Disconnection and Cognitive Dysmetria in Schizophrenia

This editorial takes a perspective on this issue's articles afforded by theories of inference and learning in the brain. It starts with a brief précis of the disconnection hypothesis and ensuing cognitive dysmetria, given recent developments in theoretical and computational neurobiology. (Dysmetria is defined as "conditions where there is improper measuring of distances required for muscular acts" by the University of Connecticut Health Center Research Computing Support [http://penguin.uchc.edu/~cns/CNScases/Definitions/dysmetria.htm].) We will then review some major findings of the four articles, in light of these theoretical considerations.

Disconnection and Dysmetria

Let us assume, without taking ourselves too seriously, that schizophrenia is caused fairly late in neurodevelopment by a misspecified gene product (1). Now, assume that this product is necessary for molecular signaling or interactions between subunits of the *N*-methyl-D-aspartic acid (NMDA) receptor and one or more receptor subtypes that mediate cholinergic and dopaminergic neurotransmission (e.g., reference 2). How might this be expressed phenotypically? The NMDA receptor has a central role in activity or experience-dependent plasticity. However, our genetic abnormality does not affect NMDA-receptor function directly, only its modulation by cholinergic or dopaminergic neurotransmission. What is the functional importance of this modulation? Theoretical neurobiology offers two answers. The first and more established comes from theoretical models of reinforcement learning (e.g., temporal difference models and dynamic programming). The second derives from ideas about how the brain encodes uncertainty about its perceptual constructs. Critically, both posit a central role for acetylcholine and dopamine in enabling changes in synaptic efficacy. In reinforcement, or emotional learning, the notion is that dopamine encodes predicted reward and can be used to consolidate synapses mediating stimulus-response links of high value (e.g., reference 3). The second set of ideas deals with perceptual learning and suggests that acetylcholine encodes uncertainty about perceptual inferences (4). Mathematical treatments of perceptual learning (4, 5) confirm the intuition that associative plasticity should be greater when conditional certainty is high.

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In short, normal interactions between dopamine and the cellular or synaptic mechanisms responsible for plasticity are essential for emotional learning, whereas the interaction between cholinergic neurotransmission and associative plasticity is important for perceptual learning. See also Barch (6), who considers working memory from a pharmacological perspective and concludes, "compounds geared towards enhancing the dopamine system and the acetylcholine system remain promising avenues for the development of pro-cognitive drugs."

The hypothetical genetic abnormality mentioned is special because it targets experience-dependent plasticity induced by emotional and perceptual learning. This means it is a genetic abnormality that can only be expressed through the phenotype's interac-

tion with the world. This fits comfortably with the stress-diathesis model of schizophrenia. If schizophrenics were unlucky enough to encounter situations that called for emotional or perceptual (re)learning (e.g., life events or a researcher with a perceptual learning paradigm), they would be compromised. This would be expressed, at a synaptic level, as abnormal connectivity leading to a disintegration of neuronal dynamics underlying response selection and perception. This is the disconnection hypothesis (7). The ensuing functional consequences would be expressed as an inability to form new stimulus-response links (impaired emotional learning) or stimulus-stimulus links (impaired perceptual learning). In terms of cognition, this could be expressed as cognitive dysmetria (8) and, at lower levels, a disruption of perceptual learning and inference (i.e., perceptual dysmetria). With this theoretical framework in place, we can now preview the main findings in this issue's articles.

Abnormal Perceptual Learning and Acetylcholine

A compelling and explicit example of abnormal perceptual learning is provided by Louchart de la Chapelle et al. (in this issue). The authors examined three electrophysiological measurements of inhibitory deficits in schizophrenia. They conclude that P50 inhibition and antisaccade error rate were the optimal paradigms to discriminate between comparison subjects, first-degree relatives, and schizophrenia patients. The P50 is an evoked electrical response component elicited by a stimulus. In the inhibition paradigm, auditory stimuli are paired so that subjects learn the temporal stimulus-stimulus association and suppress the P50 elicited by a second tone. The degree of suppression can be regarded as a measure of sensory or perceptual learning that was reduced in the schizophrenic cohort. This is consistent with theoretical predictions and relates closely to similar findings in schizophrenia with the mismatch negativity in the auditory oddball paradigm (e.g., reference 9). The mismatch negativity is a potentially important paradigm for schizophrenia research because its expression can be linked directly to NMDA receptor function. Louchart de la Chapelle et al. note that animal and human studies have suggested a role for the septohippocampal cholinergic system in sensory gating mechanisms that underlie P50 inhibition. Furthermore, a linkage between P50-inhibition deficits and a genetic marker at the locus of the α-7 subunit of the nicotinic receptor has been reported in families of patients with schizophrenia. Moreover, several studies have reported that promoter variance in the α-7 or α-7-like gene is associated with P50-inhibition deficits. This ties in nicely with a putative role for acetylcholine in perceptual learning.

Another example of abnormal perceptual learning is provided in the study by MacDonald et al. (in this issue) who report on a functional magnetic resonance imaging (fMRI) study of context processing with a continuous performance task. One of their key results was that schizophrenic patients failed to use contextual cues to inhibit their prepotent response to a target. This behavioral deficit was associated with a failure to activate the middle frontal gyrus (Brodmann's area 9) relative to comparison subjects. These results suggest abnormal perceptual learning in this instance of a contextual cue. The implications of this study go beyond perceptual learning and speak to abnormalities of contextual processing and response selection in schizophrenia. However, underlying these neurophysiological and behavioral observations is a failure of patients to learn and represent a behaviorally relevant percept.

The results reported in Symond et al. (in this issue) do not speak directly to perceptual learning deficits but do suggest a disintegration of fast dynamic signaling in early perceptual processing. Symond et al. used an auditory oddball paradigm in which subjects were required to respond to the oddballs. By measuring the phase synchronization in the gamma range as a function of peristimulus time, they were able to show that schizophrenics exhibited an early deficit (around 100 msec). Of interest, this is about the same time that abnormalities in the mismatch negativity have been noted in schizophrenia.

Why would a failure of perceptual learning result in loss of phase synchronization? The answer lies in an appreciation of the role of recurrent dynamics in sensory processing. Many theories consider the sensory cortex a hierarchically organized inference device (5). A current example of this is predictive coding in visual processing (10). Predictive coding rests upon reciprocal interactions among hierarchical levels in which top-down predictions try to suppress or cancel prediction error. This suppression is driven by bottom-up signals encoding the errors. The ensuing architecture comprises reentrant loops that provide an infrastructure for fast oscillatory dynamics. Predictive coding rests upon the inhibition of neurons encoding prediction error by afferents from high-level pyramidal cells. This is consistent with the discussion in Symond et al. of depth recording evidence, which suggests long-range synchrony results from the synchronization of γ-aminobutyric acid (GABA)-ergic interneurons and pyramidal cells. They note that schizophrenic patients show a selective decrease in the axon terminal density of GABA-ergic chandelier neurons, which synapse exclusively with pyramidal cells.

It should be noted that there is nothing specific in this argument about the particular stimuli analyzed in Symond et al. Indeed, one might suppose that similar phenomena would be observed for any induced synchronization. Furthermore, Figure 1 in Symond et al. suggests that subjects with schizophrenia show a reduction in synchrony even before the stimulus is presented.

Abnormal Stimulus-Response Learning and Dopamine

Perhaps the clearest evidence for abnormal stimulus-response learning in this issue is presented in Louchart de la Chapelle et al. In addition to showing a P50-inhibition deficit in schizophrenia, the authors also demonstrate high error rates with an antisaccade paradigm. In an antisaccade paradigm, the subject is asked to saccade away from a visual cue. Schizophrenic subjects have difficulty learning this new stimulus-response contingency and tend to saccade toward the cue. In short, they fail to learn and persevere with their prepotent response. In the theoretical treatment we presented, we supposed that dopamine-NMDA interactions are responsible for stimulus-response learning, whereas acetylcholine enables perceptual learning of stimulus-stimulus configurations. Of interest, Louchart de la Chapelle et al. found that despite superficial similarities, there was little evidence that the P50 inhibition (stimulus-stimulus) and antisaccade (stimulus-response) paradigms had similar neurobiological substrates. Specifically, P50 inhibition showed no correlation with the antisaccade measurements. Of interest, the authors note there is evidence that eye-tracking dysfunction is associated with a dopamine D_3 receptor gene polymorphism. As noted by Fu et al. (in this issue), acute psychosis in schizophrenia, but not remission, is associated with increased phasic dopamine release. The authors speculate that the differential activation in prefrontal regions in patients with active psychotic symptoms relative to remitted patients in their fMRI study of verbal fluency may be related to state-related perturbation of central dopaminergic function.

Conclusions

In summary, much of the work presented in this issue speaks to a dysmetria of cognitive and perceptual processing that would be a natural consequence of functional disconnections expressed at a synaptic level in the context of new learning. The mechanisms afforded by theoretical considerations of normal brain function go quite a long way toward explaining some of the empirical observations presented in this issue. Specifically, they point to an interaction between cholinergic neurotransmission and synaptic plasticity in perceptual learning and between dopamine and plasticity in reinforcement learning.

After completing this editorial, I was struck by the convergence among the four articles from groups with established, but distinct, expertise. This must be a good thing for patients and clinical researchers alike.

References

1. Harrison PJ, Weinberger DR: Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 2005; 10:40–68
2. Wirkner K, Krause T, Koles L, Thummler S, Al-Khrasani M, Illes P: D1 but not D2 dopamine receptors or adrenoceptors mediate dopamine-induced potentiation of *N*-methyl-D-aspartate currents in the rat prefrontal cortex. Neurosci Lett 2004; 372:89–93
3. Fiorillo CD, Tobler PN, Schultz W: Discrete coding of reward probability and uncertainty by dopamine neurons. Science 2003; 299:1898–1902
4. Yu AJ, Dayan P: Acetylcholine in cortical inference. Neural Netw 2002; 15:719–730
5. Friston KJ: Functional integration and inference in the brain. Prog Neurobiol 2002; 68:113–143
6. Barch DM: Pharmacological manipulation of human working memory. Psychopharmacology (Berl) 2004; 174:126–135
7. Friston KJ: The disconnection hypothesis. Schizophr Res 1998; 30:115–125
8. Andreasen NC, Paradiso S, O'Leary DS: "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 1998; 24:203–218
9. Baldeweg T, Klugman A, Gruzelier JH, Hirsch SR: Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. Int J Psychophysiol 2002; 43:111–122
10. Rao RP, Ballard DH: Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. Nat Neurosci 1999; 2:79–87

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