent depending on whether that parent is the same sex as the proband, and this contrasted with the sex difference in manifestation of fertility. Finally, we only locate families in which some member has decompensated, and the diagnostic statistics suggest that there must be around 10 times as many schizotypes in the population as there are diagnosed schizophrenes. The family statistics for this path diagram, even if the small and unstable figures for second-degree relatives are included, will involve fewer equations than unknowns, so no good test is available.

I am not troubled by the argument that “this all makes things too complicated to test,” since I think that is the real situation when the measured variable is formal diagnosis. The diagram of conjectured causal influences in my theory is oversimplified from what complexity we must assume to be the case, and it is salutary to compare it with a similar diagram for diabetes49 or a typical diagram of the pathophysiology of kidney disease and its effects on blood pressure, cardiac function, etc. One should take it for granted that the brain is at least as complicated as the kidney. This is why I favor emphasis on indicators closer to the gene such as psychophysiologic and soft neurologic measures, and perhaps psychometrics, although here I have become more skeptical. We also need good indicators of subtle cognitive slippage, but, with the possible exception of attention deficit, these have so far been rather disappointing.50 The occurrence of a strongly taxonomic statistical structure manifested by schizotypic indicators among parents is a neglected approach. The Bayes’ Theorem curve of inverse probabilities of taxon membership from a set of quite fallible dichotomous signs is U-shaped for a taxonic situation, as is the distribution for a single quantitative indicator when sufficiently valid.51-53 A striking example of this is the distribution of P50 scores for the first-degree relatives found by Freedman’s group,54 especially since the incidence of sign-positives is about 50%, as the dominant gene theory predicts. Replication of this finding is of first-rate importance. While it is mathematically possible (by suitable ad hoc adjustments) to square this kind of curve with a polygenic model, that is of course weaker than a successful prediction of it, and would be hard to interpret physically. The polygenic theorist has to conjecture that people have a high negative assortative mating for this neurophysiology trait, or for a highly valid behavioral proxy of it; and that the threshold “just happens” to be at the 50% cut predicted by the dominant gene theory. If even a few psychophysiology indicators behaved this way, the polygenic theory would appear badly discredited, or, I should say, definitely refuted.

In that connection I should say something about why I adopt an altered semantics from that generally received in genetics. In my theory there is a set of heritable traits, presumably polygenic in origin, around a dozen in number, that are potentiators of schizophrenia, that raise the probability of clinically diagnosable illness in a schizotype who has a heavy loading of them (Figure). The reason I prefer the word potentiator to the geneticists’ familiar word modifier is that the conception is different and therefore we need a different term. In genetics, a modifier gene (or system of polygenes), the extreme case being that of a single gene with dominant epistasis, “gets into the causal chain” between the DNA and some trait expression. For example, a gene that affects the amount of substrate that must be available for the main gene of interest to generate the causal chain that results in some exophenotypic property of the organism. That is not the kind of model involved in a theory such as mine. For example, social introversion is one of the variables that I conjecture to potentiate the probability of schizophrenic decompensation in a schizotype. The evidence is strong for the polygenic heritability of social introversion,55-57 so this does not play an ad hoc role in the theory. The same is true for most of the other polygenic potentiators, such as dominance, anxiety, energy level, mesomorphy, sex drive, etc, all of which are known to be partly heritable in humans and other mammals. However, the causal model here is not like that of a modifying gene in the fruit fly “getting in the way” of another gene’s expression in the phenotype. The schizotypic gene produces the endophenotypic hypokrisia that gives rise to certain molar-level parametric aberrations in acquiring, retaining, and generalizing positive and negative social conditions. However, I do not presume, and I do not know anybody favorable to my theory who presumes,
that there is a biochemical factor, produced by the polygenes determining variance of social introversion in the normal range, that interferes with or enhances the expression of the schizogene as a social learning parameter. Rather, we get two different dispositions in the exophenotype that interact with the social environment to move a schizotype in the direction of schizophrenic decompensation. That being a different situation from the traditional one, we need a different word than modifier. Another example would be intelligence, a strongly heritable disposition, which we do not conjecture to "modify" schizotaxic soft neurology or aversive drift, but which may very well alter probability of decompensation, as in the schizoid college professor who survives comfortably in our extroverted, competitive society because academia may provide a special niche for deviant persons with high IQ.

I take expressivity to be the primary concept, although genetics books generally introduce penetrance first (i.e., "when penetrant, a gene may vary in expression"). It seems to me that expressivity is the basic concept both conceptually and mathematically. For any given quantitative indicator of a gene, unless there is zero overlap of the expressivity distribution functions (in which case we have 100% penetrance), the penetrance coefficient is conventional, being a question of where the scientist locates the cutting score; whereas the expressivity function is an objective fact of nature, although it may at times be difficult for us to ascertain it. So, while one may accept "clinical penetrance" as a marginally satisfactory item for the proportion of schizotypes who exhibit the soft neurology and psychophysiology to look at, there is no overlap of the expressivity distribution functions when we get good evidence, based almost wholly on the statistics of objective fact of nature, although it may at times be difficult for us to ascertain it. So, while one may accept "clinical penetrance" as a marginally satisfactory item for the proportion of schizotypes who exhibit the soft neurology and psychophysiology to look at.

CONJECTURES AND RESEARCH STRATEGIES

Emboldened by my earlier success as a minor prophet, based as it was on scanty evidence at the time, I conclude by recording some "risky predictions," in harmony with my neo-Popperian philosophy of science. These risky predictions follow from my theory and do not, I think, follow from others I know about. I am preparing a longer list for publication in another place, so these are offered merely as samples of falsifiable consequences, which, pending more empirical studies using sensitive instruments, it will be found that the child-rearing practices and attitudes of mother are potentiators of subsequent schizophrenia. I also predict that there will be a greater impact of mother's personality than of father's in this respect. But I say this on the basis of clinical impressions and general psychological theory, realizing that the present evidence, based almost wholly on the statistics of formal diagnosis, does not support any appreciable distinction between the impact of the two parents.

Whether there are any true phenocopies of schizophrenia, I do not know, but I am strongly inclined to doubt it. One might use the term genocopy to refer to certain combinations of polygenes that can give rise to a syndrome quite similar to schizotypy. I doubt their existence, because while plausible candidates exist in the cognitive and, even more, the interpersonal-social domain, I doubt that there are any polygenic systems determining these that could also give rise to a taxon exhibiting the soft neurology and psychophysiology of the schizotaxic brain. One may ask, what could such polygenic systems be? There is a reasonable chance for a syndrome that might (with present methods) be difficult to distinguish from the schizotype in some degree of compensation, if we did not have the soft neurology and psychophysiology to look at. Consider a person without the schizogene who is low on dominance (I will call that "submissive"). hypohedonic, anxious, and introverted, three of which are known to be strongly heritable and presumably polygenic, and I conjecture hypohedonia to be also, although evidence here is sketchy as yet. To these unfortunate genetic loadings we now add one or more traumas in the developmental period, which could either be physical (birth injury or viral infection) or social (maternal rejection or incestuous rape). Finally, on that bad genetic and bad social learning history, we superimpose a run of bad luck in adult life. Like Sir Karl Popper, I attach great importance to "luck" and "bad genetic loadings we now add one or more traumas in the developmental period, which could either be physical (birth injury or viral infection) or social (maternal rejection or incestuous rape). Finally, on that bad genetic and bad social learning history, we superimpose a run of bad luck in adult life. Like Sir Karl Popper, I attach great importance to "luck" and FTW may suggest empirical studies to those interested in critically examining my theory. Unfortunately, some of the most interesting predictions involve measuring instruments not presently available, but that is not a departure from Popperian thinking. One reason that "When we possess good measures of constructs C_1, C_2, ..., C_m, such and such correlation patterns will be found." 68

In the realm of soft neurology and psychophysiology, I conjecture that the smooth-pursuit eye movement 10 and P50 indicators are quasipathognomonic, functioning nearly perfectly as both exclusion and inclusion tests. In the language of the epidemiologist, they will have nearly perfect sensitivity and
specificity, provided drug artifacts and coarse brain syndrome are carefully excluded. I conjecture that a quantified dysdiadochokinesia will also be pathognomonic when cerebellar lesion cases are excluded. (In the aforementioned article in preparation, I describe in some detail how I think such a test should be instrumented and numerified.) I have somewhat more doubt about a vestibular indicator, although I think it has a chance to have high validity when properly done. On the dominant gene model of schizotaxia, the prediction is that since the family data indicate that only about 10% of schizotaxic persons ever develop schizophrenia (and hence the base rate of schizotaxia must be in the neighborhood of 10%), then if we set a cutting score on a quasi-infallible neurologic or psychophysio logic indicator that will identify approximately 100% of schizophrenes or, relying on taxometric bootstrapping, will identify 100% of schizotypes whether decompensated or not; then such an indicator, when cut to yield a dichotomous sign, should yield 10% apparent false-positives in the general population. Formal diagnosis, or degree of decompensation, are here irrelevant, their only role being in bootstrapping the strong indicator in the context of discovery.

One crucial step in such bootstrapping will be to show that 100% of the monozygotic twins of schizophrenes have the sign, and that among them their quantitative amount does not depend on clinical status. It is crucial in this kind of theorizing and its associated testing method that what we are trying to track is a CNS anomaly, not clinical disease, even of a borderline character. While the “schizophrenic spectrum” is not an objectionable notion, and is analogous to the varied clinical pictures presented by nonpsychiatric diseases, the concept can hamper one’s genetic thinking if taken to require manifest psychopathology of all schizotypes. The geneticist expects to find elevated uric acid titer in the monozygotic twins of patients with gout, although only 5% of men with that biochemical endophenotype are clinically “gouty.” We do not expect these “discordant” twins to manifest a small but detectable inflammatory tetrad (rubor, calor, dolor, and turgor) in the big toe, to be in the “gout spectrum” by suffering a “teeny bit of gout,” so to speak. The genetics are elucidated via the endophenotype, not by a touch of inflammation in the toe. I have less confidence in social, cognitive, and “personality” indicators, because of their relative remoteness in the long causal chain from the DNA to those kinds of learned molar level patterns. My Manual for Use With Checklist of Schizotypic Signs was developed on a sample of patients with Hoch-Polatin syndrome seen by me in psychotherapy over the preceding decade. I had intended to carry out taxometric analysis on it by enlarging the sample with protocols from several colleagues, but it turned out that these local practitioners did not find the checklist items reliably ratable. Meanwhile, the DSM-III schizotypal criteria had preempted the field, although my checklist was used in the training of residents at several facilities around the country. I am still inclined to think it was a nice list, but proper taxometric analysis would require a larger sample than I have at my disposal.

I expect, as pointed out in my 1962 paper, that the typical genetic family configuration is that the schizophrenic receives the dominant schizogene from one parent and most of the potentiating polygenes from the other, because if the schizotypal parent had a sizable loading of the polygenic potentiators, he or she would be less likely to have mated and have offspring. Despite the absence of known difference between mothers and fathers when diagnosable schizophrenia is the criterion, I still anticipate that more sensitive measures will support the conjecture that the schizotypal female married to a neurotic male (neuroticism being partly determinative of his object choice?) is more likely than matings going in the other direction.
This is also because I believe, on purely theoretical grounds, that having a schizotypal mother should be a slightly more unfavorable environmental factor than having a schizotypal father. Ignoring formal diagnosis in favor of bootstrapped taxon membership, one would expect that the nonschizotypic parent should show heightened average values of the polygenic variables when measures of them are available sufficiently free of the influence of the phenotype itself. This is because the potentiators social introversion, anxiety proneness, low hedonic capacity, low dominance, and so on should tend to be received more often by the schizophrenic proband from the nonschizoid parent.

We require 50% of the parents of schizophrenes to be in the taxon. We further require that there must be at least one schizotypic parent per pair, although a small incidence of two schizotypic parents can be expected, so we do not expect the value to be precisely 0.50 as a taxon rate. If a fallible dichotomous sign is tallied in a fourfold table, defined not by two variables but by the two parents, and the covariance $p_{ij} = p_{ii} - p_{ij}$ (numerator of the phi coefficient) is calculated on that table, its value should be approximately one fourth the squared difference between the valid-positive and false-positive rates. With a quantitative indicator, the covariance should be one fourth the square of the difference between the taxon and complement means. The dominant gene theory, one expects family trees in which schizophrenia appears in three generations to be one-sided. This is not easily tested via recorded diagnosis of schizophrenia, because of the low clinical penetration; but using high probabilities of taxon membership obtainable by a combination of schizotypic signs, this lateral familial concentration should be easier to detect. A “normal” parent with positive single-unit pursuit movement should also be positive on P50 and conversely, and I predict this to be independent of clinical status. Psychophysiological and soft neurology indicators that are not pathognomonic of the taxon should show numerical separations (mean differences of overlaps) that follow the taxon apart from diagnosed schizophrenia, and apart from the measures of the polygenic potentiators.

It is harder to make strong predictions about the biochemical endophenotype, because doing it right would require single-unit stimulation research of a kind we cannot readily do with human subjects. One thinks, for instance, of repeated stimulation of a neuron by varied input patterns to ascertain whether the spike probability is (1) enhanced and (2) dedifferentiated when the preparation is perfused with extracellular fluid from a nonschizophrenic schizotypic’s brain. One might hope to detect this by using some other experimentally available primate, since the neurotransmitters are very much the same for us and our primate relatives (for that matter, between us and other experimentally available primate, since the brain. One might hope to detect this by using some cellular fluid from a nonschizophrenic schizotypic’s brain. This is because the potentiators social introversion, anxiety proneness, low hedonic capacity, low dominance, and so on should tend to be received more often by the schizophrenic proband from the nonschizoid parent.

Finally, I offer the rash prediction that a sizable minority of patients not diagnosed schizophrenic, major affective disorder, or an organic brain condition (the miscellany of neuroses and personality disorders that make up the rest of “functional” psychopathology) are schizotypes. My subjective estimate is that this proportion will be in the neighborhood of 35%, based on Checklist and MMPI patterns found in my private therapy practice, plus taxometric results in the University of Minnesota Hospital MMPI records. As examples, I anticipate that most of the patients called borderline are schizotypes; that at least half of the patients with what is called Briquet’s syndrome are schizotypes; that many persons with a chronic (nonepisodic) low-level “depression,” not meeting present criteria for major affective disorder, are schizotypes; and that many patients who in the old nomenclature were said to have anxiety state are schizotypes. Like Bleuler, I expect the majority of patients who in the old days would have been called hypochondriacs, and many patients with multifarious fluctuating psychosomatic disorders, are schizotypes.

The “normal” gene would be a mutation in primate evolution, this would seem to be a live option. Following Bleuler (and my colleague Heston) I expect, if not the majority, at least a very large minority of what used to be called constitutional psychopathologic inferiors, then psychopaths, and now sociopaths, are schizotypic. The current categorization of the latter is (in my view wrongly) focused on social impact criteria of psychopathy rather than the purely “psychological” traits emphasized by Cleckley and Lykken, and reflected in the MMPI psychopathic deviate pattern.

These are risky predictions and out of line with what most practitioners and behavior geneticists now believe. However, having been a successful prophet when going strongly against the received doctrines a quarter of a century ago, I do not mind going out on a limb again.

**SUMMARY**

The core conjecture is that a dominant autosomal schizogene, completely penetrant for an endophenotypic parametric aberration in the neuron’s synaptic signal selectivity (hypokrisia), produces a unique kind of CNS integrative defect (schizotypia), characterized functionally by its influencing multiple psychophysiological and soft neurologic indicators and by parametric aberrations in the acquisition and activation functions of diverse molar psychisms (perceptual-cognitive, semantic, motivational, and affective). These aberrations are considered to flow from the primary “synaptic slippage,” although not equally closely or in the same way; in that sense they all stem from Bleuler’s core defect, “associative loosening.” The imposition of mixed social reinforcement schedules on these dispositions results in a schizotypal personality structure. Core features of this personality include interpersonal alienation, ambivalence, dereism, autism, cognitive slippage, and aversive drift. The great majority of schizotypes remain free of diagnosable mental disorder, but a minority (around 10%) develop schizophrenia. These rare persons are at higher risk because of potentiating polygenes for primate evolution, this would seem to be a live option.

The “normal” gene would be a mutation in primate evolution that has a selective advantage, has been slowly taking over, and has now reached a .95 gene frequency (for a .10 schizotypic base rate, dominant model).
other, independent dimensions (eg, anxiety proneness, introversion, and hypohedonia), as well as adverse developmental factors and adult stressors. In researching such a theory, certain methodologic guidelines (not “rules”) should be kept in mind:

1. Indicators closer in the causal chain to the DNA are usually preferable; so, for example, research on soft neurology should pay off more than psychometrics, and the latter more than “spectrum” psychiatric symptoms or social impact.

2. The spectrum concept, while intrinsically valid, is not very useful in testing a theory of this sort.

3. Taxometric statistics are the preferred mode of analysis when testing a major locus conjecture, corresponding to a molar type (rather than dimension).

4. While a clear “marker” (two-way pathogenic, with sensitivity = specificity = 1) of the schizogene would be handy, with suitable taxometric methods that ideal case is not necessary. However, if such a perfect marker were to exist, it could be detected by the taxometric Super-Bootstraps Theorem applied to fallible signs.

5. One should avoid employing indicators that are qualitatively similar because they are likely to show sizable factorial covariation that is taxometrically undesirable. (Conventional thinking about this is opposite to what is optimal in indicator properties.)

6. “Exact” statistics are less useful than multiple-indicator coherence; and point values, even if crudely examined, are preferable to mere significance tests.

7. One reason for working with a major gene conjecture until clearly falsified is its higher falsifiability, predicting values that a polygenic theory can often be fitted to but usually will not have predicted.

8. Taxometric bootstrapping usually leads to taxometric drift and hence conceptual drift. This is often be fitted to but usually will not have predicted.

9. Different levels (molar and molecular) of explanation remain appropriate for different classes of indicators, despite theoretic conjectures as to interlevel derivability.

10. Hence, what we know about schizophrenia psychodynamically and psychometrically is easily compatible with a scientific etiology that is neurologic and genetic. What are inherited are merely aberrant (quantitative) dispositions to acquire socially learned contents (motives, cathexes, defense mechanisms, unconscious fantasies, etc).

11. At this stage, a theory should explain the big trends, not everything. However, smaller trends may be important as leads if they are theoretically interesting, such as the nailfold anomaly, or even (as one clinician of my acquaintance alleged) a tendency to malocclusion slightly higher than in the general population.

12. Statistical models for testing the theory on family patterns must not oversimplify to such an extent that nuisance correlations predicted by the theory itself (eg, assortative mating for polygenic potentiators and differential impact on fertility) are treated as negligible.

13. Genetic semantics needs some cleaning up when applied to the behavioral domain (“modifier,” “heterogeneity,” “penetration,” “expressivity,” “trait,” and “phenotype”).

14. When there is a tradeoff between mathematical elegance (precision, optimality, and maximum likelihood estimators) and epistemic strength, the latter should be preferred.

15. We should keep in mind, whether theorizing or experimenting, that the brain is at least as complicated as the kidney.

References


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