Perseveration in Schizophrenia

by Andrew Crider

Abstract

Perseveration in schizophrenia may take a variety of forms, which can be conceptualized as varying manifestations of an underlying neurocognitive deficit. Comparative studies have demonstrated higher than normal levels of perseverative responding among schizophrenia patients on capacity-demanding tasks, including prompted discourse, reversal learning, and the generation of guessing sequences. There is little evidence that perseveration is associated with deficit signs of schizophrenia. However, perseveration appears to covary with both positive thought disorder and voluntary motor disturbance. Perseveration in schizophrenia thus appears to be a productive sign elicited by a failure to mobilize cognitive resources in situations requiring controlled information processing and the concomitant inhibition of activated but task-inappropriate responses. An information-processing model proposed by Shallice (1988) attributes perseveration to a failure of a higher level executive control system to modulate a lower level response selection system under a requirement for novel response generation. This model suggests that perseveration is the consequence of a failure of frontal specification of striatal outputs during controlled processing, resulting in the continued reselection of previously activated outputs.

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Various forms of perseverative activity have long been noted among schizophrenia patients (Bleuler 1911/1950; Freeman and Gathercole 1966; Bilder and Goldberg 1987; Barr et al. 1989) and can be elicited in a substantial minority of chronic cases (Andreasen 1979*b*; Braff et al. 1991). Nevertheless, perseveration has received a relatively modest amount of theoretical and research attention as a component of the psychopathology of schizophrenia, possibly because a dominant post-Bleulerian paradigm dismissed neurological phenomena as irrelevant to the disorder (Rogers 1985; Crider 1991). However, a renewed appreciation of the neuropsychology of schizophrenia, including theoretical formulations of symptoms in terms of motor-programming dysfunction (e.g., Gray et al. 1991; Frith 1992), justifies a fuller consideration of the nature and significance of perseveration in schizophrenia. This article provides an overview of perseveration, reviews and examines the implications of comparative studies of perseveration in schizophrenia patients, and presents a cognitive neuropsychological formulation of underlying mechanisms.

What Is Perseveration?

Perseveration can be defined as the contextually inappropriate and unintentional repetition of a response or behavioral unit. In other words, the observed repetitiveness does not meet the demands of the situation, is not the product of deliberation, and may even unfold despite counterintention. Perseveration can therefore be differentiated from goal-directed and intentional forms of repetition, such as linguistic redundancies designed to enhance communicative or poetic impact. Perseveration in schizophrenia encompasses both simple and complex behaviors, ranging from discrete motor responses to skilled psychomotor performance.

Variety in Perseveration. Various forms of perseveration can be differentiated. After reviewing previous distinctions and typologies in the neurological literature, Sandson and Albert (1984) suggested a tripartite classification of continuous, recurrent, and stuck-in-set forms.

Continuous perseveration is a failure to terminate a discrete response, which is repeated without interruption. Common examples include the uninterrupted emission of

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single words or the graphical repetition of letters, numerals, or design elements. Bleuler (1911/1950) described several instances among schizophrenia patients, including a pianist who became stuck on a repeated musical phrase and a stage prompter whose illness was revealed by his inability to cease prompting the same line despite recognition of the problem.

Recurrent perseveration can take two major forms. The first is the repetition of a previously emitted response to a subsequent stimulus. Freeman and Gathercole (1966) cited an example of the appropriate copying of dots on the first Bender Gestalt card (Bender 1938) followed by the inappropriate use of dots on the second card. The second form is seen in the repeated intrusion of an initial response into a subsequent response sequence, as in reciting the alphabet "AbcAdeAfghijA. . . ." Recurrent perseveration of morphemes, phonemes, phrases, or syntax is a prominent characteristic of schizophrenic language disorder, as seen in the following example of lexical perseveration in the context of incoherent speech (Cutting 1985):

> Yes I mean er I mean are you from London I mean do you like London particular of London I think that London is wild buses wild buses in London and wild trains underground is wild in London bus I mean it is Lebanon bus of London and Lebanon train of London so we are the chancellor if it is the underground. [p. 250]

Stuck-in-set perseveration typically is observed on reversal tasks in which the patient fails to switch response modes after a shift in response-outcome contingencies. On the Wisconsin Card Sorting Test (WCST; Heaton 1981), for example, the schizophrenia patient may continue to sort items in terms of a previously relevant, but currently irrelevant, attribute of the stimulus figures.

Unity in Perseveration. Classical neuropsychology treats different forms of perseveration as signs of dysfunction in specific cerebral loci (e.g., Luria 1980). However, all forms of perseveration entail a common reduction in behavioral variability and a concomitant increase in the predictability of current behavior from past behavior (Frith and Done 1990). This similarity in behavioral dynamics implies that a unitary mechanism may underlie varying forms of perseveration. Goldberg (1986) has elaborated on this implication in relation to the Sandson and Albert (1984) classification by proposing that all forms of perseveration reflect a "pathological inertia" of cognitive processes: Previous activity is not terminated and a switch to new activity is not initiated. According to Goldberg, this mechanism operates at different levels of cognitive representation to produce different forms of perseveration. Stuck-in-set perseveration is produced by operation at the superordinate level of the general semantic set or cognitive mode, recurrent perseveration by operation at an intermediate level of individual task items within the cognitive mode, and continuous perseveration by operation at the subordinate level of elementary motor operations. The three levels of representation are presumed to function in hierarchical fashion such that each level is embedded in the next higher one. Goldberg's simplifying hypothesis provides a rationale for treating different forms of schizophrenic perseveration as manifestations of a common neurocognitive deficit.

Comparative Studies

Neuropsychological assessment of schizophrenia patients yields a level of perseverative responding equivalent to that shown by patients with known organic impairment (Bilder and Goldberg 1987). The degree of perseveration observed varies considerably among different tests, however (Freeman and Gathercole 1966). More specifically, comparative studies have confirmed enhanced levels of perseveration among schizophrenia patients in prompted discourse, on reversal tasks, and on insoluble guessing tasks.

Discourse. Andreasen (1979*a*) defined perseverative speech as the "persistent repetition of words, ideas, or subjects so that, once a patient begins a particular subject or uses a particular word, he continually returns to it in the process of speaking" (p. 1320). In twin reports, Andreasen showed that perseverative speech could be rated reliably in the clinical interview (Andreasen 1979*a*) and that it was observed in 24 percent of schizophrenia patients, 34 percent of mania patients, and 6 percent of depressed patients (Andreasen 1979*b*). Using a somewhat different methodology, Manschreck et al. (1985) tallied the frequencies of repeated words and multiword phrases in the speech of schizophrenia, mixed affective disorder, and normal control subjects asked to describe a painting. The schizophrenia patients were significantly more perseverative on both measures than the two comparison groups.

Several studies have assessed repetitiveness in the speech of schizophrenia subjects by means of the type-token ratio (TTR), which is the proportion of different words (types) to the total number of words (tokens) in a speech sample. Results using this metric are somewhat mixed. Three studies reported greater repetitiveness (lower TTRs) among schizophrenia patients compared with normal or medical patient controls (Fairbanks 1944; Seth and Beloff 1959; Hammer and Salzinger 1964). Three other studies found no differences between schizophrenia patients and normal, other psychiatric, or medical

patient controls (Lorenz and Cobb 1954; Feldstein and Jaffe 1962; Salzinger et al. 1964). More consistent results have been reported when schizophrenia patients are differentiated in terms of the presence or absence of positive formal thought disorder. In an initial and a replication study, Manschreck et al. (1981, 1984) found lower TTRs in thought-disordered than in non-thought-disordered patients, who in turn did not differ from mixed affective disorder patients or normal controls.

Reversal Tasks. Schizophrenia patients show an impaired ability to shift response sets on tasks when changed outcome contingencies require the inhibition of a previously reinforced response and the facilitation of a newly reinforced response. In some schizophrenia patients, impaired shifting is accompanied by nonrandom, perseverative responding. For example, Nolan (1974) studied discrimination learning shifts between two stimuli that varied simultaneously in the attributes of color and form. Schizophrenia patients were impaired on both reversal shifts within a given attribute and extradimensional shifts between attributes. Long runs of perseverative errors accounted for the poor performance of lobotomized patients generally and of 5 of 23 patients without signs of brain damage. Similarly, Crumpton (1963) found that schizophrenia patients were less able than control subjects to shift response strategies when rules were changed in games of skill.

The WCST is a robust means of eliciting perseverative responding in schizophrenia patients. The test consists of 128 cards displaying figures of varying form, number, and color. The subject is required to sort the cards according to one of the three attributes (which is unannounced) and to shift to a different attribute after 10 correct sorting responses. The test yields a variety of scores, including the frequency of sorting errors that are perseverative (Heaton 1981). An initial demonstration of an abnormally high frequency of WCST perseverative errors among schizophrenia patients (Fey 1951) has been confirmed for an automated version of the test (Berman et al. 1986; Weinberger et al. 1986) and in subsequent neuropsychological investigations (Braff et al. 1991; Litman et al. 1991; Raine et al. 1992; Rosse et al. 1993; Rubin et al. 1994).

Guessing Tasks. A guessing task can be compared to predicting the sequence of red and black cards in a shuffled deck: Correct guesses reflect no necessary contingency so that no winning strategy can be developed (Frith and Done 1990). Under these conditions, the strategy requiring the least effort is the repetition of the same guess on each trial. Although normal subjects may sometimes adopt this least-effort strategy, they are more likely to generate complex response sequences that approach the randomness of the stimulus sequence (Frith and Done 1983; Lyon et al. 1986). In contrast, schizophrenia patients tend to generate very simplified guessing sequences that are then perseverated.

Frith and Done (1983) devised a two-choice guessing task that required subjects to predict the right (R) or left (L) spatial location of a cross that appeared on a video screen by pressing one of two choice buttons. Repetitiveness was measured in four-trial response tetrads. Both acute and chronic schizophrenia patients showed a greater frequency of simple alternations (RLRL or LRLR) compared with normal subjects. One-sided perseverations (RRRR or LLLL) characterized deteriorated patients with intellectual deficits. In a replication study, Lyon et al. (1986) also found more frequent simple alternations among chronic schizophrenia patients.

Lyon and Gerlach (1988) modified the Frith and Done task, requiring subjects to produce more lengthy sequences of R or L guesses before feedback on each trial. The subjects included patients with chronic schizophrenia, affective disorder, anxiety disorder, and schizoid personality disorder, as well as normal control subjects. In general, normal subjects showed more variable and complex response sequences than the schizophrenia patients, who tended to repeat simplified sequences such as one-sided perseverations or simple alternations. Simplified sequences characterized 74 percent of guesses among schizophrenia patients compared with 36 percent among the normal control subjects. Response sequences among anxiety disorder and schizoid patients did not differ from those of the control group. However, affective disorder patients could not be distinguished from schizophrenia patients, because of schizophrenic-like repetitions among a subgroup of mania patients.

Relation to Clinical Signs. A number of studies have explored the psychopathology of perseveration by relating individual differences in perseverative activity to other signs of schizophrenia. Given the heterogeneous nature of both the measures used and the patients sampled across different studies, this literature is less cohesive than might be wished. Nevertheless, the available evidence suggests that the severity of perseveration is unrelated to deficit signs of schizophrenia but may instead covary with two productive signs: formal thought disorder and voluntary motor disturbance.

Conventionally, perseveration is considered a negative or deficit sign of schizophrenia. For example, Frith (1992) groups perseveration with affective flattening, poverty of speech, and poverty of action as manifestations of an impaired ability to generate action intentions. However, few data support the conventional view, and

there is evidence to the contrary. For example, Andreasen (1979*b*) found that the severity of perseverative speech was uncorrelated with the deficit sign of poverty of speech; Buchanan et al. (1994) reported that WCST perseverative errors did not distinguish between deficit and nondeficit subtypes of schizophrenia. In addition, no relationship between WCST perseverative errors and negative symptom severity was found in studies of chronic, medicated patients (Liddle and Morris 1991; Morrison-Stewart et al. 1992; Rosse et al. 1993), among acutely ill, medicated patients (Addington et al. 1991), or in a mixed sample of acute and chronic patients during a drug washout period (Wolkin et al. 1992). Braff et al. (1991) did find a positive relationship between WCST perseverative errors and negative symptom severity. However, the patient sample was atypical in that measures of negative and positive symptom severity were correlated rather than orthogonal.

In contrast, there is evidence of a link between perseveration and positive formal thought disorder. Andreasen (1979*b*) found perseverative speech to be correlated with ratings of derailment, incoherence, illogicality, and poverty of content of speech in a mixed sample of schizophrenia, mania, and depressed patients. The same indices of positive thought disorder also were correlated with counts of word and phrase repetition in a mixed sample of schizophrenia and affective disorder patients (Manschreck et al. 1985) and with lower TTRs (greater repetitiveness) in two samples of schizophrenia patients (Manschreck et al. 1981, 1984). Summary assessments of overall positive symptom severity, as opposed to the more specific assessment of thought disorder, may (Morrison-Stewart et al. 1992) or may not (Addington et al. 1991) predict WCST perseveration.

Factor analyses of schizophrenic signs and symptoms reveal two robust productive syndromes: a psychotic syndrome defined by hallucinations and delusions and a disorganization syndrome defined by positive thought disorder, bizarre behavior, and inappropriate affect (Liddle 1987; Andreasen et al. 1995). The apparent covariation of perseveration with positive thought disorder thus implies that perseveration is a component of a broader disorganization syndrome. This implication has been confirmed with regard to both perseverative discourse (Andreasen et al. 1995) and WCST perseveration (Liddle and Morris 1991). An understanding of schizophrenic perseveration may therefore illuminate other manifestations of disorganization.

Disturbances of voluntary motor activity, such as repetitive movements, impaired coordination, and poor response sequencing occur frequently among schizophrenia patients (Manschreck 1986, 1993; Heinrichs and Buchanan 1988). Voluntary motor disturbance is associated with the presence of positive thought disorder (Manschreck et al. 1982; Heinrichs and Buchanan 1988; Schroder et al. 1992), which in turn suggests an association between voluntary motor disturbance and perseveration. Manschreck et al. (1982) confirmed such a relationship in a carefully conducted study using the TTR measure of repetitive speech. Low TTRs were associated particularly with uncoordinated, stereotypic, and perseverative movements. Other studies have linked the frequency of WCST perseverative errors to the severity of disturbance in smooth-pursuit eye tracking (Katsanis and Iacono 1991; Litman et al. 1991), although a failure to replicate has also been reported (Friedman et al. 1995). In addition, WCST perseveration predicted the degree of impairment among schizophrenia patients in the ability to suppress saccades to a rapidly displaced visual target (Rosse et al. 1993).

Implications and Speculation. Although limited in the range of tasks explored, comparative studies have nonetheless shown heightened perseveration among schizophrenia patients in prompted discourse, reversal learning, and the generation of guessing sequences. Tasks found to elicit perseveration in schizophrenia appear to require the mobilization of substantial cognitive resources in the service of novel response generation, coupled with an inhibition of task-irrelevant alternative responses. Discourse requires the generation of a plan of utterance, the selection of syntax and lexicon, and the concomitant inhibition of task-irrelevant morphemic and phonemic associations (Chaika 1982; Maher 1983; Maher and Spitzer 1993). Reversal tasks require the simultaneous inhibition of a previous set to respond to one attribute of a stimulus array and the development of a new response set to an alternative attribute (Ridley et al. 1981*a*; Frith 1992). Two-choice guessing tasks prompt the inhibition of a normative bias toward response alternation (Ridley et al. 1988) and the generation and testing of more complex response sequences in relation to the random feedback contingency.

In information processing terms, tasks on which schizophrenia subjects perseverate require attentive, effortful, and capacity-limited (i.e., controlled) processing, as opposed to the more automatic and routine processing that unfolds without such requirements. Controlled-processing tasks are especially problematical for schizophrenia patients, but automatic processing remains relatively intact (Nuechterlein and Dawson 1984; Anscombe 1987; McGrath 1991; Serper and Harvey 1994). Perseverative activity in schizophrenia may occur as a default when the person cannot marshall sufficient cognitive capacity in a situation requiring controlled information processing.

Failures of controlled processing in schizophrenia are associated with frontal cortical dysfunction. In contrast to normal control subjects, schizophrenia patients show reduced prefrontal perfusion and/or metabolism relative to other cortical regions during performance of the WCST (Berman et al. 1986; Weinberger et al. 1986, 1988; Rubin et al. 1994), the Tower of London task (Shallice 1988; Andreasen et al. 1992), the Chicago word fluency test (Lewis et al. 1992), and a difficult version of the Continuous Performance Task (Buchsbaum et al. 1990). Hypofrontality in these paradigms does not appear to be secondary to medication effects (Andreasen et al. 1992; Buchsbaum et al. 1992; Rubin et al. 1994). Conversely, schizophrenia patients usually, but not always (Cohen et al. 1987), show normal levels of prefrontal activity in response to tasks requiring mere identification of readily discriminated stimuli, such as number matching (Berman et al. 1986; Weinberger et al. 1986, 1988) and certain vigilance tasks (Jernigan et al. 1985; Berman et al. 1986). Hypofrontality in response to capacity-demanding tasks may therefore permit the emergence of perseverative activity in schizophrenia. Confirmation of this hypothesis will require observations of frontal function and perseverative activity on tasks whose information processing demands can be varied systematically.

There is little evidence that the severity of perseveration covaries with deficit signs of schizophrenia. However, perseveration has been associated in various investigations with the severity of positive thought disorder, suggesting that perseveration is a productive sign of schizophrenia. The productive nature of perseveration is also consistent with the higher than normal levels of perseveration observed in acutely manic patients (Andreasen 1979*a*; Lyon and Gerlach 1988).

Because dopaminergic hyperactivity has long been linked to the productive symptoms of schizophrenia (Swerdlow and Koob 1987; Gray et al. 1991; Frith 1992), perseveration may also be a dopamine-dependent phenomenon. The repetitive dynamic of behavior elicited by dopamine agonists such as amphetamine, methylphenidate, and apomorphine has been noted frequently (Robbins and Sahakian 1983; Segal and Geyer 1985; Crider et al. 1986). Well-known examples include stereotyped locomotion and oral-facial-head movements in rodents, perseverative grooming in rhesus monkeys, and "punding" behavior in human amphetamine abusers (Segal and Geyer 1985; Cooper and Dourish 1990). Controlled studies of dopamine agonist–induced perseveration in human subjects are rare. However, Bilder et al. (1992) demonstrated increased lexical perseveration after methylphenidate infusion in schizophrenia patients, and Ridley et al. (1988) found that normal subjects showed an increase in schizophreniclike alterations in the Frith and Done guessing task after amphetamine infusion (Ridley et al. 1988).

Various forms of dopamine agonist-induced perseveration have also been observed in animals. For example, Evenden and Robbins (1983) found that rats treated with systemic amphetamine showed a dose-dependent increase in perseverative lever pressing in an operant paradigm. Similarly, Koek and Slangen (1983; see also Sahgal and Clincke 1985) reported a dose-dependent increase in perseverative responding with amphetamine in an operant discrimination paradigm. Dopamine agonists also prompt perseverative responding in monkeys on reversal learning and guessing tasks. Ridley et al. (1981*a*, 1981*b*) reported that amphetamine disrupted object choice reversal learning in the marmoset because of perseveration on the previously rewarded object; this effect was reversed by pretreatment with the dopamine antagonist haloperidol. Amphetamine also increased one-sided perseverations in marmosets tested in an analog of the Frith and Done two-choice guessing task (Ridley et al. 1988). Thus, studies on both humans and animals strongly implicate a dopaminergic mechanism in various forms of behavioral perseveration.

The anatomical substrate of dopamine agonist-induced perseveration has not yet been specified. However, hyperdopaminergic activity in both the dorsal and ventral striatum is known to underlie the stereotyped and repetitive behavior patterns elicited in animals with stimulant drugs (Robbins et al. 1990; Robbins 1991). By extension, the striatum is plausibly involved in repetitious behavior in humans (Pedro et al. 1994). Striatal involvement in schizophrenic perseveration is also consistent with the apparent association of perseveration with disturbances of voluntary motor activity. In schizophrenia, disturbances of voluntary motor activity may occur simultaneously with involuntary hyperkinesias (e.g., choreo-athetosis), which are thought to reflect, in part, dopamine hyperactivity in the dorsal striatum (Swerdlow and Koob 1987; Manschreck 1993; Walker 1994). In contrast to hyperkinesias, voluntary motor disturbance in schizophrenia may be secondary to hyperdopaminergic activity in the ventral striatum (McKenna 1990).

A Cognitive Neuropsychological Formulation

Cognitive neuropsychological approaches to schizophrenia attempt to explain both the cognitive deficits and the associated neuropathophysiology underlying specific clinical signs and symptoms (Frith 1992). In the present context, such a formulation should provide an information-

processing account of perseveration with reference to presumed frontal cortical hypofunction and striatal dopamine mechanisms.

A cognitive model elaborated by Shallice (Shallice 1988; Shallice and Burgess 1991) explicitly treats perseveration as a default resulting from the failure of controlled information processing. The model distinguishes between two cognitive modes involved in the selection of action or thought sequences: a lower level contention-scheduling system and a higher level supervisory system that modulates the former. The contention-scheduling system, which contains representations of response programs (schemas), enables the selection of routine action or thought sequences. The contention-scheduling system is capable of effective operation in demanding situations if appropriate schemas are sufficiently specified by environmental inputs (triggers). Under such conditions, schema selection proceeds more or less automatically by means of overlearned associations between triggers and specific schemas. Schema selection entails a process of contention scheduling in which an activated schema exercises lateral inhibitory control over potentially competitive schemas and their outputs.

There are two major cases in which the supervisory system overrides the contention-scheduling system by activating or inhibiting particular schemas. The first case occurs when a strong external trigger threatens to disrupt ongoing behavior by capturing the contention-scheduling system, that is, when resistance to distraction is required. The second case occurs when an activated but task-irrelevant schema must be inhibited in favor of the deliberate selection of a novel but task-relevant weaker schema, that is, when resistance to perseveration is required. An impairment of the supervisory function has little effect on relatively automatic information processing in routine situations. However, supervisory impairment permits perseverative activity in situations requiring controlled processing in the service of novel response generation. In terms of the model, then, perseveration involves an impairment of the supervisory system, which in turn permits the repetitive selection of a previously activated schema at the contention-scheduling level.

The Shallice model has the advantage of readily mapping onto neural substrates. The higher level supervisory system was in fact devised to describe aspects of frontal lobe functioning, including perseveration, in brain-damaged patients (Shallice 1988). In addition, Robbins (Robbins and Sahakian 1983; Robbins et al. 1990; Robbins 1991) has argued for a correspondence between the operation of the contention-scheduling system and functions of the basal ganglia, particularly the striatum. At the neural level, therefore, perseveration in schizophrenia may reflect an impairment of normally integrated frontal corticostriatal activity.

The interaction between frontal cortex and striatum is characterized by parallel and segregated neural circuits: Frontal efferents are relayed back to frontal targets after sequential processing in the basal ganglia and thalamus (Swerdlow and Koob 1987; Alexander and Crutcher 1990; Robbins 1990; Walker 1994). Cortical efferents to the striatum form excitatory synapses, presumably glutamatergic, on the densely arborated dendrites of medium spiny cells, which comprise the vast majority of striatal output neurons. The medium spiny outputs in turn form inhibitory gamma-amino-butyric acid (GABA)ergic pathways with downstream structures (Gray et al. 1991; Gerfen 1992).

Activity in medium spiny cells is modulated by ascending dopamine projections that form dendritic synapses in close proximity to the excitatory cortical inputs (Deutch et al. 1993). The majority of medium spiny cells exhibit dopamine receptors of either the D_1 or the D_2 subtype (Gerfen 1992). The distinction between D_1 and D_2 receptors is doubly significant. First, the D_1 receptor is excitatory, and the D_2 receptor is inhibitory. Second, striatal neurons exhibiting the D_1 receptor initiate a direct striato-nigro-thalamic pathway, whereas D_2 receptor neurons initiate an indirect striato-pallido-nigro-thalamic pathway (Alexander and Crutcher 1990; Gerfen 1992). Because the inhibitory D_2 receptor is thought to be involved critically in the pathophysiology of schizophrenia (Davis et al. 1991; Walker 1994), activity in the associated indirect pathway is implicated as well. Swerdlow and Koob (1987) refer to specific loops in the indirect pathway as cortico-striato-pallido-thalamic (CSPT) circuits.

The striatum often is likened to a filter of cortical information (Stevens 1989). Information reduction is accomplished in three ways. First, neuronal volume reduction occurs as cortical inputs synapse with a smaller number of striatal output cells (Nauta and Domesick 1984). Second, these output cells form a collateral inhibitory network, an excited subset of neurons producing an inhibitory surround of suppressed activity. Third, striatal outputs initiate a positive feedback loop that sustains and augments the originating cortical input. As described by Penney and Young (1983) for motor circuits of the dorsal striatum and elaborated by Swerdlow and Koob (1987) for "cognitive" circuits of the ventral striatum, the inhibitory striatopallidal projection is succeeded by another inhibitory pallidothalamic pathway. Activation of striatal output neurons thus excites the pallidothalamic pathway by disinhibition, resulting in increased thalamic drive to the cortex. This mechanism allows for sustained activity in specified CSPT circuits. In sum, striatal mecha-

nisms select and maintain response schemas by volume reduction, collateral inhibition, and the specification of CSPT-positive feedback circuits.

In this analysis, perseveration in schizophrenia occurs when there is a failure to switch from an activated CSPT process to a succeeding CSPT process required by task demands. Normally, switching depends in part on the D_2 receptor-mediated interruption of an activated CSPT process. Such D_2 receptor activation disrupts both local collateral inhibition and any currently active CSPT process via the inhibition of striatal output cells. This momentary disruption creates a "temporal window" (Gray et al. 1991) for the activation of an alternative subset of output cells specified by environmental triggers during automatic processing or by cortical inputs during controlled processing. In the case of schizophrenia, automatic processing should proceed in the normal fashion. However, controlled processing is disrupted because of a failure of frontal cortical specification of task-relevant schemas. In the absence of frontal specification, the previously activated schema is likely to be reselected. Schizophrenic perseveration is therefore viewed as the consequence of a task-inappropriate reselection of a previously activated CSPT process.

This formulation is only approximate, because it is silent regarding important specifics. It does not, for example, identify any particular CSPT loop that subserves perseveration. In light of animal studies of perseveration after orbital frontal lesions (Fuster 1989; Ridley et al. 1993), the lateral orbitofrontal circuit identified by Alexander et al. (1986) is a plausible candidate. However, any such specification is premature in the absence of pertinent evidence from schizophrenia patients. In addition, this formulation does not identify the precise striatal dopamine mechanism of perseveration. Clearly, an abnormality of striatal dopamine release, for which there is little evidence in schizophrenia, is not required. Conversely, the formulation is compatible with current views of an upregulation of striatal dopamine receptors or other anomalies of dopamine homeostasis in schizophrenia (Carlsson and Carlsson 1990; Heritch 1990; Davis et al. 1991; Grace 1991).

Neural circuit models figure in several recent formulations of the neuropathophysiology of schizophrenia (Swerdlow and Koob 1987; Robbins 1990, 1991; McGrath 1991; Early et al. 1994; Pantelis and Nelson 1994). The present formulation is primarily informed by, and most compatible with, Robbins' (1990, 1991) frontostriatal hypothesis and the generalized CSPT model described by Swerdlow and Koob (1987). Interestingly, the present formulation also bears some similarity to CSPT models of obsessive-compulsive disorder (Modell et al. 1989; Baxter et al. 1992), which suggests the ultimate possibility of arriving at a general neurocognitive understanding of the differing presentations of pathological perseveration.

Summary

Perseveration is the contextually inappropriate and unintentional repetition of a response or behavioral unit. In schizophrenia, perseveration may take a variety of forms. These can be conceptualized as varying manifestations of an underlying neurocognitive deficit.

Comparative studies have shown higher than normal levels of perseveration among schizophrenia patients in prompted discourse, reversal learning, and the generation of guessing sequences. A plausible hypothesis arising from these studies is that perseveration occurs in schizophrenia as a default when the patient fails to mobilize cognitive resources in situations requiring controlled information processing and the concomitant inhibition of activated but task-inappropriate responses. This hypothesis is consistent with the reduced frontal cortical function seen in schizophrenia patients during the performance of capacity-demanding tasks.

There is little evidence that perseveration is associated with deficit signs of schizophrenia. However, perseveration appears to covary with both positive thought disorder and disturbances of voluntary motor activity. Some studies also report higher than normal levels of perseveration among acutely manic patients. In addition, dopamine agonists reliably elicit perseverative responding in both human and animal subjects. Perseveration can therefore be considered a productive sign of schizophrenia and is plausibly linked to dopaminergic activity at the striatal level.

An information-processing model developed by Shallice (1988) attributes perseveration to the failure of a higher level executive control system to modulate a lower level routine action system under a requirement for novel response generation. This model suggests that behavioral perseveration occurs as a consequence of a failure of frontal specification of striatal outputs during capacity-demanding tasks. In this analysis, the absence of frontal specification permits the continued reselection of a previously activated but task-inappropriate response schema at the striatal level.

References

Addington, J.; Addington, D.; and Maticka-Tyndale, E. Cognitive functioning and positive and negative symp-

toms in schizophrenia. *Schizophrenia Research*, 5:123–134, 1991.

Alexander, G.E., and Crutcher, M.D. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. *Trends in Neurosciences*, 13:266–271, 1990.

Alexander, G.E.; DeLong, M.R.; and Strick, P.L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, 9:357–381, 1986.

Andreasen, N.C. Thought, language, and communication disorders: I. Clinical assessment, definition of terms, and evaluation of their reliability. *Archives of General Psychiatry*, 36:1315–1321, 1979*a*.

Andreasen, N.C. Thought, language, and communication disorders: II. Diagnostic significance. *Archives of General Psychiatry*, 36:1325–1330, 1979*b*.

Andreasen, N.C.; Arndt, S.; Alliger, R.; Miller, D.; and Flaum, M. Symptoms of schizophrenia: Methods, meanings, and mechanisms. *Archives of General Psychiatry*, 52:341–351, 1995.

Andreasen, N.C.; Rezai, K.; Alliger, R.; Swayze, V.W. II; Flaum, M.; Kirchner, P.; Cohen, G.; and O'Leary, D.S. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Archives of General Psychiatry*, 49:943–958, 1992.

Anscombe, R. The disorder of consciousness in schizophrenia. *Schizophrenia Bulletin*, 13(2):241–260, 1987.

Barr, W.B.; Bilder, R.M.; Goldberg, E.; Kaplan, E.; and Mukherjee, S. The neuropsychology of schizophrenic speech. *Journal of Communication Disorders*, 22:327–349, 1989.

Baxter, L.R.; Schwartz, J.M.; Bergman, K.S.; Szuba, M.P.; Guze, B.H.; Mazziotta, J.C.; Alazraki, A.; Selin, C.E.; Ferng, H.K.; Munford, P.; and Phelps, M.E. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Archives of General Psychiatry*, 49:681–689, 1992.

Bender, L. A visual motorgestalt test and its clinical use. *American Orthopsychiatric Association Research Monographs*, Vol. 3, 1938.

Berman, K.F.; Zec, R.F.; and Weinberger, D.R. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: II. Role of neuroleptic treatment, attention, and mental effort. *Archives of General Psychiatry*, 43:126–135, 1986.

Bilder, R.M., and Goldberg, E. Motor perseverations in schizophrenia. *Archives of Clinical Neuropsychology*, 2:195–214, 1987.

Bilder, R.M.; Lieberman, J.A.; Kim, Y.; Alvir, J.M.; and Reiter, G. Methylphenidate and neuroleptic effects on oral word production in schizophrenia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 5:262–271, 1992.

Bleuler, E. *Dementia Praecox or the Group of Schizophrenias*. (1911) Translated by J. Zinkin. New York, NY: International Universities Press, 1950.

Braff, D.L.; Heaton, R.; Kuck, J.; Cullum, M.; Moranville, J.; Grant, I.; and Zisook, S. The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. *Archives of General Psychiatry*, 48:891–898, 1991.

Buchanan, R.W.; Strauss, M.E.; Kirkpatrick, B.; Holstein, C.; Breier, A.; and Carpenter, W.T., Jr. Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. *Archives of General Psychiatry*, 51:804–811, 1994.

Buchsbaum, M.S.; Haier, R.J.; Potkin, S.G.; Nuechterlein, K.; Bracha, H.S.; Katz, M.; Lohr, J.; Wu, J.; Lottenberg, S.; Jerabek, P.A.; Trenary, M.; Tafalla, R.; Reynolds, C.; and Bunney, W.E. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. *Archives of General Psychiatry*, 49:935–942, 1992.

Buchsbaum, M.S.; Nuechterlein, K.H.; Haier, R.J.; Wu, J.; Sicotte, N.; Hazlett, E.; Asarnow, R.; Potkin, S.; and Guich, S. Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. *British Journal of Psychiatry*, 156:216–227, 1990.

Carlsson, M., and Carlsson, A. Schizophrenia: A subcortical neurotransmitter imbalance syndrome? *Schizophrenia Bulletin*, 16(3):425–432, 1990.

Chaika, E. A unified explanation for the diverse structural deviations reported for adult schizophrenics with disrupted speech. *Journal of Communication Disorders*, 15:167–189, 1982.

Cohen, R.M.; Semple, W.E.; Gross, M.; Nordahl, T.E.; DeLisi, L.E.; Holcomb, H.H.; King, A.C.; Morihisa, J.M.; and Pickar, D. Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 40:2031–2039, 1987.

Cooper, S.J., and Dourish, C.T. An introduction to the concept of stereotypy and a historical perspective on the role of brain dopamine. In: Cooper, S.J., and Dourish, C.T., eds. *The Neurobiology of Stereotyped Behaviour*. Oxford, England: Clarendon Press, 1990. pp. 1–24.

Crider, A. Motor disturbances in schizophrenia. *Behavioral and Brain Sciences*, 14:22–23, 1991.

Crider, A.; Blockel, L.; and Solomon, P.R. A selective attention deficit in the rat following induced dopamine receptor supersensitivity. *Behavioral Neuroscience,* 100:315–319, 1986.

Crumpton, E. Persistence of maladaptive responses in schizophrenia. *Journal of Abnormal and Social Psychology,* 66:615–618, 1963.

Cutting, J.C. *The Psychology of Schizophrenia.* Edinburgh, Scotland: Churchill Livingstone, 1985.

Davis, K.L.; Kahn, R.S.; Ko, G.; and Davidson, M. Dopamine in schizophrenia: A review and reconceptualization. *American Journal of Psychiatry,* 148:1474–1486, 1991.

Deutch, A.Y.; Bourdelais, A.J.; and Zahn, D.S. The nucleus accumbens core and shell: Accumbal compartments and their functional attributes. In: Kalivas, P.W., and Barnes, C.D., eds. *Limbic Motor Circuits and Neuropsychiatry.* Boca Raton, FL: CRC Press, 1993. pp. 45–88.

Early, T.S.; Haller, J.W.; Posner, M.I.; and Raichle, M. The left striato-pallidal hyperactivity model of schizophrenia. In: David, A.S., and Cutting, J.C., eds. *The Neuropsychology of Schizophrenia,* Hillsdale, NJ: LEA Publishers, 1994. pp. 15–37.

Evenden, J.L., and Robbins, T.W. Increased response switching, perseveration and perseverative switching following *d*-amphetamine in the rat. *Psychopharmacology,* 80:67–73, 1983.

Fairbanks, H. The quantitative differentiation of samples of spoken language. *Psychological Monographs,* 56:19–38, 1944.

Feldstein, S., and Jaffe, J. Vocabulary diversity of schizophrenics and normals. *Journal of Speech and Hearing Research,* 5:76–78, 1962.

Fey, E.T. The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Test. *Journal of Consulting and Clinical Psychology,* 15:311–319, 1951.

Freeman, T., and Gathercole, C.E. Perseveration—the clinical symptoms—in chronic schizophrenia and organic dementia. *British Journal of Psychiatry,* 112:27–32, 1966.

Friedman, L.; Kenny, J.T.; Jesberger, J.A.; Choy, M.M.; and Meltzer, H. Relationship between smooth pursuit eye-tracking and cognitive performance in schizophrenia. *Biological Psychiatry,* 37:265–272, 1995.

Frith, C.D. *The Cognitive Neuropsychology of Schizophrenia.* Hillsdale, NJ: Lawrence Erlbaum Associates, 1992.

Frith, C.D., and Done, D.J. Stereotyped responding by schizophrenic patients on a two-choice guessing task. *Psychological Medicine,* 13:779–786, 1983.

Frith, C.D., and Done, D.J. Stereotyped behavior in madness and in health. In: Cooper, S.J., and Dourish, C.T., eds. *The Neurobiology of Stereotyped Behaviour.* Oxford, England: Clarendon Press, 1990. pp. 232–259.

Fuster, J.M. *The Prefrontal Cortex.* 2nd ed. New York, NY: Raven Press, 1989.

Gerfen, C.R. The neostriatal mosaic: Multiple levels of compartmental organization in the basal ganglia. *Annual Review of Neuroscience,* 15:285–320, 1992.

Goldberg, E. Varieties of perseveration: A comparison of two taxonomies. *Journal of Clinical and Experimental Neuropsychology,* 8:710–726, 1986.

Grace, A.A. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. *Neuroscience,* 41:1–24, 1991.

Gray, J.A.; Feldon, J.; Rawlins, J.N.P.; Hemsley, D.R.; and Smith, A.D. The neuropsychology of schizophrenia. *Behavioral and Brain Sciences,* 14:1–84, 1991.

Hammer, M., and Salzinger, K. Some formal characteristics of schizophrenic speech as a measure of social deviance. *Annals of the New York Academy of Sciences,* 105:861–889, 1964.

Heaton, R.K. *A Manual for the Wisconsin Card Sorting Test.* Odessa, FL: Psychological Assessment Resources, 1981.

Heinrichs, D.W., and Buchanan, R.W. Significance and meaning of neurological signs in schizophrenia. *American Journal of Psychiatry,* 145:11–18, 1988.

Heritch, A.J. Evidence for reduced and dysregulated turnover of dopamine in schizophrenia. *Schizophrenia Bulletin,* 16(4):605–615, 1990.

Jernigan, T.L.; Sargent, T.; Pfefferbaum, A.; Kusubov, N.; and Stahl, S.M. ^{18}Fluorodeoxyglucose PET in schizophrenia. *Psychiatry Research,* 16:317–329, 1985.

Katsanis, J., and Iacono, W.G. Clinical, neuropsychological, and brain structural correlates of smooth-pursuit eye tracking performance in chronic schizophrenia. *Journal of Abnormal Psychology,* 100:526–534, 1991.

Koek, W., and Slangen, J.L. Effects of *d*-amphetamine and morphine on discrimination: Signal detection analysis and assessment of response repetition in the performance deficits. *Psychopharmacology,* 80:125–128, 1983.

Lewis, S.W.; Ford, R.A.; Syed, G.M.; Reveley, A.M.; and Toone, B.K. A controlled study of ^{99m}Tc-HMPAO single-photon emission imaging in chronic schizophrenia. *Psychological Medicine,* 22:27–35, 1992.

Liddle, P.F. The symptoms of chronic schizophrenia: A reexamination of the positive-negative dichotomy. *British*

Journal of Psychiatry, 151:145–151, 1987.

Liddle, P.F., and Morris, D.L. Schizophrenic syndromes and frontal lobe performance. *British Journal of Psychiatry,* 158:340–345, 1991.

Litman, R.E.; Hommer, D.W.; Clem, T.; Ornsteen, M.L.; Ollo, C.; and Pickar, D. Correlation of Wisconsin Card Sorting Test performance with eye tracking in schizophrenia. *American Journal of Psychiatry,* 148:1580–1582, 1991.

Lorenz, M., and Cobb, S. Language patterns in psychotic and psychoneurotic subjects. *Archives of Neurology and Psychiatry,* 72:665–673, 1954.

Luria, A.R. *Higher Cortical Functions in Man.* New York, NY: Basic Books, 1980.

Lyon, N., and Gerlach, J. Perseverative structuring of responses by schizophrenic and affective disorder patients. *Journal of Psychiatric Research,* 22:261–277, 1988.

Lyon, N.; Mejsholm, B.; and Lyon, M. Stereotyped responding by schizophrenic outpatients: Cross-cultural confirmation of perseverative switching on a two-choice task. *Journal of Psychiatric Research,* 20:137–150, 1986.

Maher, B.A. A tentative theory of schizophrenic utterance. In: Maher, B.A., and Maher, W.B., eds. *Progress in Experimental Personality Research.* Vol. 12. New York, NY: Academic Press, 1983. pp. 1–52.

Maher, B.A., and Spitzer, M. Thought disorders and language behavior in schizophrenia. In: Blanken, G.; Dittmann, J.; Grimm, H.; Marshall, J.C.; and Wallesch, C.-W., eds. *Linguistic Disorders and Pathologies.* Berlin, Germany: Walter de Gruyter, 1993. pp. 522–533.

Manschreck, T.C. Motor abnormalities in schizophrenia. In: Nasrallah, H.A., and Weinberger, D.R., eds. *Handbook of Schizophrenia.* Vol. I. New York, NY: Elsevier Science Publishers, 1986. pp. 65–96.

Manschreck, T.C. Psychomotor abnormalities. In: Costello, C.G., ed. *Symptoms of Schizophrenia.* New York, NY: John Wiley & Sons, 1993. pp. 261–290.

Manschreck, T.C.; Maher, B.A.; and Ader, D.N. Formal thought disorder, the type-token ratio, and disturbed voluntary motor movement in schizophrenia. *British Journal of Psychiatry,* 139:7–15, 1981.

Manschreck, T.C.; Maher, B.A.; Hoover, T.M.; and Ames, D. The type-token ratio in schizophrenic disorders: Clinical and research value. *Psychological Medicine,* 14:151–157, 1984.

Manschreck, T.C.; Maher, B.A.; Hoover, T.M.; and Ames, D. Repetition in schizophrenic speech. *Language and Speech,* 28:255–268, 1985.

Manschreck, T.C.; Maher, B.A.; Rucklos, M.E.; and Vereen, D.R. Disturbed voluntary motor activity in schizophrenic disorder. *Psychological Medicine,* 12:73–84, 1982.

McGrath, J. Ordering thoughts on thought disorder. *British Journal of Psychiatry,* 158:307–316, 1991.

McKenna, P.J. Basal ganglia dysfunction in schizophrenia? In: Franks, A.J.; Ironside, J.W.; Mindham, R.H.S.; Smith, R.J.; Spokes, E.G.S.; and Winlow, W., eds. *Function and Dysfunction in the Basal Ganglia.* Manchester, England: Manchester University Press, 1990. pp. 247–255.

Modell, J.; Mountz, J.; Curtis, G.; and Greden, J. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. *Journal of Neuropsychiatry,* 1:27–36, 1989.

Morrison-Stewart, S.L.; Williamson, P.C.; Corning, W.C.; Kutcher, S.P.; Snow, W.G.; and Merskey, H. Frontal and non-frontal lobe neuropsychological test performance and clinical symptomatology in schizophrenia. *Psychological Medicine,* 22:353–359, 1992.

Nauta, W.J.H., and Domesick, V.B. Afferent and efferent relationships of the basal ganglia. In: Evered, D., and O'Connor, M., eds. *Functions of the Basal Ganglia.* London, England: Pitman, 1984. pp. 3–22.

Nolan, J. A within-subjects analysis of discrimination shift behavior in schizophrenics. *Journal of Abnormal Psychology,* 83:497–511, 1974.

Nuechterlein, K.H., and Dawson, M.E. Information processing and attentional functioning in the developmental course of schizophrenic disorders. *Schizophrenia Bulletin,* 10(2):160–203, 1984.

Pantelis, C., and Nelson, H.E. Cognitive functioning and symptomatology in schizophrenia: The role of frontal-subcortical systems. In: David, A.S., and Cutting, J.C., eds. *The Neuropsychology of Schizophrenia.* Hillsdale, NJ: LEA Publishers, 1994. pp. 215–229.

Pedro, B.M.; Pilowsky, L.S.; Costa, D.C.; Hemsley, D.R.; Ell, P.J.; Verhoeff, N.P.; Kerwin, R.W.; and Gray, N.S. Stereotypy, schizophrenia and dopamine D_2 receptor binding in the basal ganglia. *Psychological Medicine,* 24: 423–429, 1994.

Penney, J.B., and Young, A.B. Speculations on the functional anatomy of basal ganglia disorders. *Annual Review of Neuroscience,* 6:73–94, 1983.

Raine, A.; Lencz, T.; Reynolds, G.P.; Harrison, G.; Sheard, C.; Medley, I.; Reynolds, L.; and Cooper, J.C. An evaluation of structural and functional prefrontal deficits

in schizophrenia: MRI and neuropsychological measures. *Psychiatry Research: Neuroimaging,* 45:123–137, 1992.

Ridley, R.M.; Baker, H.F.; Frith, C.D.; Dowdy, J.; and Crow, T.J. Stereotyped responding on a two-choice guessing task by marmosets and humans treated with amphetamine. *Psychopharmacology,* 95:560–564, 1988.

Ridley, R.M.; Baker, H.F.; and Haystead, T.A.J. Perseverative behaviour after amphetamine: Dissociation of response tendency from reward association. *Psychopharmacology,* 75:283–286, 1981*a*.

Ridley, R.M.; Clark, B.A.; Durnford, L.J.; and Baker, H.F. Stimulus-bound perseveration after frontal ablations in marmosets. *Neuroscience,* 52:595–604, 1993.

Ridley, R.M.; Haystead, T.A.J.; and Baker, H.F. An analysis of visual object reversal learning in the marmoset after amphetamine and haloperidol. *Pharmacology, Biochemistry and Behavior,* 14:345–351, 1981*b*.

Robbins, T.W. The case for frontostriatal dysfunction in schizophrenia. *Schizophrenia Bulletin,* 16(3):391–402, 1990.

Robbins, T.W. Cognitive deficits in schizophrenia and Parkinson's disease: Neural basis and the role of dopamine. In: Willner, P., and Scheel-Krüger, J., eds. *The Mesolimbic Dopamine System: From Motivation to Action.* Chichester, England: John Wiley & Sons, 1991. pp. 497–528.

Robbins, T.W.; Mittleman, G.; O'Brien, J.; and Winn, P. The neuropsychological significance of stereotypy induced by stimulant drugs. In: Cooper, S.J., and Dourish, C.T., eds. *The Neurobiology of Stereotyped Behaviour.* Oxford, England: Clarendon Press, 1990. pp. 25–63.

Robbins, T.W., and Sahakian, B.J. Behavioral effects of psychomotor stimulant drugs: Clinical and neuropsychological implications. In: Creese, I., ed. *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives.* New York, NY: Raven Press, 1983. pp. 301–338.

Rogers, D. The motor disorders of severe psychiatric illness: A conflict of paradigms. *British Journal of Psychiatry,* 147:221–232, 1985.

Rosse, R.B.; Schwartz, B.L.; Kim, S.Y.; and Deutsch, S.I. Correlation between antisaccade and Wisconsin Card Sorting Test performance in schizophrenia. *American Journal of Psychiatry,* 150:333–335, 1993.

Rubin, P.; Holm, S.; Madsen, P.L.; Friberg, L.; Videbech, P.; Andersen, H.S.; Bendsen, B.B.; Strømsø, N.; Larsen, J.K.; Lassen, N.A.; and Hemmingsen, R. Regional cerebral blood flow distribution in newly diagnosed schizophrenia and schizophreniform disorder. *Psychiatry Research,* 53:57–75, 1994.

Sahgal, A., and Clincke, G.H.C. A comparison of different methods of assessing patterns of responding in discrete trial choice procedures. *Psychopharmacology,* 87:374–377, 1985.

Salzinger, K.; Portnoy, S.; and Feldman, R. Verbal behavior of schizophrenic and normal subjects. *Annals of the New York Academy of Sciences,* 105:845–860, 1964.

Sandson, J., and Albert, M.L. Varieties of perseveration. *Neuropsychologia,* 22:715–732, 1984.

Schröder, J.; Niethammer, R.; Geider, F.-J.; Reitz, C.; Binkert, M.; Jauss, M.; and Sauer, H. Neurological soft signs in schizophrenia. *Schizophrenia Research,* 6:25–30, 1992.

Segal, D.S., and Geyer, M.A. Animal models of psychopathology. In: Judd, L.L., and Groves, P.M., eds. *Psychobiological Foundations of Clinical Psychiatry.* Philadelphia, PA: Lippincott, 1985. pp. 1–21.

Serper, M.R., and Harvey, P.D. The need to integrate neuropsychological and experimental schizophrenia research. *Schizophrenia Bulletin,* 20(1):1–11, 1994.

Seth, G., and Beloff, H. Language impairment in a group of schizophrenics. *British Journal of Medical Psychology,* 32:288–293, 1959.

Shallice, T. *From Neuropsychology to Mental Structure.* Cambridge, England: Cambridge University Press, 1988.

Shallice, T., and Burgess, P. Higher-order cognitive impairments and frontal lobe lesions in man. In: Levin, H.S.; Eisenberg, H.M.; and Benton, A.L., eds. *Frontal Lobe Function and Dysfunction.* New York, NY: Oxford University Press, 1991. pp. 125–138.

Stevens, J.R. The search for an anatomic basis of schizophrenia: Review and update. In: Mueller, J., ed. *Neurology and Psychiatry: A Meeting of Minds.* Basel, Switzerland: Karger, 1989. pp. 64–87.

Swerdlow, N.R., and Koob, G.F. Dopamine, schizophrenia, mania, and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behavioral and Brain Sciences,* 10:197–245, 1987.

Walker, E.F. Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophrenia Bulletin,* 20(3):453–480, 1994.

Weinberger, D.R.; Berman, K.F.; and Illowsky, B.P. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. *Archives of General Psychiatry,* 45:609–615, 1988.

Weinberger, D.R.; Berman, K.F.; and Zec, R.F. Physiologic dysfunction of dorsolateral prefrontal cortex in

schizophrenia: I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, 43:114–124, 1986.

Wolkin, A.; Sanfilipo, M.; Wolf, A.P.; Angrist, B.; Brodie, J.D.; and Rotrosen, J. Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry*, 49:959–965, 1992.

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Announcement of Available Research Funds

The Theodore and Vada Stanley Foundation, in collaboration with the National Alliance for the Mentally Ill, welcomes applications for the 1997 Stanley Foundation Research Awards Program. The purpose of the awards is to support research directly related to the causes or treatment of schizophrenia and bipolar disorder. The research awards are intended to attract established scientists from other areas of biology and medicine (e.g., biochemistry, immunology, virology, and neurology) into research on schizophrenia and bipolar disorders as well as to provide support for innovative research by scientists already in the field whose funding sources are limited. Applicants are invited from all stages of career development. Awards are for 1 or 2 years. They may be up to $75,000 per year for studies involving human subjects and up to $50,000 per year for other studies. Funds may be used for salaries, supplies, and equipment, but it is the policy of the Stanley Foundation not to pay indirect costs for administration of the award. In 1996, 50 applications were funded out of a total of 253 received.

The deadline for receipt of applications is March 1, 1997. The four-page application consists of a brief outline of the proposed project, a budget, and a list of current and pending sources of funding. Notification of awards is made in May and funding to award recipients begins in August. The research award applications are reviewed by a professional selection committee.

Requests for applications and questions should be directed to:

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