Motor syntax disorder in schizophrenia

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Schizophrenia is a complicated neuropsychiatric disease. The diverse clinical symptoms that characterize the pathophysiology of schizophrenia are concisely summarized in Lewis and Gonzalez-Burgos [2006; see their Box 1]. A core feature is a deficit in working memory, including spatial working memory [Park & Holzman 1992]. Working memory (WM) was originally defined as the process of actively holding information on-line, in the mind's eye, and manipulating it in the service of guiding behavior [Baddeley 1992]. More succinctly, WM prolongs responses to events to allow linkages with past memories, lexical labels and other events [Mesulam, 1998]. It is easy to understand why a deficit in WM can lead to thinking problems and disordered language.

The participation of the dorsolateral prefrontal cortex (DLPFC) in WM is now well established, but the nature of its participation has been difficult to understand. In 1992, Park & Holzman introduced the spatial WM of visual target location as a new task for studying schizophrenia. Patients demonstrated difficulty remembering the location of a spatial target over a brief WM period. Part of the motivation for introducing this task was to promote cross-species comparisons. Published neurophysiological, neuroanatomical and behavioral results in monkeys provided a wealth of data that assisted their task design and the interpretation of the deficits that they, and others [Fuster 1997; Goldman-Rakic 1991], observed.

1 The Replicate task

A cross-species approach was also crucial in our design of the Replicate task, a procedure for studying spatial serial-order recall performance. Replicate was introduced to study schizophrenia [Fraser, Park, Clark, Yohanna & Houk 2004], and we recently demonstrated that essentially the same behavior is present in the monkey [Botvinick et al. 2009]. The idea for studying spatial serial order recall in schizophrenia originated during a reception at which graduate student Dave Fraser, psychologist Sohee Park and neuroscientist Jim Houk happened to encounter each other. Jim was talking to Dave about the neurophysiological mechanisms monkeys use for keeping track of the serial order of events [Beiser & Houk 1998]. Sohee joined the conversation be-

cause Dave was just starting a project on schizophrenia with her. We came to the conclusion that serial order recall needed to be studied in schizophrenia and designed the task Replicate.

In Replicate, K targets are presented on an NxN grid of squares in a randomized sequence, and the subjects are required to remember their positions and serial order over a brief delay. The subjects are then cued to move to the K positions in the same order in which targets were originally presented. The phase of target presentation requires the setting up of a working memory representation, which must be sustained through the delay period and then decoded in order to produce correct movements. We refered to the three phases of the task as *encoding*, *maintenance*, and *decoding* [Houk et al 2007]. Encoding is analogous to coming up with a thought. Maintenance is remembering that same thought until it is used "in the service of guiding behavior." Decoding is analogous to using syntax to guide the formation of a sentence. If schizophrenia subjects have difficulty with the decoding phase, we might consider calling their problem a motor syntax disorder.

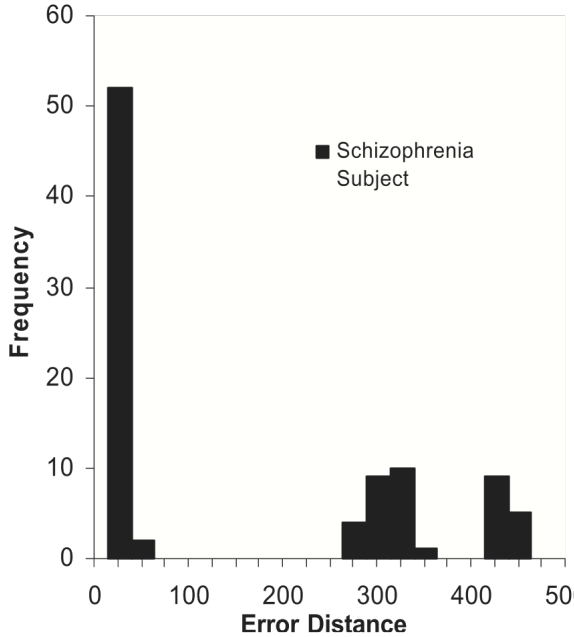

Figure 1: Responses of a schizophrenia patient for the four-target sequence. The cluster of responses around the error distance = 0 represent correct responses within a small ''sensorimotor accuracy'' range. The responses clustered around x = 300 pixels show an erroneous choice of a target that was directly horizontal or vertical to the correct target, while the responses clustered around x = 425 show an erroneous choice of the target that was directly diagonal. The range of values for the correct responses are clearly smaller than the range for incorrect responses.

Our analysis of the responses of one schizophrenia patient using K=4 targets and a 2x2 grid is shown in Figure 1. Summary results for all of the subjects demonstrated insignificant sensorimotor errors in patients versus controls (Figure 2A). Errors in choice (Figure 2B) were small, but significant, for 1 or 2 targets and became large when patients had to choose amongst 3 or 4 targets.

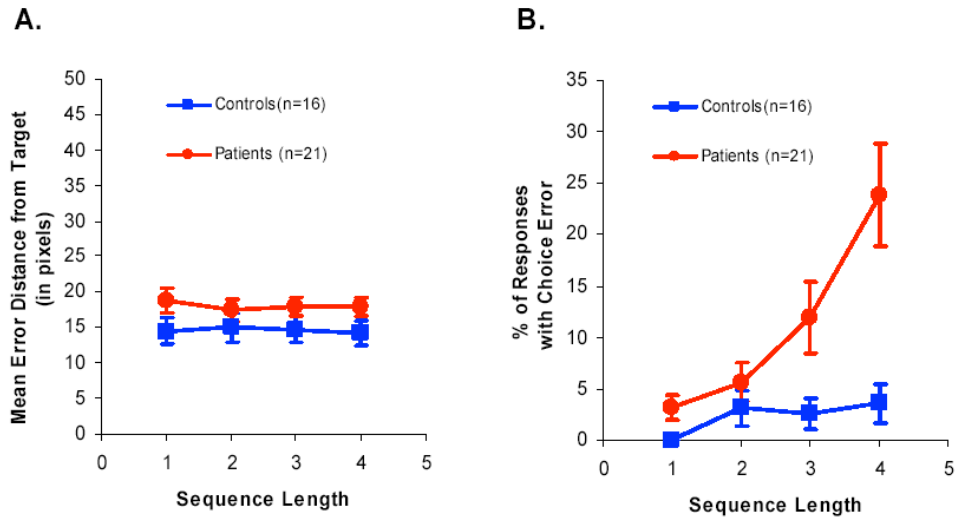

Figure 2: Percentage error rates for sensorimotor (A) and choice (B) components of response. [Modified from Figure 3 in Fraser et al 2004]

Note how small the choice error is when only 1 or 2 targets are used. This small, but statistically significant, difference seems adequate for detecting a disorder in the maintenance phase of WM. Instead, using 3 or 4 targets may be the best way to test for deficits in decoding.

2 Interpretation of the data

What is it that causes such huge deficits in the performance of Replicate when WM load is 3 or 4 items? Answering this question seems to require an integration of about seven different research topics:

1. The capacity model of WM load
2. A neural network model of serial order processing
3. Paced read-out in Replicate
4. Functional neuroimaging of Replicate
5. Models of pattern classification
6. Pattern classification in phylogeny and ontogeny
7. A central paradox in schizophrenia

Each of these topics is discussed in separate subsections below.

2.1 The capacity model

In a review article, Manoach [2003] attempted to decipher discrepant functional imaging data which suggested the lack of a reliable relationship between brain activity in DLPFC (an accepted site of WM in the brain) and WM load (the number of items in the task, analogous to K in Replicate). In some cases activation in schizophrenia patients was greater than in controls (A's in Figure 3), whereas in other cases it was either less (C's in Figure 3) or the same (B's in Figure 3). Manoach hypothesized that activation depends on WM load in a nonlinear manner, i.e. the bell-shaped curves shown in Figure 3. Postulating this nonlinearity explained the discrepant reports in the literature.

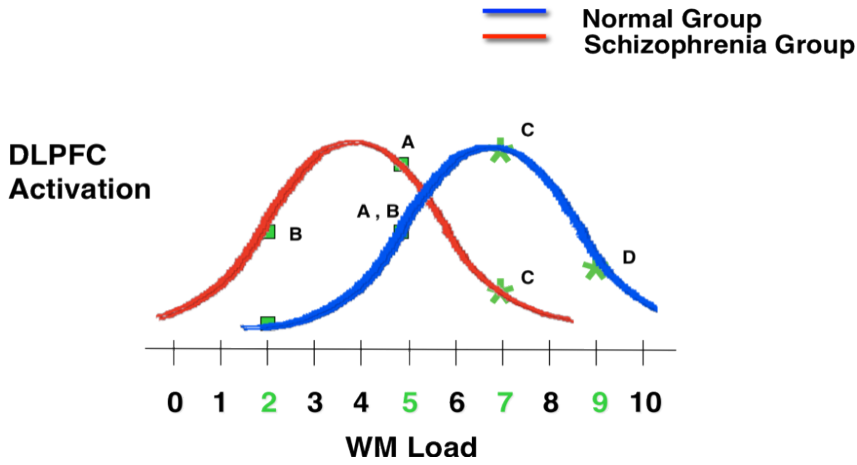

Figure 3: Discrepant fMRI data is fit by a nonlinear relationship between activation and WM load.

The capacity model is valuable for characterizing the Replicate data in terms of WM load. The schizophrenia group has a lower WM capacity, which is probably why it reaches peak DLPFC activation earlier.

2.2 A neural network model of serial order processing

Our next step was to define a linkage between Replicate and the neural circuits that are likely to control its operation. For guidance, we turned to a neural network model of the loop between DLPFC and the basal ganglia [Beiser & Houk 1998].

As summarized in Houk [2007], the focus of the Beiser-Houk model was serial order processing, a crucial feature of higher order intelligence [Lashley 1951]. The model's ability to encode the serial order of events resulted from the combination of 3 computational features:

1. A classification of spatiotemporal patterns in the cortical input vector by computations within the striatum,
2. A working memory of the outcome of pattern classification in positive feedback loops between cortex and thalamus,
3. A recursion-like operation brought about because the loop deposits the working memory of prior classifications into an updated input vector from cortex to the striatum.

Because of step 3, the updated vector represents prior events, in addition to current events. As a consequence, the next step 1 will profit from temporal context. This dependence on past events is a fundamental requirement for serial order processing. Actually, working memory (maintenance) and pattern classification, steps 1 and 2, are also clearly needed. It's all 3, in an appropriate combination, that accomplishes serial order processing.

2.3 Paced read-out in Replicate

No deficit was observed for serial order recall when reproduction of a "read sequence" instruction was unpaced [Hill et al 2011]. However, schizophrenia patients exhibited significant impairments when responding was paced by an external cue, regardless of sequence length or retention delay. Intact performance by schizophrenia patients during the unpaced condition indicates that prefrontal storage and striatal output systems are sufficiently intact to learn novel response sequences and hold them in working memory to perform serial order tasks. However, retention for newly learned response sequences was disrupted in schizophrenia patients by paced responding, when read-out of each element in the response sequence was externally controlled. The disruption of memory for serial order in the paced read-out condition suggests that there is a deficit in frontostriatal interaction characterized by an inability to update working memory stores and deconstruct "chunked" information.

The sharp distinction between paced and unpaced read-out documents a dependence on being able to use a flexible linkage between each movement in a sequence. In fact, the use of a flexible temporal sequence of words is a key feature of the syntax of language. We conclude that the deficit in the selection of the next spatial target, when there are 3 or more targets amongst which to choose, seems appropriately designated a **movement syntax disorder**.

2.4 Functional neuroimaging of Replicate

Our brain imaging experiments were designed to investigate the loop through the basal ganglia [Houk et al 2007]. In the control task, dubbed Chase, a sequence of location cues appears just as in Replicate, but subjects use a joystick to track these cues immediately as they appear. Chase involves similar stimulus and response sequences to Replicate, but eliminates the sustained components characterizing plans.
Brain fMRI activity of subjects performing 4x4 Replicate with K = 3 items utilized two primary BOLD (Blood Oxygen Level Dependent) contrasts. An Execute contrast

was made between the period of sensory guided joystick movements in the Chase task and a rest period in the same task. This contrast was designed to simply show the standard neural correlates of motor execution. A more sophisticated Decode contrast was made between the memory guided movement period of the Replicate task and the sensory guided movement period of the Chase task. This contrast was designed to reveal the neural correlates of the decoding operation while simultaneously controlling for BOLD activity related to pure motor execution. Whole brain Echo Planar Imaging data (24 6 mm slices, TR=2000 ms) were collected from 10 subjects, and a partial-brain scanning protocol focusing on the basal ganglia (12 6mm slices, TR=1000 ms) was used for 9 subjects.

Our whole brain data will only be partially presented, because our analysis is still in progress [Fraser et al 2008]. Basically, the results show activation patterns in a large network of brain areas, considerably larger than the minimal network that would be required to model Replicate [Houk et al 2007]. Regarding the decoding operation, the DLPFC appears to do a cognitive manipulation of the WM, but this is only the first stage of decoding. Apparently there is a second decoding stage in which a premotor area (the PMd) supports some sort of consolidation of a motor plan. Then the primary motor cortex (M1) receives the consolidated motor plan and generates the actual motor commands that are sent to the spinal cord to move the limb.

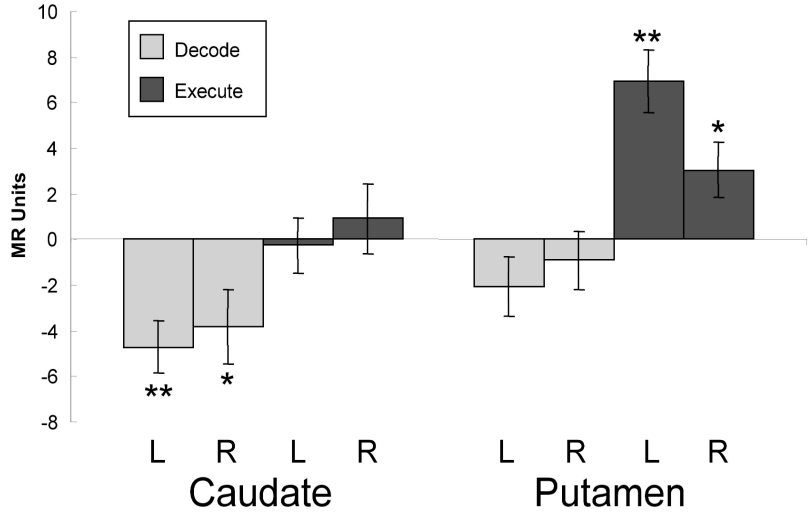

Figure 6: Differential BOLD activity in the right and left head of the caudate and putamen for the Decode (gray), and Execute (black) contrasts**.** Error bars indicate standard error. Single asterisk (*) indicates a significant difference ($t(8) \geq 2.36$, $p < 0.05$) while double asterisks (**) indicate a highly significant difference ($t(8) \geq 4.16$, $p < 0.01$). A significant decrease in activity was found in the caudate nucleus for decoding, whereas a significant increase in activity was found in the putamen for execution. Deactivation, representing a statistically significant de-

crease in blood flow in caudate for the Decode contrast, was surprising. (From Houk et al [2007])

Excellent sensitivity to changes within the striatum of the basal ganglia was provided by the partial-brain imaging protocol. The differential BOLD activity in the caudate nucleus and putamen were strikingly different for the Execute and Decode contrasts (Figure 6). A significant increase in activity was found in the putamen for Execute, as expected, whereas a significant decrease in activity was found in the caudate nucleus for Decode. The deactivation, representing a statistically significant decrease in blood flow in caudate during the decoding operation, was puzzling. Brain processing is believed to require increased synaptic activity, which recruits increased metabolism and blood flow, as detected by an increase in BOLD signal [Logothetis, 2002].

Decreases in BOLD are considered mysterious [Gusnard and Raichle, 2001] and are usually explained by greater synaptic processing in the control task as opposed to the main task. In our Decode contrast, this could happen if caudate were actively engaged in the sensory-guided control task Chase, due to the presence of visual targets for each movement of the joystick. However, Figure 6 indicates that caudate is not particularly active in the Execute contrast. The statistically significant decrease in BOLD for the Decode contrast seems to need a better explanation, which motivated us to model pattern classification in the neostriatum.

2.5 Models of pattern classification in the neostriatum

Although many authors have suggested that the loop through the basal ganglia plays an important role in action selection, there are diverse views concerning the mechanism by which this might occur. Most authors agree that action selection occurs in the input nucleus of the basal ganglia loop, namely the striatum. There are diverse views about the mechanisms for preventing actions; they will not be discussed here.

The dorsal part of the striatum, the neostriatum, is comprised of two divisions, the caudate nucleus and the putamen. The principal neurons of both caudate and putamen, the medium spiny neurons, are inhibitory GABAergic projection neurons. They emit an elaborate array of collaterals to neighboring spiny neurons before they project to output stages of the basal ganglia, namely to either globus pallidus or substantia nigra pars reticulata. The drawing on the left side of Figure 7 shows schematically two of these spiny neurons receiving excitatory input from cortex. Spiny neurons have collaterals that inhibit each other and give rise to an inhibitory feedback network entirely within the neostriatum. This local feedback network mediates a competitive pattern classification operation. Collateral inhibition is deemed an effective mechanism for competition by some authors [Plenz 2003] and ineffective by others, the latter believing that feedforward inhibition regulates the pattern classification operation [Tepper et al. 2004]. Beiser and Houk [1998] modeled both mechanisms and found that both worked, but the inhibitory feedback network worked more effectively than the feedforward network.

What had not been considered before the report by Houk et al [2007] is the possibility that the inhibitory feedback network relies on presynaptic, as opposed to postsynaptic, inhibition. This is surprising since presynaptic inhibition of cortical input to the neostriatum has been demonstrated electrophysiologically [Calabresi et al. 1991; Nisenbaum et al. 1993] and morphologically [Lacey et al. 2006]. Indeed, the operation of a presynaptic mechanism for collateral inhibition could also explain the mysterious fMRI BOLD deactivation that we found in caudate for the Decode contrast (Figure 6). Synaptic input is believed to be a strong contributor to BOLD signals [Arbib et al. 2000; Logothetis, 2002]. Since presynaptic inhibition would decrease synaptic input, that could explain the deactivation for caudate. The activation seen for putamen presumably results from a greater dependence on postsynaptic inhibition.

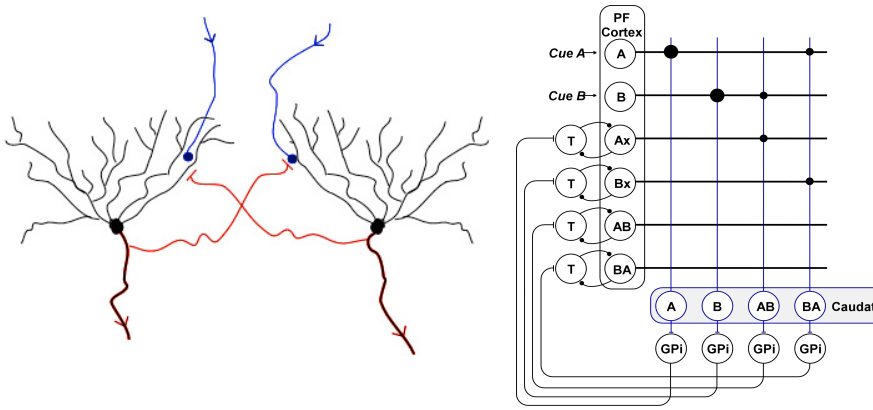

Figure 7: Two striatal spiny neurons are shown schematically on the left. Their inhibitory collaterals, shown in red, make intrastriatal pattern classification competitive. Competition can be mediated by either presynaptic or postsynaptic inhibition. We tested both possibilities by simulating the model of the loop through basal ganglia shown on the right. [Modified from Houk et al 2007]

In Houk et al [2007] we modeled a minimal network of recurrent loops from cortex through basal ganglia and back to cortex that encodes the serial order of two visual cues, A and B (Figure 7). The reader is referred to the "Implementation details" posted in the Electronic Appendix of that article. Recurrent loops in the direct pathway through the prefrontal (PF) cortex, caudate (CD) nucleus, internal segment of the globus pallidus (GPi), and thalamus (T) were used to encode two visual cues, A and B. Computational units AB and BA are labeled for the sequence they respond to best, whereas Ax (Bx) is activated by A (B) independent of its serial order. Prefrontal cortex projections are excitatory, with synaptic weights represented by dot sizes. Caudate spiny units are interconnected by inhibitory collaterals to form a competitive network (shown symbolically by the shaded gray area). Via their projections, CD units are inhibitory to GPi units. The high spontaneous activity of GPi units provides

a tonic inhibitory background to thalamus, and inhibition of this background activity provokes a disinhibition of thalamic units. Rebound activity of thalamic units starts positive feedback and sustained activity in the reciprocal excitatory pathway between thalamus and cortex. This would initiate activity in the loop through cerebellum but that additional feature was not included in the present model.

Medium spiny neurons were simulated [Houk et al 2007] using a minimal biophysical model [Gruber et al 2003] to which we added excitatory and postsynaptic inhibitory conductance inputs. Presynaptic inhibition was modeled by dynamically decreasing the excitatory synaptic weights of the input from PF Cortex. The GPi-T-PF loop was abstractly modeled based upon the Beiser-Houk model [1998] with a sigmoidal function to transform membrane potentials into firing rates. The network was instantiated using either no inhibition, presynaptic inhibition, or postsynaptic inhibition in caudate, and the model was then subjected to noise.

Presynaptic inhibition yielded improved noise tolerance and decreased energy requirements compared with postsynaptic inhibition. When the network was subjected to noisy inputs, the misclassification rate without inhibition was 54.6% but fell to 24.1% for postsynaptic inhibition and 19.4% for presynaptic inhibition (a 4.8% decrease with presynaptic versus postsynaptic inhibition, $p<0.001$). Presynaptic inhibition also decreased the summed magnitude of synaptic activity in caudate from 118 to 98 (difference of -16.9%, $p<0.001$). The decreased excitatory synaptic activity in the presence of presynaptic inhibition can account for the reduced fMRI BOLD signal seen in caudate during the decoding contrast (Figure 6). In summary, presynaptic inhibition yields improved pattern classification while also explaining the puzzling decrease in fMRI BOLD.

2.6 Pattern classification in phylogeny and ontogeny

The above simulation results offer an explanation for a puzzling imaging result. The decrease in BOLD seen in caudate indicated that decreased synaptic activity occurred under conditions when caudate neurons were actively engaged in the decoding operation. This was explained by using presynaptic inhibition to mediate competitive pattern classification in the model. But why instead was an increase in BOLD observed in the putamen in association with execution? We believe this observation relates to phylogeny. The circuit that operates on working memories via a loop from dorsolateral prefrontal cortex (DLPFC) through the caudate nucleus [Kelly and Strick, 2004] is phylogenetically newer than the loop through the putamen to and from primary motor cortex. Preuss [1995] reviewed the phylogeny of prefrontal cortex and concluded that this frontal region is likely to be unique to primates, and for an update of this discussion, see Wise [2008]. The phylogenetically older loop between motor cortex and basal ganglia generates the voluntary motor commands that control each individual movement, whether or not it belongs to a sequence.

This phylogenetic hypothesis fits well with our simulation finding that performance is superior when competition is mediated by presynaptic inhibtion as opposed to postsynaptic inhibition. Since presynaptic inhibition in the striatum is mediated by GA-

GABAb receptors, it is quite relevant that GABAb receptor binding sites are found in extremely high density in the caudate nucleus of the monkey [Bowery et al. 1999], but in unremarkable density in the rat [Bowery et al. 1987]. This combined morphological evidence from the same laboratory supports the hypothesis that a predominance of presynaptic inhibition of cortical input to the neostriatum is phylogenetically more recent than is a predominance of postsynaptic inhibition. The above logic fits well with our contention that presynaptic inhibition is favored in the phylogenetically newer loop between DLPFC and caudate, as opposed to postsynaptic inhibition in the loop between M1 and putamen. Furthermore, this can explain why we found a BOLD deactivation in caudate associated with decoding along with a BOLD activation in putamen associated with execution.

In summary, we postulate that a superior mechanism for competitive pattern classification in the striatum evolved in primates, and that this adaptation is expressed late in ontology, shortly after the development of the basal ganglia loop with motor cortex. In the next subsection this concept is used to propose a potential phenotype of schizophrenia.

2.7 A central paradox of schizophrenia

A central paradox of schizophrenia is that a condition which is considered to be genetic in origin survives in the population in spite of a fecundity disadvantage. The magnitude of the latter is such that any genetic predisposition should be eliminated from the population within a few generations. Instead, since the incidence of schizophrenia remains steady at 1-2%, one can conclude that there is an accompanying genetic advantage [Huxley et al. 1964]. In analyzing this issue, Kuttner et al. [1967] offered three advantageous functions that might accompany the inheritance of schizophrenia: (1) a capacity for complex social relations, (2) intelligence, and (3) language. Crow and colleagues have made a strong case for an evolutionary link between the origin of language and the etiology of schizophrenia [Crow 1997; Berlim et al 2003]. Their hypothesis is consistent with the prominent deficit in competitive pattern classification in schizophrenia mentioned above -- language contains abundant examples of serial order processing.

The model of competitive pattern classification presented earlier might assist further analysis of these schizophrenia findings. To review, simulating normal subjects, we found that presynaptic inhibition, in addition to out-performing postsynaptic inhibition, also explained the mysterious decrease in BOLD signal in the caudate nucleus (Figure 6). If patients suffer from a deficit in presynaptic inhibition, the caudate BOLD decrease in the Decode contrast should be attenuated or even reversed. This prediction could be tested by imaging the Replicate task in schizophrenia patients.

Earlier we suggested that the presynaptic mechanism for competitive pattern classification in the striatum is defective in schizophrenia. Since GABAb receptors mediate presynaptic inhibition in the striatum, it is reasonable to search the literature for genetic evidence relevant to this hypothesis. In fact, there is a modified expression of the GABAb receptor in schizophrenia [Enna & Bowery, 2004]. This implicates the

modified GABAbR1 gene on chromosome 6p21.3 [Martin et al. 2001] as a major contributor to schizophrenia. It is interesting that Matthysse et al [2004] reported a linkage of eye tracking disorder, one of the best known traits associated with schizophrenia, to 6p21.1, which is very close to the locus for GABAbR1 (GABBR1).

In summary, the central paradox of schizophrenia [Crow 1997] is that the genetic deficit survives in about 1% of the population in spite of a fecundity disadvantage. We propose that a DNA sequence change that improved GABAb presynaptic receptor function occurred in primates and led to the evolution of language, intelligence and complex social relations. Improved pattern classification could explain the survival of the gene in the population, whereas a genetic polymorphism that encodes a protein having reduced activity with a 1% incidence could explain the central paradox of schizophrenia. In other words, we are proposing that a very positive mutation leads the way, via unfavorable epigenetic expression, to this potentially devastating pathophysiological trait, albeit rarely.

3 Overall summary

In section 1 of this paper, we introduced a task dubbed Replicate, an immediate serial order recall task that uses the spatial location of targets as the individual items. Replicate was used to demonstrate prominent choice errors when 3 or 4 targets were presented to schizophrenia patients. The decision to call this deficit a ***motor syntax disorder*** required an integration of diverse behavioral and neuroscientific reports. The integration process itself yielded some enhanced understanding in other fields, including the enunciation of a novel phenotype contributing to schizophrenia. However, the main goal of this paper has been to show that motor syntax is a viable terminology, and it has important shared features with the syntax of language. Knowing this, together with our knowledge concerning many of the neural mechanisms that underlie motor syntax, should eventually contribute to a resolution of some of the disputes that pervade linguistic discussions of syntax.

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