A new nosology of psychosis and the pharmacological basis of affective and negative symptom dimensions in schizophrenia

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Abstract

Although first rank symptoms focus on positive symptoms of psychosis they are shared by a number of psychiatric conditions. The difficulty in differentiating bipolar disorder from schizophrenia with affective features has led to a third category of patients often loosely labeled as schizoaffective. Research in schizophrenia has attempted to render the presence or absence of negative symptoms and their relation to etiology and prognosis more explicit. A dichotomous population is a recurring theme in experimental paradigms. Thus, schizophrenia is defined as process or reactive, deficit or non-deficit and by the presence or absence of affective symptoms. Laboratory tests confirm the clinical impression showing conflicting responses to dexamethasone suppression and clearly defined differences in autonomic responsiveness, but their pathophysiological significance eludes mainstream theory. Added to this is the difficulty in agreeing to what exactly constitutes useful clinical features differentiating, for example, negative symptoms of a true deficit syndrome from features of depression. Two recent papers proposed that the general and specific cognitive features of schizophrenia and major depression result from a monoamine-cholinergic imbalance, the former due to a relative muscarinic receptor hypofunction and the latter, in contrast, to a muscarinic hypersensitivity exacerbated by monoamine depletion. Further development of these ideas will provide pharmacological principles for what is currently an incomplete and largely, descriptive nosology of psychosis. It will propose a dimensional view of affective and negative symptoms based on relative muscarinic integrity and is supported by several exciting intracellular signaling and gene expression studies. Bipolar disorder manifests both muscarinic and dopaminergic hypersensitivity. The greater the imbalance between these two receptor signaling systems, the more the clinical picture will resemble schizophrenia with bizarre, incongruent delusions and increasingly disorganized thought. The capacity for affective expression, by definition a non-deficit syndrome, will remain contingent on the degree of preservation of muscarinic signaling, which itself may be unstable and vary between trait and state examinations. At the extreme end of muscarinic impairment, a deficit schizophrenia subpopulation is proposed with a primary and fixed muscarinic receptor hypofunction.

The genomic profile of bipolar disorder and schizophrenia overlap and both have a common dopaminergic intracellular signaling which is hypersensitive to various stressors. It is proposed that the concomitant muscarinic receptor upregulation differentiates the syndromes, being marked in bipolar disorder and rather less so in schizophrenia. From a behavioral point of view non-deficit syndromes and bipolar disorder appear most proximate and could be reclassified as a spectrum of affective psychosis or schizoaffective disorders. Because of a profound malfunction of the muscarinic receptor, the deficit subgroup cannot express a comparable stress response. Nonetheless, a convergent principle of psychotic features across psychiatric disorders is a relative monoaminergic-muscarinic imbalance in signal transduction.

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Introduction

Historically, classifications have addressed the heterogeneity within psychotic presentations and course of illness. Kraepelin's seminal works on manic-depression and schizophrenia still form the basis of current diagnostic systems. Nonetheless, the boundary between these two broad clinical groups remains sketchy with a general emphasis on the coextensive positive symptoms of psychosis. A major challenge has been the attribution of affective comorbidity as a criterion of exclusion for schizophrenia. This has often led to a trade-off in clinical practice by failing to highlight affective symptoms. Thus, arbitrary decisions are made based on the relative pre-eminence of symptom clusters, in order to meet strict DSM or ICD requirements. The introduction of a schizoaffective diagnosis where both frankly depressive and bizarre psychotic symptom dimensions are given equal weighting would appear an unsatisfactory compromise to many. Indeed, the lifetime prevalence of major depression in schizophrenia is at least 25%. Others would argue that depression, or at least dysphoria, is an inherent aspect of schizophrenia itself. The latter position is confounded by the classic descriptions of many chronic schizophrenics with marked negative symptoms and a lack of any emotional expression that appears qualitatively distinct from the motor retardation of severe depression.

The paper will propose an empirical model of negative symptoms based on both primary and secondary muscarinic hypofunction. A primary receptor defect will correspond closely to what is known as the deficit group. A proposal for a secondary dysfunction is a state-dependent, cortisol-sensitive and potentially reversible dysregulation of muscarinic receptor function in a non-deficit group. According to this model, muscarinic receptor upregulation can occur at the same time as a net monoaminergic-muscarinic imbalance. It is the relative imbalance in signaling hypersensitivity that determines the dimensional structure of psychotic reactions and the potential masking of depressive symptoms. In other words, the positive psychotic process antagonizes or subverts the normal functional outcome of muscarinic receptor modulation. Instability of monoaminergic-cholinergic interactions in the non-deficit group suggests a process of masked cholinergic mechanisms giving rise to secondary negative symptoms. Secondary negative symptoms proposed here and as implied throughout the text are distinct from the common usage of the term and do not refer to treatment-induced side effects. This state dependence will not be considered a 'typical' feature of the deficit group and would explain the divergence in longitudinal outcomes of deficit and non-deficit outcomes.

A nosology that assumes a distinct pathophysiology of deficit and non-deficit groups cannot rely entirely on a symptom-based classification. Such measures may reflect multiple instances of a wrong assignment of category because of the severity of disease rather than clear or known biological mechanisms. Atypical non-deficit cases may be difficult to distinguish, at least in theory, from the deficit syndrome using the current diagnostic criteria. A nosology informed by subtyping of pharmacological endophenotypes is proposed as currently the most objective measure discriminating schizophrenic subgroups. Much of the empirical data used to argue for the present classification are not new, but the theoretical significance attributed to these studies is orig-

inal. It will be shown that the integrity of the muscarinic receptor as measured by the responsiveness or not of the peripheral nervous system is of potential theoretical significance in understanding not only the diversity of symptom presentations in schizophrenia, but also provides a unique and unexplored window into its pathophysiology. A detailed account of the muscarinic underpinnings of cognitive function and preattentive deficits in schizophrenia is given elsewhere[1] and will not be pursued here except where it highlights differences between the two broad subgroups.

A proposal for a primary cholinergic muscarinic dysfunction as a causal process in the deficit syndrome finds support from electrodermal response data. Variability in skin conductance has been noted in a subgroup of schizophrenic patients for some time. Although non-responders make up about 10% of acute schizophrenia (similar to the normal population) this proportion increases to 50% in chronic schizophrenia.[2] Responders were found to score more highly on measures of 'manic state, psychotic belligerence, anxiety, attention demanding and assaultive' scales than non-responders.[3] In addition, pupil constriction in non-responders is markedly reduced leading the author of another study to a tentative conclusion of a cholinergic hypothesis differentiating this group from responders.[4] Cholinergic muscarinic receptors mediate both pupillary constriction and sweat gland secretion (the basis for skin conductance responses). Autonomic dysfunction was cited as fundamental evidence for muscarinic dysfunction in schizophrenia in a recent report[5] and the evidence will be extended below for the purpose of a descriptive nosology. However, this position must be qualified because of lack of specificity and an experimental design aimed at revealing central rather than peripheral indicators of autonomic derangement should be developed. New evidence from gene expression studies and intracellular signaling of peripheral blood cells reveal an unambiguous cholinergic muscarinic signature for schizophrenia. Marked reductions in muscarinic receptors of the prefrontal cortex have also been observed in a subgroup of patients, but the relationship of these findings to clinical profiles has yet to be addressed.

A discussion will be appended at the end of the paper to look at the convergent effects on mood regulation of dopaminergic-cholinergic muscarinic signaling. It will address the role of the complexity of receptor subtypes and their function in the sensitization of affective dysregulation that typically appears as psychiatric comorbidities. Apart from depression, obsessive-compulsive and anxiety disorders, smoking, alcoholism and other drug addictions are common sequelae of the putative non-deficit schizophrenias. Exploration of specific dopaminergic-muscarinic synergisms provides a necessary, albeit speculative departure from the simplistic model of a natural antagonism between these two classes of neurotransmitters. In other words, it looks at how dopamine can promote the cholinergic dysregulation of affective disorders. The theory extends the useful principle of monoamine-cholinergic antagonism to one that embraces sensitization on the one hand and plasticity of behavioral repertoires on the other.

A pharmacological conception of psychotic mood disorders

A theoretical anomaly is posed by the emergence of psychosis in affective disorders. Unipolar depression is marked by a cholinergic hypersensitivity and monoamine depletion. Conversely, effective treatments of psychosis point at excessive monoamine signaling. Bipolar disorder, which manifests both manic and depressive phases, often presents with mixed features including agitation, impulsivity and high suicide risk. Parsimonious with psychotic as well as depressive features is the concept of an abnormal augmentation of both cholinergic and monoaminergic modulated networks. In bipolar disorder, enhanced cholinergic sensitivity may be partially masked by monoaminergic activity. If there is a state-dependent functional inhibition of muscarinic receptor activity the antagonism is inherently unstable and the underlying cholinergic tone can reveal itself in mood swings, mixed states and explains instances of post-psychotic depression. To resolve this anomaly it will be necessary to invoke the concept of dopaminergic mediated sensitization of cholinergic modulated networks in an appended discussion. This extends the putative mechanism beyond well-defined antagonistic properties of the two signaling cascades.

Evidence for a cholinergic theory of depression comes from limited but well-established sources. The acetyl cholinesterase inhibitor physostigmine, which increases synaptic ACh levels, induces dysphoria in manic as well as depressed patients.[6,7] Consistent with the putative pharmacological basis of a mixed picture in bipolar spectrum, another study showed a subgroup of 3 manic patients with a predominantly irritable picture became more aggressive and irritable at the end of a physostigmine infusion.[8] The predominantly euphoric patients, in contrast, responded to physostigmine with a decrease in manic mood, and thought content with increasing depression.

Cortisol

A biochemical feature of stress provides a link across the spectrum of affective psychoses. The hypothalamo-pituitary-adrenal axis and hypercortisolemia in response to stress plays a core role in theoretical models of affective dysregulation. In non-psychotic depression cortisol nonsuppression is substantially less prevalent than in psychotic depression. Higher cortisol levels of psychotic subjects, particularly during the evening, are related to the severity of depression and manifest psychotic symptomatology. Psychiatric sequelae are well recognized complications of high-dose corticosteroid therapy and in Cushing's disease, a condition associated with hypercortisolemia.[9,10] Hypomania, manic episodes, depression and psychosis have all been reported and tend to resolve upon reducing the dosage or discontinuation of the medication. The antiglucocorticoid mifepristone improves spatial working memory performance as well as mood in a group of bipolar patients.[11]

Cortisol increases intracellular calcium and up-regulates the effects of both cholinergic and monoaminergic G-protein coupled signal transduction.[12] Thus, chronically raised cortisol levels sensitize dopaminergic effects in the striatum. This environmentally contingent model acknowledges a gene-environment interaction of the phenomenology of psychotic mood disorders. In genetically susceptible individuals it is a major factor in the phenomenology of psychotic mood disorders.

A nosology of psychosis

A case for subtyping: cognitive dimensions and the muscarinic cholinergic system

Heterogeneity within psychotic disorders and the assumption of schizophrenia subtypes is generally based on the clinical picture and implied by modern genomics. Evidence from electrophysiological studies of the peripheral autonomic nervous system suggests that schizophrenia with a predominant picture of primary negative symptoms has a pathophysiology fundamentally distinct from the clinical form of the non-deficit group. The latter subgroup, in turn, has features of affective psychoses. In accordance with this concept, stress-related vulnerability appears to apply to a limited subpopulation of schizophrenics with HPA axis dysfunction.[13] Conversely, the theory states that a relative muscarinic receptor hypofunction distinguishes schizophrenia as a group from bipolar disorder and that the observed impairment of preattentive function in these patients, such as prepulse inhibition, P50 waves and antisaccade tasks, results from intrinsically defective cholinergic modulation.[1] A cholinergic hypothesis of affective dysregulation would thus predict qualitative differ-

ences in preattentive capacity for psychotic patients with and without affective comorbidity. No trait-like endophenotypes of PPI and P50 wave suppression were found in euthymic bipolar patients and there is great variability in P50 wave suppression in manic patients.[14,15] State-like deficits in suppression varied from 8-78% in a single testing session. In schizophrenia, trait-like deficits are regularly demonstrated. Another study of saccadic abnormalities in psychotic patients showed that the measure, which separated schizophrenia from bipolar disorder, was a failure of suppression in an antisaccade paradigm.[16]

Preattentive capacity and the putative muscarinic hypofunction in schizophrenia can have heuristic value in classifying the psychoses. Accordingly, one would expect intact trait-like or highly variable state-like deficits as measured by PPI, negative prime masking, P50 suppression and antisaccades in affective psychoses. A study did show diminished suppression of P50 auditory evoked potential in bipolar subjects with a history of psychosis irrespective of current clinical state, but the reduction was of intermediate severity between schizophrenia and normal subjects.[17] One might also expect no reduction in muscarinic receptor status. A decreased density of the m1 muscarinic receptor was found in the anterior cingulate cortex of only the schizophrenic but not bipolar or major depressive groups.[18] Within this framework, the terms schizoaffective and non-deficit schizophrenia are somewhat anomalous as they imply both reduced and enhanced cholinergic function. The demonstration of a relative as opposed to absolute muscarinic receptor hypofunction may help resolve their status in the group of psychoses. Of interest, schizoaffective patients have reduced P50 evoked potential resembling more the bipolar patient in severity, i.e. intermediate as compared to schizophrenia.[17] The literature suggests that schizoaffective disorder is a psychotic mood disorder.[19] Although a subgroup of schizoaffective subjects, i.e. with predominant schizophrenic symptoms, have a course of illness resembling schizophrenia,[20] prognosis will not be used as a strict arbiter of diagnostic subtyping in the present model. Furthermore, neurocognitive testing of preattentive capacity may not distinguish state-like negative symptom profiles associated with secondary hypomuscarinic function in non-deficit schizophrenia. Peripheral autonomic markers may provide an endophenotype not confounded by current clinical state.

If a hypercholinergic state underlies the clinical syndrome of affective disorder, then an intrinsically low muscarinic tone in schizophrenia would underlie certain aspects of the negative symptom profile such as negative affect. Consistent with this hypothesis, a strong positive correlation was found between increased muscarinic occupancy by olanzapine in the striatum and negative symptoms of schizophrenic subjects, as assessed by the Positive and Negative Symptom Scale (PANSS).[21] The authors proposed that antagonism of muscarinic receptors exacerbated negative symptoms. There is more direct evidence for a differential neuropathology in schizophrenia and the affective psychoses. An open label 7-day trial of the glucocorticoid receptor antagonist mifepristone in psychotic major depression showed a 50% decline in the Brief Psychiatric Rating Scale (BPRS) for 12 of 19 patients.[22] Forty percent of subjects taking higher doses had more than a 50% reduction in their Hamilton Rating Scales for depression. Placebo response rates were very low. HPA axis dysfunction is a prominent feature of bipolar disorder even in remitted patients and 43% of depressed bipolar patients are DST nonsuppressors.[23,24] In contrast to bipolar subjects, mifepristone appears to have no effect on neurocognitive function or symptoms in schizophrenia.[25] This finding is in agreement with a low DST nonsuppression rate in nonaffective psychoses such as schizophrenia.[26] As could be expected though, studies exhibit a great deal of variability with high rates of DST nonsuppression, 51% in one,[27] or present only in half of a group of suicide attempts.[28] Another study found high rates of DSM IV depression (36% of 64 schizophrenic patients) but very low DST suppression.[29] None the less, consistent with an intermediate phenotype on other behavioral and laboratory measures shown by a schizoaffective group, post-dexamethasone cortisol correlated significantly with depression (HRSD) and the Brief Psychiatric Rating Scale (BPRS) but not with the Scale for the Assessment of Negative Symptoms (SANS). SANS and HRSD also remained uncorrelated. Medication status was a particular confound in this study.

Dichotomous populations with regards to DST nonsuppression, are an indicator of heterogeneity in schizophrenia. The central role of the muscarinic receptor in HPA dysfunction is revealed by studies that show increased levels of ACTH and cortisol to cholinergic stimulation.[30] Arecoline, a muscarinic receptor agonist, administered in doses that minimize adverse events can facilitate DST nonsuppression in normal males.[31]

Clinical impression of stable schizophrenia subtypes

There is a substantial subgroup of schizophrenics in whom negative symptoms are not prominent, who tend to have a better functional outcome and are more likely to have comorbid affective spectrum symptoms. This may include the paranoid subtype, which is clearly a distinct entity from hebephrenic schizophrenia. However, like most historical and current attempts at subtyping, progress of the clinical state from one to the other subtype has been observed often enough to pose problems for diagnostic systems. During an acute episode of schizophrenia, a study found pronounced depressive symptoms (a Hamilton score of 16 or more) in 28% of patients.[32] Seventy-four percent of patients in the original sample were paranoid schizophrenics and 15% had a diagnosis of schizophreniform disorder. A study looking at the long-term outcome of different subtypes found a 3-fold increase in risk of suicide amongst paranoid schizophrenics compared to the undifferentiated subtype, but no suicides were reported for the hebephrenic cohort.[33] The illness onset and subsequent exacerbations in the paranoid subgroup appeared to be partly reactive to life events. There was a high degree of stability over six years but this became modest over a 25-year period. Even at this later time point, reclassification of hebephrenic patients as undifferentiated or paranoid group and paranoid as hebephrenic was relatively uncommon.

Reduced muscarinic receptor density

Reduced muscarinic receptor numbers of multiple subtypes has been replicated.[34] There is also a reduced density of cholinergic interneurons in the ventral striatum.[35] A clear subgroup of patients with schizophrenia, representing 26% of the sample, was reported recently with a markedly reduced muscarinic-m1 receptor number in the dorsolateral prefrontal cortex.[36] The mean reduction in uptake was 74%. The finding describes a muscarinic receptor-deficit subgroup (MRDS). How this relates to autonomic sensitivity is yet to be determined and the study was inadequately powered for phenotypic delineation. Another problem is the nature of the cohort in this post-mortem study with a high proportion of suicides. A trend towards a lower suicide rate for MRDS (36% vs. 55%) as one would expect in a deficit group, failed to reach statistical significance, P=0.50.

Autonomic cholinergic effects

An early study does suggest differential response charateristics to cholinergic stimulation among subgroups of psychotic patients that is consistent with the nosology developed here.[37] Using the cholinesterase inhibitor diisopropylfluorophosphonate (DFP), the schizophrenic group showed markedly less muscarinic effects (e.g. they had an increase in blood pressure) than manic-depressive patients who demonstrated a cholinergic hypersensitivity with regard to induced decreases in blood pressure. No changes were found in normal controls. Although, there was a general autonomic hyporeactivity in the schizophrenic subjects, those individuals that showed a response comparable to the manic-depressive group were of the paranoid subtype.

State versus trait negative symptom dimension

A concept being advanced here is that a dimensional affective component to the psychosis, including paranoia, implies a relative preservation of m1-like receptor function. A study has shown an association of increasing depressive symptoms in schizophrenic patients following the administration of choline chloride.[38] The latter is known to increase brain acetylcholine levels. A dichotomous response to muscarinic receptor agonism further validates the subgrouping of the schizophrenias along reactive and deficit lines. A caveat is the state-dependent secondary manifestations of negative symptoms and preattentive deficits in a putative 'non-deficit' group. Adopting the model of hypersensitive dopaminergic signaling that can mask a normal or up-regulated cholinergic system produces a clinical picture at times indistinguishable from the deficit syndrome and is consistent with relative muscarinic hypofunction. In theory, a secondary muscarinic dysfunction will become evident in these cases by following a longitudinal course.

A cholinergic basis for subtyping

Consistent with a separate affective subtype of schizophrenia, an earlier study of a subgroup of patients with a 'schizophrenia-like' illness that were responsive to lithium also showed transient improvement in psychotic symptoms when an infusion of the cholinesterase inhibitor physostigmine was administered.[39] The author suggested this subgroup would be better placed within an "atypical affective disorder biologically similar to mania". Consonant with this recategorization, 2 of the 4 lithium responders received an RDC diagnosis of schizoaffective disorder, compared to only 2 of 7 non-responders. The 4 patients in the response subgroup rated low on the withdrawal-retardation score which corresponded to emotional withdrawal, blunt affect and motor retardation. The 7 patients classed as lithium non-responders had a much higher withdrawal-retardation score (negative symptoms) which markedly improved during the physostigmine infusion (Edelstein *et al.*[39]). This was not associated with any apparent improvement in psychotic symptoms as measured by the brief psychiatric rating scale (BPRS). The findings might reflect a partial response due to cholinergic resistance in the negative syndrome subgroup. Consistent with this interpretation the Rowntree *et al*.[37] study showed a marked tolerance of muscarinic effects induced in some schizophrenic subjects by the cholinesterase inhibitor DFP as compared to a manic-depressive group. The same study revealed an anomalous effect of DFP on positive symptoms. The dopamine-cholinergic imbalance hypothesis would predict a reduction in psychotic symptoms with DFP. However, in 6 of 17 schizophrenic patients exacerbation of florid symptoms was observed. If one assumes that this reactive subgroup represents responders as defined by autonomic reactivity (see below) the administration of DFP could mimic the stress response. This is consistent with a rat model of relative dopamine depletion producing a hypersensitive rise in ACTH levels to physostigmine.[40] Cholinergic activation of HPA axis can account for the worsening of psychosis.

The model explains the anomaly shown by the trend to improvement of negative symptoms in the Edelstein *et al.* study;[39] this is in the opposite direction to that predicted by the 'anergic' model of cholinergic agonism. Of course, one has to be careful in making generalizations from such small numbers. A further caveat should be raised that negative symptom ratings are not a pure measure of affective blunting, as severely depressed patients may be withdrawn and show motor retardation in addition to agitation. This highlights the difficulties in basing the classification of psychiatric diseases largely on a descriptive phenomenology.

Implicit memory as a measure of the negative syndrome

Vakalopoulos proposed the hypothesis that implicit and explicit memories are a function of the phasic activation of cholinergic and monoaminergic systems, respectively.[1] The hypomuscarinic model of schizophrenia implies a positive correlation then between deficits in preattentive function, negative symptoms and implicit memory. A recent study revealed a core implicit but not explicit memory deficit in a group of chronic schizophrenics with an average duration of the disorder from 15-19 years.[41] Similarly, an intact explicit verbal encoding contrasted with an assumed implicit memory deficit in an enacted condition of the free recall task and this was confirmed by the absence of an enactment effect on response times in the item recognition task.[42] Recall of phrases is facilitated by performing the actions described by them. This function is preserved in typical amnesia cases with preserved procedural memory such as Alzheimer and Korsakoff syndromes. Furthermore, implicit memory loss was positively correlated with the sub-items of the Scale for the SANS: poverty of content of speech, unchanging facial expressions and lack of local inflections. Implicit memory performance in schizophrenia has also been correlated with P50 sensory gating.[43] Data on unipolar depression by contrast has consistently demonstrated intact implicit but impaired explicit memory and enhanced preattentive abilities.[5]

A state-dependent induction of negative or deficit syndrome need not be a core or premorbid feature and may coexist but be separate from depressive features in the acute state. Preattentive deficits, markedly increased reaction times, negative symptoms and impaired implicit memory in schizophrenia may be common but are unstable features of the affective psychoses (including non-deficit schizophrenia) (see the highly variable state-dependent gating deficits in manic patients described above). Thus, one study showed schizophrenia subjects to be severely impaired on a sequence-specific procedural learning task during the acute episode.[44] Visuo-motor performance normalized during remission 20 months later. Importantly, the average duration in this sample was 1.5 years, a prognostic indicator of affective psychoses. Pedersen *et al.* likewise demonstrated an implicit memory deficit in first episode schizophrenia and implicit learning correlated with the speed of attentional performance.[45]

Evidence for deficit syndrome as a separate subgroup

It has been suggested that negative symptoms in schizophrenia are independent of depressive symptoms[46] and a number of studies have shown that affective flattening does not correlate with depression.[47,48] Symptom overlap, as referenced by rating scales, tends to be explained by motor retardation. Whereas they are an enduring trait in deficit schizophrenia, symptoms like anhedonia do not persist in resolving depression according to this model. Dysphoria has been significantly associated with positive but not negative symptoms.[49] Indeed, depression had a negative correlation with negative symptoms.[50] There is also a reduced prevalence of suspiciousness and substance abuse in deficit compared to non-deficit patients, in spite of having similar ratings on a global severity scale of psychosis.[51,52]

That the negative syndrome represents a distinct subgroup from stress responsive psychosis is supported by a number of other studies.[53] Positive symptoms and cognitive disorganization but not negative symptoms were associated with stress in one study.[54] Poor premorbid social functioning and negative symptoms will generally precede the onset of psychosis, whereas stress reactive psychosis occurs in more discrete episodes with often good recovery in between. A subgroup of schizophrenic patients with negative affect-induced disordered speech demonstrated greater habituation of an acoustic startle response and a trend towards greater prepulse inhibition than non-reactive patients.[55] One study, with a 56% incidence of depressive symptoms in first episode schizophrenia or schizophreniform

disorder, demonstrated a lack of association between baseline depressive and negative symptom scores.[56] Indeed an inverse relationship was established as higher acute depressive scores predicted fewer negative symptoms later in the course of the illness.

A number of studies looking at chronic schizophrenia defined a subgroup of Kraepelinian patients with very poor outcome (defined as at least five years of complete and continuous dependence on others). They had more severe negative symptoms and the near absence of an affective component compared with another group of chronic schizophrenics whose longitudinal course was marked by periods including total or partial remission.[57,58] Roy *et al*. suggested that this latter group is related to mood disorders.[59] A recent study replicated the findings showing that only 5% of a sample of Kraepelinian patients had a Hamilton depression rating score over 16.[60] This is much less than the reported modal prevalence rate of 25%. There was also a low incidence in this study of core depressive features, i.e. depressed mood, suicidal ideation and guilt. The authors further concluded that Kraepelinian schizophrenia is a distinct subtype, questioned the boundary between non-Kraepelinian schizophrenia and schizoaffective disorder, and raised the old concept that the preservation of core functional abilities is critical for a depressive reaction in schizophrenia. The study also sheds light on the subjective experience of deficit syndrome based on the self-rating scale used in the study and thus contradicts other studies that have revealed a disjunction between blunt affect and normal or even heightened emotional experience in the deficit syndrome subgroup.[61,62]

Autonomic responders and non-responders: a pharmacological subtyping

Of unknown significance in schizophrenia is response as measured by autonomic parameters. A review of pupillary reactions of patients was performed as early as Kraepelin.[63] Pupillary responses were 15-75%. In one of the cited studies, 40% of patients had an increased pupillary response. In a recent study, psychometric testing revealed a subgroup of schizophrenic patients with reduced pupillary dilation to effortful cognitive tasks had greater negative symptom severity than the normal group but did not differ on a positive symptom scale.[64] A decrease in dilation of pupils is secondary to tonic elevated β-receptor reactivity, which in turn is due to reduced muscarinic receptor tone.

Electrodermal non-responding is also a well-documented feature of chronic schizophrenics. One study showed hyporesponsiveness in 40% of a recent cohort, half of whom were unmedicated and did not differ from those who were medicated.[65] The rate of normal control non-response in this study varied was 3-8%. Non-responders showed greater withdrawal, thought disorganization and motor retardation. Non-responders also show less anxiety and assaultive behavior.[3] This subgroup generally have poorer outcome rated on a comprehensive scale.[66] Normal responders scored significantly higher on excitement and mannerisms as measured by BPRS. Hyporeactive skin conductance and reduced pupillary constriction are largely overlapping subgroups.[4] Within the responder subgroup there exists a further number with abnormally high tonic and phasic skin conductance. These patients show poor functional outcome as measured by social and employment scales and greater negative symptoms than responders who do not differ from controls on this measure.[67] A previous study demonstrated in a select group of largely responding patients that skin conductance non-habituation and insidious onset was associated with a poor prognosis.[68] Both hypo- and hyper-responsiveness being associated with poorer prognosis are non-trivial findings, adding support to the clinical impression of distinct pathophysiologies, rather than a continuum of illness dimensions.

SCR responders and non-responders do not simply fit classical Kraepelinian subtypes.[3] It is evident from his case descriptions that a large proportion of his patients classified under the rubric dementia praecox would be reclassified under a schizoaffective spectrum of psychotic mood disorders using the proposed nosology. Thus, autonomic non-responders corresponding to a pharmacological division would represent a more restrictive subgrouping. Furthermore, single measures of SCR response status may change with time and confound a putative pathophysiological subtyping. For example, Gruzelier found higher ratings on manic state, compulsive-obsessive and psychotic belligerence scales for the institutionalized as compared to non-institutionalized non-responders.[3] In the latter group, non-responding was also coincident with low skin conductance levels and spontaneous fluctuations. In contrast, some cases of the former non-responding group were associated with normal levels of skin conductance and spontaneous fluctuation suggesting a central mechanism of reactivity. They may be wrongly subtyped with the true non-responders evaluation of who should be based on multiple parameters of skin conductance to reflect an accurate assessment of dysfunction in this division of the sympathetic nervous system. None the less, non-responding is considered a stable long-term trait[66] and could fulfil an ideal endophenotype but requires refinement as a diagnostic tool.

Pupillary constriction, skin conductance (sweat glands) and heart rate variability are all mediated by muscarinic receptors, supporting a generalized primary cholinergic dysfunction hypothesis in the non-responder subgroup. Additional evidence comes from a series of studies on systolic blood pressure response to administration of methacholine.[69] Methacholine (mecholyl) has greater selectivity for muscarinic rather nicotinic cholinergic receptors and doesn't readily cross the blood brain barrier, reflecting the measurement of peripheral effects. A marked fall in blood pressure was associated with severe anxiety, generally greater affective components and included a higher proportion of paranoid patients. A milder reaction was found in hebephrenics, patients with poor premorbid adjustment and prognosis and relative absence of precipitating stress. Conversely, stress was often attributable to the onset of psychosis in responders who also manifested a 'neurotic' premorbid personality. A small number of studies did not confirm these results. Variability in response could be one factor contributing to this inconsistency, as could the smaller number in these latter studies. Premorbid history was associated with long-term prognosis in first admission cases but not methacholine response.[70] The scales used in this study did not measure affective lability and disturbances which was raised as a point of difference with another study that did show a methacholine effect. This latter study correlated reaction to mecholyl along a process-reactive dimension with higher autonomic responsiveness associated with greater reactivity.[71] Other studies using a decrease in pulse rate and meant to overcome the limitations inherent in quantifying BP changes tended to achieve consensus with the main body of data.

Supporting the current distinction are some early studies in autonomic response to mecholyl as a prognostic indicator for electroshock therapy in both schizophrenics and manic-depressives.[72] Poor prognosis was associated with reduced response and this was particularly marked for the schizophrenic subjects. However, a number of problems are inherent in the past methodology of autonomic testing and its findings.

Specificity of skin conductance response

Much of the promising early work in skin conductance measures culminated in a study demonstrating poor specificity of non-response between schizophrenia, bipolar and major depressive disorders and their relatives.[73] The same study did propose, however, a high rate of non-specific fluctuations in responders as a more specific psychophysiological marker of risk for schizophrenia and

psychotic depression. Later studies also demonstrated much higher rates of autonomic non-responding even in normal populations.[74] The problem inherent in these and other similar studies is that they confound central effects. Indeed, the structure of their methodological design entails a presumption of central causality and a search for correlates of arousal. Rarely do studies purport a direct measure of peripheral autonomic integrity. The original study by Funkenstein *et al*. gauged prognostic significance to electroshock treatment of schizophrenic and affective psychotic patients subdivided into favorable (highly responsive) and unfavorable (less responsive) groups according to the nature of the systolic blood pressure response to the administration of methacholine (mecholyl).[72] Of the favorable subgroups, 95% of schizophrenic and 93.6% affective psychoses showed clinical improvement; of the unfavorable subgroups, the figures were 13% and 54.5%, respectively. Fifty-four schizophrenic and 15 manic-depressive subjects made up the unfavorable group. The results of this study and the non-specificity of the SCR implies that a proportion of schizophrenia SCR non-responders could be indexing a non-peripheral cause of aberrant electrodermal response. Unfortunately, the Funkenstein *et al*. study stands in relative isolation and apart from the age of the study other limitations include a potentially less rigorous definition of diagnostic groups and the general validity of outcome measures.

There are technical limitations to the study of blood pressure and I am not aware of any studies that have used mecholyl to categorize schizophrenic subgroups by measuring differential SCR or pupillary effects. Thus, it remains to be proven whether a subgroup of schizophrenic subjects can be defined by a more general muscarinic receptor deficit as indexed by direct peripheral autonomic measures. Optimism that peripheral measures can open a window to CNS dysfunction comes from other sources of data, i.e. blood markers and gene microarrays.

Blood markers

Schreiber *et al*.[75] found that β-adrenergic (Gsα) and muscarinic (Giα) agonist-stimulated increases in binding of a non-hydrolyzable GTP-analog to lymphocyte membranes in manic patients was markedly elevated compared to controls.[75] This was considered a feature of manic but not depressed patients.[76] However, Gs and Gi proteins were elevated in mononuclear leukocytes (MNLs) of patients with bipolar depression but not major depressive disorder indicating specificity between subgroups.[77] Further differences in signal transduction between bipolar disorder and schizophrenia were demonstrated in a recent study with dopamine-enhanced guanine nucleotide binding capacity to Gs protein in MNLs of untreated schizophrenic patients but no change in isoproterenol- (adrenergic) or carbamycholine- (muscarinic) induced G-protein function relative to controls.[78] The dopamine effect was positively correlated with the positive subscale of the PANSS. The relative muscarinic-monoaminergic differential is thus specific to schizophrenia.

Immune function is altered in schizophrenic subjects. Cytokine serum levels were examined in both drug-naïve first episode and chronic patients with schizophrenia.[79] Interleukin-2 (IL-2) levels were significantly lower and tumor necrosis factor-alpha (TNFα) higher compared to healthy controls. The muscarinic agonist Oxo-M augments IL-2 production in human blood lymphocytes.[80] Dopamine increases TNFα secretion by T-lymphocytes, mediated by D3 receptor. The evidence is currently indirect for heightened dopaminergic and lower cholinergic function in peripheral immune cells but blood markers provide an exciting avenue for study of signal transduction in psychiatric disease.

High-density gene microarrays

New techniques using recombinant DNA microarray to perform genome-wide gene expression analyses promote hypothesis-free studies. They have revealed consistent signature decreases in gene expression in schizophrenia involved in synaptic signaling, mitochondrial oxidative energy metabolism and myelination.[81-85] A metabolic hypofunction model of schizophrenia was suggested because of a reversal of these changes by insulin and IGF-1.[86] Although, metabolic proteins were reduced in schizophrenia, mostly increases in gene expression were observed for bipolar disorder.[87] Differential genomic signals are considered relatively sparse for bipolar disorder.[88] In one study, 14 neuroblastoma genes were selected for a multiparameter high-throughput screen of 1,940 drug compounds, based on uniform decreases in schizophrenia and a demonstrated response to insulin.[86] Of these, most did not alter the expression of the genes and only 36 had insulin-like effects, the majority being muscarinic agonists. Muscarinic antagonists blocked these effects while the D2-antagonists raclopride and haloperidol did not. Given the likely underlying heterogeneity of the clinical entity, small size effects of multiple allelic variations and a consistent failure in replication of many of these, the emerging pattern of muscarinic dysfunction from this study is extraordinary.

Extending the concept of schizo-affective disorders

Obsessive-compulsive disorder

Comorbid major depression, obsessive-compulsive disorder and panic disorder are common in schizophrenia and are often excluded by current diagnostic systems.[89] Obsessive-compulsive symptoms appear to be a separate symptom cluster from psychosis.[90] In one study, OC symptoms not related to delusions had a much higher prevalence rate in schizoaffective than schizophrenic patients.[91] In first episode schizophrenia, OCD had less formal thought disorder on the SAPS subscale and less flattened affect as measured by SANS.[92] The lack of correlation of OC symptoms with positive, negative and disorganized symptoms indicates they are not part of the core symptoms of schizophrenia.[93] In this hospitalized group, schizo-obsessive patients scored significantly higher for the items of hostility, demanding attention, suicidal ideas, panic attacks and phobias, and overactivity and restlessness. That schizo-obsessive disorder is part of a broader schizoaffective spectrum is further suggested by a comparative study where the group had a significantly higher depression score on both the Hamilton depression rating scale and the depression subscale of the Positive and Negative Symptom Scale.[94] There was a trend towards greater comorbidity with anxiety disorders and schizo-obsessive patients were more likely to have paranoid symptoms.

Appendix

Dopaminergic-cholinergic interactions

The potential synergies of monoaminergic-muscarinic interactions and their involvement in behavioral sensitization and thus production of troublesome psychiatric comorbidities will now be explored. According to one theory, cognitive restructuring of negative thoughts, impulsivity and flexibility of behavior reflects the efficiency of 5-HT1A and D2-like modulation of m1 receptor-mediated cholinergic activity.[1,5] Recent studies support the specificity of D2-like receptors in reversal of learned discrimination in monkeys using the D2/D3 receptor antagonist raclopride[95] and reduced D2/D3 receptor availability in the nucleus accumbens predicts trait impulsivity and cocaine reinforcement in rats.[96] Dysregulation of this system may result from either monoaminergic depletion, as in major depression, or from a hypersensitization of the same mechanism proposed for the affective psychoses. It is a somewhat speculative but

informed treatment of the latter process that will occupy us here.

Although the underlying pathophysiology of reactive psychosis may be a hypersensitivity of catecholaminergic intracellular signaling cascades to stress, the affective manifestations of bipolar disorder and non-deficit schizophrenia are due to a concomitant sensitization of cholinergic m1-like receptor function by dopamine. Thus, mania, paranoia, agitation, depression and anxiety, obsessive-compulsive symptoms and addictive behavior are all mediated by this interaction. What is the support for this and how can we define its molecular mechanism? A promising area of empirical research is drug addiction. There is some evidence that reward associated with dopaminergic activity in the mesocorticolimbic system is translated to habitual seeking behaviors, impulsiveness and preconscious motivational processes by sensitizing cholinergic activity.

The D3 receptor has a structure homologous to the D2 receptor and is likewise linked to a G-protein complex that inhibits adenylyl cyclase but also has trophic effects. The receptor is distributed within the basal ganglia and limbic cortex, the D3-preferring agonist pramipexole reducing cerebral blood flow in orbitofrontal, subgenual cingulate and insula cortex.[97] D3 receptor antagonists reduce cocaine self-administration under both progressive ratio and fixed ratio schedules with a high response requirement.[98] They also prevent stress-induced reinstatement of cocaine seeking behavior and conditioned place preference (CPP). CPP is an animal model that refers to an environmental cue associated with previous drug administration eliciting an approach response. D3 receptor agonists also dose-dependently decrease cocaine self-administration. However, in addition to dopamine being implicated, studies demonstrating an important cholinergic role have not been fully integrated into a pharmacological model of addiction. For example, adding the muscarinic receptor antagonist scopolamine decreases the rate of cocaine self-administration at low doses of cocaine but not at higher doses.[99] Muscarinic m1 receptor knockout mice have an attenuated CPP to both cocaine and morphine which is reversed only at higher doses of the drugs.[100] A simple model of dopamine-muscarinic ACh receptor antagonism would predict a potentiated drug effect of anticholinergics not a deficit. The attenuation is not itself a result of an inverted-U type effect on D1 receptor function as the highest doses of the drugs actually reverse rather than exacerbate the deficit in CPP. Thus, an alternative to D1 intracellular signaling pathway and cAMP is proposed and/or involves a D2-like receptor (D2, D3R) mechanism.

In an operant runway procedure the relationship to dopamine and ACh levels in the nucleus accumbens core of the conditioned acquisition to cocaine and a μ-opioid agonist was studied in rats.[101] Acquisition, as measured by decreasing runtime paralleled a continuous increase in ACh but not dopamine. This effect was blocked by atropine and mecamylamine, implicating both muscarinic and nicotinic receptors. It has previously been proposed that the phasic activation of the basal forebrain cholinergic nucleus is controlled by the lateral prefrontal cortex, including the anterior insula.[1] Of interest in this regard, a recent study has shown that damage to the insula in humans disrupts cigarette addiction[102] and in another study inactivation of the same structure in rats disrupts drug craving.[103]

The treatment of Parkinson's disease with dopaminergic agonists has implicated dopamine in the sensitization of appetitive behaviors. Impulse control disorders, compulsive behaviors and punding appear to primarily implicate the D3R.[104] Successful treatments have variously included atypical neuroleptics and amantadine which have in common a direct or indirect anticholinergic effect.[105] The authors concluded that the effects of D3 agonist activity of drugs like pramipexole mediate the neuropsychiatric effects through inhibition of cortical areas such as the orbitofrontal area. An alternative explanation is that D3R sensitizes cholinergic activity. Gi-protein linked receptors such as D3 promotes the trophic effects of dopamine.

Convergent intracellular signaling of D2-like (D3)-m1 muscarinic receptors unifies the respective known roles of these neurotransmitters in reward and emotional dysfunction. Psychostimulants can induce anxiety, depression and paranoid states. Dopamine-muscarinic receptor interactions are a proposed mechanism of sensitization to negative life events and could prove critical in understanding reactive pathology. It explains both the emergence and persistence of symptoms after withdrawal and is a model for the apparent polarity or mixed nature of the symptoms in manic depression.

BDNF and D3 receptor interactions

Brain derived neurotrophic factor (BDNF) is a key factor in the D3 related sensitization of cortical networks. D3R knockout mice are more resistant to stressful situations such as the forced swim test (FST).[106] Increased immobility in FST is used as an animal model of learned helplessness and human depression. Increased BDNF levels in the nucleus accumbens, due to the upregulation of activity in the dopaminergic ventral tegmental area (VTA), is associated with greater susceptibility to social defeat.[107] BDNF mediates the overexpression of D3R in the striatum, the latter being responsible for the behavioral sensitization to levodopa.[108] A polymorphism of BDNF results in an increased potency of intracellular signaling and hence a risk of rapid cycling in bipolar disorder[109] and a lifetime history of depressive symptoms in schizophrenia.[110]

Pramipexole, a D2/D3 agonist, and fluoxetine or sertraline coadministration act synergistically to confer an antidepressant effect as measured by FST in rats.[111] The Gi pathway and 5-HT1A receptor are also implicated in neural plasticity associated with the effects of antidepressants as are elevated levels of BDNF in recovery. Analogous signaling mechanisms are involved in both emotional dysregulation and the capacity for neural plasticity associated with the antidepressant effect. Thus, blockade of D2 autoreceptors by sulpiride enhances extinction of conditioned fear in mice by increasing dopamine levels and sulpiride conversely increases measures of dysphoria following the acute treatment of depression by SSRIs, presumably acting on sensitized postsynaptic D2/3 receptors.[112,113]

Activation of intracellular signal cascades within the amygdala by BDNF mediates fear-potentiated startle.[114] The memory-enhancing effect involves the phosphorylation of mitogen-activated protein kinase (MAPK and Akt), through Ras and phosphotidylinositol 3-kinase (PI3K), respectively. Trkβ receptor mediates the neurotrophic effects of BDNF and there is widespread convergent signaling with G-protein activated complexes. Agonists at Gi-Trk complexes can function as co-mitogens activating MAPK by a common pathway.[115] In an embryonic fibroblast line, activation of the PI3K/Akt pathway was dependent on both Gq and Gi-protein coupled receptors mediated through β-arrestin membrane translocation and Ras activation, respectively.[116] Activation of the m1 muscarinic receptor (Gq) increases the survival of retinal ganglion cells and this effect appears to require the release of BDNF and both PI3K and MAPK.[117] This may explain the interference with conditioning to cocaine by antimuscarinic agents and m1 knockout mice discussed above. Thus, the increase in cholinergic activity corresponding to the decrease in runtime in the operant runway procedure would reflect consolidation of automatic behaviors. Sensitization and plasticity of behavior are subsumed under a convergent but non-exclusive molecular mechanism involving Trk-Gi-Gq signaling, where the dopamine-ACh interaction is a specific example.

Conclusions

Recent advances in molecular genetics and family studies have questioned the dichotomy of schizophrenia and bipolar disorder.[118,119] However, the current analysis clearly demonstrates it is premature to abandon the neo-

Kraepelinean system of classification for psychosis. It suggests redrawing diagnostic boundaries based on old and new empirical findings that remain commensurate with a two-disease model. Theory has been dominated by monoaminergic, glutaminergic and, more recently, GABAergic hypotheses. The muscarinic hypothesis of psychosis and affective disorder offers promising new insights into the dimensional structure of mental illness.

The current model predicts that an examination of the relative potency of muscarinic receptor transduction will form a basis for the classification of psychotic and mood disorders. It can nonetheless accommodate heterogeneity in the clinical picture of either subgroup due to polygenic contributions to risk and symptom profile. Although the muscarinic hypothesis makes very specific predictions with regards to a pathophysiology underlying negative versus affective symptomatology, it does not necessarily exclude a common genetic inheritance of some risk alleles across the proposed subtypes. For example, calcium channelopathies and variance in GABAergic receptor function may independently promote risk of schizophrenia and psychotic mood disorders.[120,121] For the *PIP5K2A* gene, which is located in a region of linkage with both schizophrenia and bipolar disorder, a strong association was discovered for both deficit and non-deficit schizophrenia subtypes, whereas a single nucleotide polymorphism of *RGS4* was associated with the non-deficit syndrome only.[122] The exact impact of many identified genes still needs to be enumerated, but as gene transcription studies have illustrated, insulin and muscarinic signaling pathways provide overarching principles of convergent dysfunction.

The model also makes sense of the multifarious receptor properties of the atypical neuroleptics such that in the proposed two broad subgroups of schizophrenia, alternatively procholinergic and anticholinergic and 5-HT1AR properties are desirable, based on the affective profiles and responsivity to stress. A true pharmacological nosology of schizophrenia and psychosis in general is prescient, as the advent of an increasing number of effective drugs possess a bewildering array of properties. This will render the appropriate theory-based treatment of heterogeneous subgroups of patients within our grasp and guide more efficient research into etiology and future drug development. Research directed into autonomic response and its clinical correlates, and the integrity of the peripheral muscarinic receptor are further avenues for testing the present hypothesis. This paper makes a convincing case for a dimensional nosology of psychosis based on the muscarinic receptor. However, the relationship of functional findings of monoaminergic-muscarinic imbalance and deficit subgroup to the reduced density M1 receptor in some probands remains to be clarified.

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