Context, connection and co-ordination: the need to switch

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Commentary on Phillips and Silverstein
"Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia"

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Abstract

'Context, connection and co-ordination' (CCC) describe well where the problems that apply to thought disordered patients with schizophrenia lie. But they may be part of the experience of those with other symptom constellations. Switching is an important mechanism to allow context to be applied appropriately to changing circumstances. In some cases NMDA voltage modulations may be central, but gain and shift are also functions that monoaminergic systems express in CCC.

Commentary

"An apple falls not far from the tree." So runs a proverb familiar to many, particularly if living in Germany. If in doubt about a diagnosis of schizophrenia, it can be helpful to ask the patient for an explanation of such a proverb. Especially, but not only, persons with a disorganized form of schizophrenia experience difficulties that may range from a shrug to profuse, tangential explanations (Straube and Oades, 1992). It is reasonable, and in line with the thesis of P & S, to describe such problems in terms of context, connection and co-ordination (CCC).

Conditioned blocking places an aspect of CCC in to a laboratory setting. Normal persons experience a temporary problem with learning about the associations of a stimulus component (B) that has just become part of a stimulus complex AB, where one has already started to learn about A. Persons with negative schizophrenic or schizotypal symptoms learn about B quicker! (Oades et al. 1996; Bender et al., 2001, Moran et al 2003). The normal interaction of events, whereby conditioning to B is blocked by conditioning to A, is reduced in these patients. This example illustrates the contention of Hemsley et al (1993, cit. p. 4) that such patients have difficulties in selecting current responses on the basis of stored regularities. This view is assimilated in the thesis advanced by P & S here.

A change of context requires a change of co-ordination to effect a switch between the appropriate connections in order to mediate an adaptive response. A problem for the viewpoint of P & S lies with the nature of the systems mediating the switches. In the case of conditioned blocking mesocortical dopamine systems control the expression of the blocking effect (Oades et al. 1987). A parsimonious interpretation of the role of dopamine is that it facilitates switching between channels within the innervated region that controls the output that determines response (Oades 1985). Too little dopamine reduces the probability of

change (perseveration, inhibit set-shift, Coull 1998), while too much jams the system (e.g. stereotypy).

However, neuroimaging studies repeatedly find marked activity related to switching elsewhere; for example, in part of the left or right intra-parietal sulcus during covert or overt reversal-like shifts of attention (Beauchamp et al. 2001; Dove et al. 2000; Gurd et al. 2002). This region is not known to receive a major dopamine innervation. Indeed these very reports also noted another patch of activity much further forward in the inferior frontal gyrus, close to one of the frontal generators of mismatch negativity (MMN: Jemel et al. 2002). The MMN is an event-related potential that has been postulated to demonstrate an involuntary switching mechanism (Näätänen 1990) and is repeatedly referred to by P & S. (I may add that we have looked for associations of MMN with peripheral measures of dopamine metabolism in healthy and schizophrenic subjects in vain [unpublished data] and haloperidol is without effect on MMN [Kähkönen et al. 2002]).

These parietal and frontal loci of course depend much on glutamatergic and perhaps voltage-dependent NMDA channels for the expression of their functions, even though the basis of the mechanism for a switch remains a subject for speculation. Certainly local GABA mechanisms may inhibit/disinhibit local input and output, and some of these local circuits interacting with glutamate and dopamine are known to be dysfunctional in schizophrenia (Benes 2000). But is it a hyper- or a hypo-active state that in these loci disrupts the glutamatergic contribution to switching in attention-related thought disorder (Shim 2002)? In the exchange of communications referred to the question revolves around whether the inhibition of the psychiatric effects of ketamine by lamotrigine and the attenuation of glutamate release reflects downstream or upstream effects of the drug (or neither). In addition the question is raised whether ketamine (as a model for the induction of psychosis) induces a hyper-glutamatergic state (Shim) or in fact the blockade of the NMDA site induces a hypofunctional receptor that should represent the target of therapy in schizophrenia (Olney).

A further complication is that one of the mainstays of P & S's thesis, the ketamine and PCP models for inducing psychotic features, is insecure. The affinities of ketamine and PCP for NMDA sites is astonishingly similar to the affinity for dopamine D2 and serotonergic 5-HT2 sites, respectively (Kapur and Seeman 2002). The potentially non-selective effects of these substances in eliciting psychotic phenomena are disturbing for the neatly specific voltage-dependent effect that forms the basis of P & S hypothesis. Indeed we believe that the report in Section 3 from Umbricht et al. (2002) cited to support the ketamine-glutamate model is better viewed in these terms. The reported relationship between psychotic-like effects of ketamine and a small MMN was based more on scores from a less-widely rather than the more commonly-used rating scale, and the effect noted was but marginally more than that achieved with a serotonergic hallucinogenic agonist psilocybin.

Finally this raises the relationship of saliency and serotonin activity, where again part of the argument of P & S relies on MMN studies. In the context of MMN and change detection care must be exerted in assuming that the saliency of a stimulus, another mainstay of the disruption of context perception in the hypothesis of P & S, is crucial to change detection in schizophrenia. While the authors relate reduced MMN to the poor

ability to discriminate tone frequencies (Javitt et al. 2000: section 4.2), MMN is relatively insensitive to the loudness and length of the tone (Michie 2001). Further both Javitt and we (Oades et al. 1993) noted the strong association of MMN reduction with negative symptoms. This is not immediately consistent with the emphasis of P & S on thought-disorder. The activity of serotonin, a transmitter that mediates gain-like effects in stimulus-processing (Reuter et al. 1997), naturally affects stimulus salience in perception (Winter et al. 1999), stimulus context in learning (latent inhibition, McDonald et al. 2003), MMN (Ahveninen et al. 2002) and is anomalous in schizophrenia character-ised by paranoid (Angelopoulos et al 2002), disorganized (Oades et al. 2000) and negative symptoms (Jockers-Scherubl et al 2001).

Windfalls may make a great apple pie, be poison for Dr Spock or represent youth following in the footsteps of their elders. It remains difficult, *a priori*, to determine which of these (or other) circumstances, that require switches between stored regularities for an appropriate response, depends on glutamatergic or monoaminergic mechanisms. P & S, to their credit recognise this and call for refinements in our understanding about monoaminergic-glutamatergic interactions in CCC.

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Footnote 1: Dr. Oknina is on leave from the Institute of Higher Nervous Activity and Neurophysiology, Moscow.

Target article abstract

Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia

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Abstract

The concept of locally specialized functions dominates research on higher brain function and its disorders. Locally specialized functions must be complemented by processes that coordinate those functions, however, and impairment of coordinating processes may be central to some psychotic conditions. Evidence for processes that coordinate activity is provided by neurobiological and psychological studies of contextual disambiguation and dynamic grouping. Mechanisms by which this important class of cognitive functions could be achieved include those long-range connections within and between cortical regions that activate synaptic channels via NMDA-receptors, and which control gain through their voltage-dependent mode of operation. An impairment of these mechanisms is central to PCP-psychosis, and the cognitive capabilities that they could provide are impaired in some forms of schizophrenia. We conclude that impaired cognitive coordination due to reduced ion flow through NMDA-channels is involved in schizophrenia, and we suggest that it may also be involved in other disorders. This perspective suggests several ways in which further research could enhance our understanding of cognitive coordination, its neural basis, and its relevance to psychopathology.