Commentary on **William A. Phillips & Steven M. Silverstein (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. BBS 26(1):65–82.**

Abstract of the original article: 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 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.

Autism and schizophrenia: Similar perceptual consequence, different neurobiological etiology?

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Abstract: Phillips & Silverstein (P&S, 2003) propose that NMDA-receptor dysfunction may be the fundamental neurobiological mechanism underlying and associating impaired holistic perception and cognitive coordination with schizophrenic psychopathology. We discuss how the P&S hypothesis shares different aspects of the weak central coherence account of autism from both theoretical and experimental perspectives. Specifically, we believe that neither those persons with autism nor those with schizophrenia integrate visuo-perceptual information efficiently, resulting in incongruous internal representations of their external world. However, although NMDA-hypofunction may be responsible for perceptual impairments in schizophrenia and possibly autism, we suggest that it is highly unlikely that NMDA-hypofunction is specifically responsible for the autistic behavioral symptomology, as described by P&S in their target article.

Autism and schizophrenia are heterogeneous and complex neurobiological disorders defined by a continuum of subtypes that are differentiated by cognitive and behavioral manifestations. In line with the Phillips & Silverstein (P&S, 2003) statement that "[the] fragmentation of mental functions is prima facie evidence of impaired cognitive coordination" (sect. 4.4, para. 1) insight regarding the nature of cognitive dysfunction in these two conditions may be derived from an evaluation of visuo-perceptual capabilities necessitating different levels of neural information processing. The motive for such assessment and subsequent interpretation originates from the fact that persons affected by these disorders share a common perceptual manifestation, namely, impaired perceptual organization reflected by abnormal performance on tasks requiring Gestalt-like or holistic visual analysis. It is therefore not surprising that interest regarding perceptual processing in autism has increased significantly since the introduction of neurobehavioral theories suggesting that a portion of abnormal autistic cognition and behavior may be explained in terms of the inefficient integration of visuo-perceptual information (e.g., Frith 1989; Mottron & Belleville 1993). Such theories share the notion that persons with autism do not integrate visuo-perceptual information efficiently into coherent percepts, characterized by a predominantly *local* approach to visual processing to the detriment of holistic information analysis. The *weak central coherence* (WCC) account of autism (Frith 1989) is arguably the most flexible of these theories because it offers a theoretical framework describing inefficient integration of information at different levels, including at a perceptual level (i.e., *perceptual coherence;* Happé 1999). These theories encapsulate anecdotal accounts of the fragmented visual world described by persons with autism (see, e.g., Gerland 1997; Gradin 1996).

Interestingly, accounts of "perceptual and apperceptual fragmentation" have also been described in schizophrenia studies (Arieti 1966) and have provided experimental evidence of inefficient perceptual grouping in this disorder. Such impairments have been exemplified by demonstrations of impaired performance necessitating the integration or grouping of complex static and dynamic visual information into meaningful percepts. As it has in autism, such evidence has led to notions of "spatio-temporal disintegration" of visual perception (Izawa & Yamamoto 2002) and anomalies regarding perceptual grouping schizophrenia (Place & Gilmore 1980; Silverstein et al. 2000).

How then, can one evaluate the integrity of early or preattentive neuro-integrative mechanisms mediating perceptual grouping? One method is to investigate the complex motion analysis capabilities of persons with autism and schizophrenia. Considered to be a form of dynamic grouping (Watt & Phillips 2000), complex motion analysis exemplifies early neuro-integrative processing since local motion information must be integrated across space and time before a global or coherent motion direction can be discriminated. Results from recent psychophysical studies directly assessing complex motion analysis mediated by extrastriate motion-sensitive mechanisms (i.e., V2/V3, MT) have demonstrated a decreased sensitivity to complex motion in autism (see, e.g., Bertone et al. 2003; Blake et al 2003; Gepner & Mestre 2002; Milne et al. 2002; Spencer et al. 2000). Results from these studies have been for the most part interpreted as a dysfunction of the dorsal stream processing or as a localized neural impairment of motion-sensitive areas in autism (Blake et al. 2003; Gepner & Mestre 2002; Milne et al. 2002; Spencer et al. 2000). In the only study investigating *both* simple and complex motion perception (Bertone et al. 2003), decreased sensitivity was evidenced for *only* complex motion types necessitating increased neural circuitry and integration to be resolved. For this reason, these findings were interpreted as a decreased capacity to integrate complex perceptual information rather than specific motion processing impairment per se (Bertone et al. 2003). The results from this study are very similar to those of Chen et al. (2003), who also demonstrated a decrease for complex but not simple (or local) motion in schizophrenia. Although the Chen et al. interpretation is more congruent with local neural dysfunction (i.e., dysfunction implicating motion-sensitive areas), when considered along with those of Bertone et al. (2003) they provide clear evidence of impaired dynamic Gestalt organization in both schizophrenia and autism. As mentioned by P&S, these analogous results can be interpreted as exemplary evidence of impaired cognitive coordination or, analogously, weak central coherence, in either condition.

Persons with autism and schizophrenia therefore share the following perceptual consequences: predominant local analysis of visual information and inefficient neuro-integrative perceptual processing, as well as anecdotal accounts of a fragmented perceptual

world. The logically ensuing question is whether such common perceptual manifestations are the consequences of similar neurobiological etiology, specifically NMDA-hypofunction. If one interprets inefficient complex motion analysis as manifestation of impaired cognitive coordination, then the tentative answer is yes. Since such analysis involves gestalt-like integration over time and space that is believed to be mediated by NMDA-receptor activity, it is possible that autism and schizophrenia share impaired analysis of complex information at a *perceptual* level due to NMDA-hypofunction. However, impaired complex motion analysis has been demonstrated and interpreted differently for a variety of conditions defined by different behavioral manifestations. Such conditions include normal aging (Habak & Faubert 2000), dementia of the Alzheimer's type (Gilmore et al. 1994; Trick & Silverman 1991), dyslexia (Cornelissen et al. 1998; Talcott et al. 2000), and Parkinson's disease (Trick et al. 1994). Therefore, a consistent association between perceptual dysfunction defined by impaired complex motion analysis and clinical symptomology is not evidenced.

P&S's argument for associating NMDA-receptor hypofunction with perceptual, cognitive, and behavioral manifestations in schizophrenia is based in part on the schizomimetic effects of NMDA-antagonists. Blocking NMDA-receptor channels in non-schizophrenic persons results in schizophrenia-like symptomology (referred to as PCP-psychosis), which according to P&S is congruous with symptoms of "cognitive disorganization" (see Table 1 in the target article). Interestingly, Carlsson (1998) has used a similar argument to explain autistic perceptual and behavioral symptomology, adding that, like schizophrenia, abnormal glutamatergic interactions with other neurotransmitter systems (i.e., dopaminergic or serotonergic) may at least in part be responsible for the described autistic symptomology. Given the implication of NMDA-receptor activity in long-term potentiation (LTP), it can be argued that meaningful internal neural representations of their physical environment based on the efficient integration of perceptual information is compromised in persons with schizophrenia and in persons with autism. Consequently, appropriate behavior based on these representations would be abnormal and interpreted as being a part of the characteristic symptomology of either condition.

It can be argued that persons with autism and schizophrenia share (1) similar subjectively described and objectively measured manifestations of impaired Gestalt-like perception, probably the result of the inefficient integration of perceptual information, and (2) respective mimetic effects of NMDA-receptor antagonists. Given these similarities, can autism be considered to be a hypoglutamatergic disorder at a behavioral level if viewed within the context of P&S's working hypothesis? Probably the most important discrepancy between schizophrenia and autism regarding the possible implication of NMDA-hypofunction in their respective psychopathology concerns the onset of clinical symptomology. Although both conditions are considered to be congenital, their clinical symptoms are initially evidenced at different ages: between adolescence and young adulthood in the case of schizophrenia and around the age of three for autism. Taking this into account, even if the perceptual consequences of both disorders implicate NMDA-hypofunction, the effects of these consequences on symptomology is less evident. For example, it can be argued that the nature of schizophrenic hallucinations and delusions, which are not typically manifested in autism, are based on previously constructed percepts that have some associated affective value. In most cases, persons with schizophrenia associate a predominantly adverse affect (i.e., terror or confusion) to their abnormal perceptual experience, much like what is experienced during a drug-induced psychosis. In the case of autism, it can be argued that such constructs are never fully developed and, therefore, associations between perceptions and affects are never fully developed. Furthermore, persons with autism *grow up* with an abnormal perception of the world and, therefore, although maladaptive, their characteristic visually-related autistic behavior is usually void of negative affect (i.e., the pleasurable feeling experienced when fascinated with a specific part of an object). Consequently, one can argue that persons with schizophrenia and autism have different affective reactions to incongruent representations of their visual environment.

Finally, one must take into account that at the onset of autistic symptomology, the neural development of the autistic perceptual system is incomplete (i.e., neural pruning) compared to that of persons with schizophrenia, making the behavioral link between NMDA-hypofunction and clinical manifestations in these two disorders that much more complicated. In conclusion, although there is the possibility that NMDA-hypofunction may underlie the *perceptual* consequence manifested in schizophrenia and autism, it is much less probable that NMDA-hypofunction is selectively responsible for *behavioral* symptomology, a general association made by P&S regarding schizophrenia.

A common link between aging, schizophrenia, and autism?

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Abstract: Phillips & Silverstein (P&S, 2003) have proposed that NMDA-receptor hypofunction is the central reason for impaired cognitive coordination and abnormal gestalt-like perceptual processing in schizophrenia. We suggest that this model may also be applicable to non-pathological (or normal) aging given the compelling evidence of NMDA-receptor involvement during the aging process that results in age-related change in higher-level perceptual performance. Given that such deficits are present in other neurological disorders such as autism, an argument for a systematic assessment of perceptual functioning in these conditions may be posited.

Phillips & Silverstein (P&S, 2003) propose that there are reduced numbers of NMDA-receptors in schizophrenia that result in abnormal gestalt-like perceptual grouping. Fundamental to their argument is the implication of NMDA-receptor activity in long-term potentiation (LTP) which allows local events to be integrated into more global (or higher-level) perceptual constructs. As is the case for schizophrenia, there is abundant evidence of reduced LTP caused by NMDA-receptor dysfunction in the non-pathological (or normal) aging process that is accompanied by a decline in cognitive functioning (Gazzaley et al. 1996; Wenk et al. 1991; see also Segovia et al. 2001 and Rosenzweig & Barnes 2003 for reviews). We suggest that there exists a parallel and selective decline in higher-level perceptual information processing in normal aging, supporting P&S's notion that NMDA-receptor activity is involved in perceptual organization. This suggestion is based on results from a series of recent studies demonstrating that the normal aging process has a much greater impact on mid- to high-level perceptual functioning, which requires increased neural integration, than on lower-level perceptual processes (Faubert 2002). The differential efficacy of low-level and higher-level perceptual processing may also have consequences within certain types of cognitive functioning in aging, such as performance on visual working memory tasks.

As P&S have pointed out, perception is not a monolithic process, for it involves context integration and complexity constructs based on an infinite number of neural events. Recent studies have examined this exact process in normally aging observers in a number of visual modalities including motion and orientation (Habak & Faubert 2000), texture (Herbert et al. 2002), and form perception (Faubert & Bellefeuille 2002; Sara & Faubert 2000). Findings from these studies have demonstrated that as the amount of neural processing required to generate complex perceptual constructs increases, so does age-related loss in performance (Fau-

bert 2002). The goal of this commentary is to bring to light the similarities between normal aging and schizophrenia regarding inefficient higher-level integrative or gestalt-like perception. In addition, we propose that P&S's hypothesis implicating NMDA-receptor hypofunctioning in abnormal higher-level perception in schizophrenia may also be applicable to normal aging given the comparable evidence of increasing NMDA-receptor dysfunction during the aging process.

Perceptual complexity can be exemplified by the differential amount of neural integration needed to resolve first- and second-order visual information (Cavanagh & Mather 1989), the latter of which necessitates the activity of larger neural networks to be perceived (e.g., Bertone & Faubert 2003; Chubb et al. 2001; Nishida et al. 1997; Wilson et al. 1992). Habak and Faubert (2000) demonstrated a larger age-related increase in motion and orientation discrimination thresholds when the stimuli are defined by second-order attributes (e.g., texture). These results suggest that the age-related loss in performance is due to perceptual complexity of the second-order information and is not specific for visual attribute (motion or orientation). Because second-order image resolution implicates additional neural processing regardless of the type of information, it can be argued that decreased NMDA-mediated LTP may be the neurobiological mechanism responsible for the decrease in perceptual performance.

Gestalt-like perceptual grouping, as described by P&S, is exemplified by symmetry perception; it involves the spatial organization (e.g., symmetrical) of local stimulus elements (e.g., dots) into meaningful percepts. Therefore, perceiving symmetry involves the integration of local elements across the putative axis. Given the evidence of NMDA-receptor hypofunction in aging, we would expect an age-related loss in this type of spatial grouping task. In effect, a clear age-related deficit regarding the detection of bilateral symmetry detection has been demonstrated (Herbert et al. 2002).

The P&S NMDA-perception hypothesis predicts that long-range perceptual processes are affected in normal aging because NMDA depletion results in reduced LTP. Therefore, task performance based on the processing of information within a specific image attribute would be less affected by aging when compared to performance necessitating the processing and integration of information from two separate image attributes. A recent study by Faubert and Bellefeuille (2002) demonstrated that spatial frequency discriminations performed within an attribute condition (e.g., luminance vs. luminance or color vs. color) are less affected by age than are intra-attribute discriminations (e.g., luminance vs. color) when compared with younger observers. Similar age-related deficits in long-range processing have been demonstrated for tasks necessitating the simultaneous integration of information within a large spatial area prior to efficient perceptual decision making (e.g., size discrimination) compared to tasks for which the information is presented in sequence (temporal forced choice in same location; Sara & Faubert 2000). Taken together, these findings suggest a selective age-related loss for tasks soliciting long-range perceptual processing, as proposed with regard to schizophrenia by P&S. Again, these age-related decreases in performance are compatible with abnormal LTP.

As mentioned, the differential efficacy of low-level and higher-level perceptual functioning in aging may also have consequences affecting performance on visual working memory tasks (Faubert 2002). Recent studies have clearly demonstrated that normal aging has little effect on the capacity to retain either spatial frequency or size information defined by low-level perceptual information (Faubert & Bellefeuille 2002; Sara & Faubert 2000). This has led Faubert (2002) to conclude that perception and visual working memory are affected in similar ways during aging, in that processing of low-level information that does not require long-range processing (or complex networks, as termed by Faubert) is minimally affected. However, perceptual or working memory processes that require more sophisticated neural network structures will show age-related decline. Faubert (2002) suggested that this is the result of the Simultaneous Access Network Deficit (SAND) hypothesis of aging, which appears to us to be comparable to the NMDA-perception hypothesis offered by P&S in both a functional and possibly a neurobiological perspective.

In conclusion, we believe there is evidence in the normal aging process of the impaired gestalt-like visuo-perceptual grouping and accompanying neurobiological mechanism proposed by P&S which is comparable to that in schizophrenia and, possibly, other neurological disorders such as autism (cf. the preceding commentary by Bertone et al. [2004] in this issue). This suggestion is based on the fact that NMDA hypofunction and its relation to cognitive deficits appear to be relatively elaborated and specific to the aging literature, particularly with respect to currently available animal and human models demonstrating reversibility of some age-related effects (e.g., Baxter et al. 1994; Held et al. 2002). Furthermore, if impaired cognitive coordination, as reflected by abnormal gestalt-like perceptual performance, is the consequence of reduced glutamatergic neurotransmission, then the aging model is more suitable than schizophrenia for unidirectional hypotheses testing because glutaminergic NMDA receptor density decreases progressively with age. If NMDA hypofunction and gestalt-like information processing are functionally related, then one could predict not only a decline in higher-level perceptual information processing with increasing age but also the rate at which such a decline in performance would occur (Trick & Silverman 1991). These suggestions do not in any way detract from the proposal posited by P&S implicating NMDA hypofunction to abnormal holistic perceptual processing in schizophrenia. It simply states that if a link does exist between NMDA hypofunction, perceptual organization, and higher-order cognitive processing, non-pathological aging seems to be just as compatible a neuro-behavioral model for the P&S hypothesis as schizophrenia.

Authors' Response

Unity and diversity in disorders of cognitive coordination

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Abstract: Studies of aging and autism as outlined by **Bertone, Mottron, & Faubert** (**Bertone et al.**) and by **Faubert & Bertone** suggest that disorders of cognitive coordination involving impairments of dynamic gestalt grouping and context-sensitivity may be common to several different disorders. We agree that such studies may shed light on these processes and their neuronal bases. However, we also emphasize that dynamic grouping and context-sensitivity can fail in various ways, and that, although the underlying pathophysiology may often involve NMDA-receptor malfunction, many different malfunctions are possible, and each of these may result from any one of a number of different etiologies.

R1. Disorders of cognitive coordination in aging and autism

The commentators suggest that cognitive coordination is impaired in both cognitive aging and autism. They empha-

size disorders of perception, but do not imply that other domains of cognition are of lesser consequence. The target article also emphasized perception, though it made clear that coordinating interactions are of crucial importance to all cognitive domains. Here we discuss aging in section R2 and autism in section R3. In each section we discuss psychological and then neurobiological issues. Section R4 raises the issue of individual differences within each of the different disorders, and section R5 presents a simple conclusion.

R2. Age, perception, and NMDA-receptor malfunction

Faubert & Bertone note that many cognitive capacities tend to decline with age, and suggest that several of these may involve processes which we include under the broad heading of *cognitive coordination.* Their central suggestion is that, in accord with our general conceptual framework, these changes in cognition may be the result of an age-related decline in NMDA-receptor activity. Within our conceptual framework, coordinating processes can be divided into those concerned with dynamic grouping and those concerned with contextual disambiguation. They are most obviously related to perception but, as coordination is relevant to all cognitive domains, an analogous discussion in relation to other domains such as memory, language, and motor control would be worthwhile.

Different cognitive functions decline with age to different extents. Decline is greatest in tests of "fluid intelligence," those that require novel solutions to novel problems, and is least in tests of "crystallized intelligence," those that depend predominantly on the use of well-learned bodies of knowledge such as vocabulary (Rabbitt 1993; Robbins et al. 1998). This is consistent with the view that cognitive coordination is particularly sensitive to the effects of aging because tests of fluid intelligence are likely to rely strongly on processes of dynamic organization and contextual modulation. However, we know of no evidence that normal cognitive aging involves anything analogous to formal thought disorder or phenomenal experiences of self-fragmentation, so a close analogy with schizophrenia seems unlikely. Nevertheless, **Faubert & Bertone**'s formulation recalls the similarity between aging and schizophrenia as conceptualized by Kraepelin, whose term for the illness was *dementia praecox* (early dementia). Though schizophrenia and normal aging differ in many ways, Faubert & Bertone's argument reminds us that there may be important similarities. If confirmed by future research, this could have important practical implications because it could lead to improvements in cognitive and pharmacotherapies aimed at reversing the impairments in both populations.

R2.1. Age-related changes in coordinating perceptual processes

As reviewed by Faubert (2002) there is evidence for a specific pattern of age-related changes in the perception of symmetry, motion, size, spatial frequency, and stereoscopic depth, and so forth. Faubert (2002) suggested that the common pattern running through all these changes is that age-related decline is greater when processing is in some way or other more "complex." To account for the various findings, the notion of complexity was outlined in various ways: (i) less hardwired is more complex; (ii) some tasks and spatial configurations require more complex processing (e.g., symmetry detection and tasks requiring comparison of figures at different locations); (iii) inter-attribute processing is more complex than intra-attribute; (iv) complexity increases with the number of stages of processing required; and, (v) long-range interactions are more complex than short-range ones. Faubert's emphasis on processes that are less hardwired is in accord with our conception of dynamic grouping, which also emphasizes processes that cannot be prespecified (Watt & Phillips 2000). The central issue here, however, is whether the findings Faubert reviews provide evidence for a specific age-related decline in processes of perceptual coordination.

Symmetry detection as studied by Herbert et al. (2002) is a clear example of a task that requires dynamic grouping (Watt & Phillips 2000, Fig. 2). On each trial a novel pattern of many dots was presented, with the discrimination to be made depending on the discovery of a symmetry axis that maximized the coherence of pairing across the axis for that particular stimulus. As this pairing could not be prespecified, it had to be discovered by processes of dynamic organization. The large age-related deficits that Herbert et al. observed in this task could therefore be due to deficits in dynamic grouping. To establish more firmly whether that is the case, it would be useful to develop versions of the symmetry detection task in which dynamic grouping is not necessary, and then to use those to determine whether age-related deficits depend specifically on the need for dynamic grouping. Knight et al. (2000) studied symmetry perception in a paradigm not requiring dynamic grouping. No dynamic grouping was required in their paradigm because simple familiar letter forms were shown on a blank background, with no need to discover new groupings defined only by symmetry. Using this paradigm, Knight et al. (2000) found no evidence of any abnormality in the use of symmetry as a figural descriptor by schizophrenic patients. Thus, Herbert et al. (2002) found evidence that symmetry detection requiring dynamic grouping tends to decline with aging, and Knight et al. (2000) found evidence that symmetry perception not requiring dynamic grouping is normal in schizophrenic patients. If both have deficits that are specific to paradigms requiring dynamic grouping, then aging will not be associated with deficits in the paradigm used by Knight et al. (2000) and schizophrenia will be associated with deficits in the paradigm used by Herbert et al. (2002).

In the case of motion perception we have well-developed paradigms with two versions, one that requires dynamic grouping and one that does not – that is, paradigms that compare the perception of local motion with the perception of global or coherent motion. Habak and Faubert (2000) found greater age-related decline for the perception of motion defined by second-order texture cues than for that defined by first-order cues. This is evidence for a specific deficit in the perception of global or coherent motion, but it requires confirmation using other paradigms for comparing the perception of local and global motion.

Prima facie, comparisons of figures at different locations may seem to have little to do with the dynamic processing implemented by coordinating interactions. Receptive fields in general integrate information from different locations and are primarily achieved by the prewired feed-forward connections with which coordinating interactions are contrasted. On further consideration, however, it seems that

the size-comparison task used by Sara and Faubert (2000) may well have involved processes of dynamic coordination as it required an arbitrary comparison of figures across locations that were arbitrary and task dependent.

Interattribute processing is by far the most frequently used example of the need for "binding." Prima facie then, the evidence for an increased age-related decline in interattribute comparisons (Faubert & Bellefeuille 2002) is evidence for a specific decline in coordinating interactions. Though we are skeptical of this frequently used example, we can interpret the task used as requiring dynamic coordination because that too required comparisons across attributes that were arbitrarily selected and task-dependent.

Prima facie, the suggestion that complexity can be related to the number of stages in a feature extraction hierarchy does not fit well with our distinction between the primary driving receptive field (RF) interactions that specify semantic content, and the coordinating interactions that modulate the primary processing to make it as coherent and task-relevant as possible (Phillips & Singer 1997). Within perceptual systems the RF synaptic connections are predominantly mediated by feed-forward connections, though some may be lateral, and the modulatory contextual field (CF) connections are predominantly mediated via lateral and descending connections. As the CFs have a distinct role, they have a distinct synaptic physiology – the NMDA-receptor channels, via which they modulate the primary RF processing. Therefore, in contrast to Faubert's notion of complexity, coordinating interactions are defined by their distinct function and physiology, not by where they occur in a hierarchy of processing. The findings interpreted by Faubert (2002) as evidence for greater age-related decline in higher-order features could nevertheless be interpreted as being due to deficits in coordinating interactions. This is because under certain conditions processing at higher levels depends in part on the coordinating interactions that occur at lower levels, and the higher the level the greater the possibility that failures in lower level coordination will affect processing. The conditions under which this is most likely are those in which dynamic grouping or contextual disambiguation at lower levels, or both, are most needed.

Similar arguments apply to the suggestion that long-range interactions are more complex than short-range interactions. Some RF connections may be long-range, for example, those necessitating callosal connections or those linking different cortical regions. Nevertheless, it is likely that cortical anatomy is such that RF connections are short so that a first sweep of primary feed-forward processing can be achieved rapidly, with coordinating interactions involving longer-range lateral and descending connections applying later. Overall, therefore, there will be a correlation between connection length and type of interaction, with coordinating CF connections tending to be longer than the primary feed-forward RF connections.

In summary, the evidence cited by Faubert (2002) supports the suggestion that age-related perceptual decline involves coordinating interactions. This raises many specific issues that require further research. For example, are the deficits in symmetry and coherent motion perception specific to versions of the paradigms that require dynamic grouping? Are there age-related disturbances of top-down influences on perceptual processes that are reversible by contextual and psychological manipulations as seen in schizophrenia (Silverstein et al. 1996a; 1996b; 1998)? Are there age-related deficits in context-sensitivity?

R2.2. Age-related NMDA-receptor malfunctions

Faubert & Bertone suggest that age-related NMDA-receptor malfunctions may cause the deficits in perceptual coordination. Before discussing this suggestion we must clarify two aspects of our perspective that may have been misunderstood. First, malfunction of the NMDA-receptor system does not necessarily involve any reduction in the number of NMDA-receptors. There are many other possibilities. Different subtypes have different subunit compositions, conferring subtly different physiological properties. It could therefore be that in some disorders it is the subunit composition that is abnormal, rather than the total number of receptors. Another important possibility is that it is not the NMDA-receptors themselves that are abnormal but the way in which they are modulated. NMDA-receptor function is dynamically modulated by several complex mechanisms, some pre- and some postsynaptic, and several genes that encode components of these mechanisms or regulate their expression have been shown to be susceptibility genes for schizophrenia (Moghaddam 2003). Although our target article emphasized the coordinating role of NMDA-receptors, it is now becoming clear that they are themselves modulated in various ways by several distinct mechanisms. This may explain why disorders of NMDA-receptor function can be subtle and specific to some aspects of cognition despite the fact that NMDA-receptors in general are widespread and fundamental to many aspects of brain function ranging from early embryological development to learning, memory, and coordination (Moghaddam 2003).

Faubert & Bertone's commentary also shows that a second aspect of our perspective needs further emphasis. This concerns long-term potentiation (LTP). Neither LTP nor any other form of plasticity is involved in the direct effect of NMDA-receptor-mediated neurotransmission on current activity. This was discussed briefly in section 3 of the target article, but needs further emphasis because our view differs from the standard textbook view that is still too frequently held by many researchers in the area. This standard view is that the primary role of NMDA-receptors is to facilitate learning. We disagree. Their primary effect, and their primary role, is to directly alter ongoing processing, and in particular to increase its coherence. In so doing they greatly increase postsynaptic depolarization, and thereby initiate the complex cascade of processes that lead to LTP and learning. Thus, what is learned are coherent, rather than incoherent, patterns of activity. NMDA-receptors have an important role in learning because they directly influence processing. If all forms of learning were suddenly suppressed, then this would not of itself directly alter the effect of NMDA-mediated neurotransmission on current activity. In the long-run, and in accord with Hemsley's (2003) perspective, it could, however, have an effect by suppressing adaptation to new statistical regularities. Our perspective sees this adaptation as including learning what predicts what, with the RF connections embodying the "whats" and the CFs the predictive relations between them. Therefore, in addition to their direct effect on current processing, NMDA-receptors can have an effect on later processing via their effect on learning. For formal and computational demonstrations of the possibility of neural networks that simultaneously discover

both the predictive relations and the entities between which they hold, see Phillips et al. (1995) and Kay et al. (1998).

We can now ask whether NMDA-receptor malfunction is likely to produce perceptual and other cognitive disorders associated with aging, and, if so, whether these malfunctions are likely to be the same as those producing cognitive disorganization in schizophrenia. In brief, the answer to the first question is "probably" and to the second is "probably not." We are not well acquainted with the evidence on changes in NMDA-receptor function with aging, but agree that some changes seem likely. As NMDA-mediated neurotransmission has a central role in both coordination and learning, impairments in several aspects of cognition are a likely consequence. NMDA-receptor malfunctions in aging are not likely to be the same as those in schizophrenia, however. As there are various subtypes of NMDA-receptors, and several ways in which they are modulated, it is highly likely that they can malfunction in many different ways. This would lead to a large family of disorders which are similar in that all are disorders of some aspects of learning and coordination, but which differ in the particular aspects involved. This predicts that though there may be similarities between NMDA-receptor malfunction in schizophrenia and aging, there are also likely to be important differences.

An analogy with color vision may be useful here. There are several different forms of color blindness, some inherited, some acquired, but, despite these differences, they are all impairments of color vision. Similarly, there may be several different disorders of coordination, with both similarities and differences. In contrast to color vision, however, coordination is not of relevance only to certain specialized domains of cognition, but to all.

R3. Analogies between schizophrenia and autism

Despite differences in clinical symptomatology between schizophrenia and autism there may be similarities in underlying cognitive deficits. We agree with many others in considering schizophrenia to be a developmental disorder, and therefore assume that our understanding of schizophrenia and other developmental disorders, such as autism, will be advanced by focusing on similarities and differences in underlying mechanisms rather than focusing only on outward signs and symptoms, which is the current approach adopted in DSM-IV. Therefore, when **Bertone et al.** state, for example, that the clinical symptoms of autism and schizophrenia are evident at different ages, this is technically correct only to the extent that DSM-IV criteria are used to define the onset of these disorders. There is much evidence, however, that abnormalities are evidenced at a very early age in people who go on to meet DSM-IV criteria for schizophrenia in adolescence or adulthood. For example, children born to mothers with schizophrenia demonstrate abnormalities in infancy, which has been called a pandysmaturation syndrome (Fish 1977; Fish et al. 1992). High-risk children also demonstrate cognitive and social functioning deficits in childhood and early adolescence (Erlenmeyer-Kimling 2000; Neumann 1995). Interestingly, it is the subgroup of schizophrenia patients that demonstrate perceptual organization deficits after illness onset (as defined by DSM-IV) who have the histories of poorest "pre-illness" functioning of all schizophrenia patients (Knight & Silverstein 1998). Therefore, although there are clearly differences between schizophrenia and autism, their different ages of onset, as defined by DSM-IV, should not be taken as evidence that their underlying illness mechanisms are operative at distinctly different ages.

R3.1. Impairments of cognitive coordination in autistic spectrum disorders

Evidence that schizophrenia and autism may, at least in the case of an impairment in cognitive coordination, be on a continuum comes from several sources. One is that there is a group of children, typically called multidimensionally impaired or multiplex developmentally disordered (Kumra et al. 1998), that is characterized by several features of schizophrenia (e.g., psychotic symptoms, cognitive deficits, elevated rates of schizophrenia in first-degree relatives) *and* by features characteristic of pervasive developmental disorders such as autism (e.g., impaired social skills, linguistic impairment, cognitive decline). There is also evidence for elevated rates of psychosis and disorganization in people with autism spectrum disorders (Dykens et al. 1991; Konstantareas & Hewitt 2001) and in those with milder developmental disorders such as dyslexia (Duggan & Brylewski 2002; Sanderson et al. 1999), along with evidence of failures in contour integration and mismatch negativity in the latter group (Demonet & Habib 2001; Simmers & Bex 2001). Autistic-like problems may also antedate the "onset" of schizophrenia in many cases (Asarnow et al. 1988), and cases of DSM-IV-defined schizophrenia can occur in childhood. Therefore, as the commentaries suggest, it may be fruitful to examine commonalties between these various developmental disorders, and to define the most relevant dimensions on which to conceptualize the similarities and differences other than simply the age at "onset of illness."

In pursuing this goal, however, we should not assume that similar test performance is necessarily due to similar abnormal mechanisms. For example, it has been suggested that the superior part processing in autism may be due to an enhanced ability to process elementary physical properties of stimuli (Mottron et al. 2000), whereas in schizophrenia the tendency to process parts over wholes has been attributed to a deficit in processing holistic stimulus properties (Knight & Silverstein 1998). Similarly, whereas visual perceptual learning deficits in autism are related to a reduced ability to discriminate familiar forms compared to controls, an increased ability to learn novel stimuli has also been observed (Plaisted et al. 1998). This contrasts with the finding that in schizophrenia learning for shape-like forms was equivalent to that of controls, whereas learning of novel patterns was impaired (Silverstein et al.1998).

We agree with **Bertone et al.**'s view that the similarities between the deficits of motion perception in autism and schizophrenia are particularly striking. Rigorous psychophysical tests have now established that in both disorders local motion perception is preserved but global coherent motion perception is impaired. This is strong evidence for a specific deficit in dynamic grouping in each of the disorders. Furthermore, this echoes the findings in studies of cognitive aging discussed above, indicating that deficits of dynamic grouping can be part of several different disorders.

There is also evidence for deficiencies of context-sensi-

tivity in autism. Happé (1997) found evidence that autistic subjects are less susceptible to several standard illusions. Some of the illusions used depend on context-sensitivity, and this applies in particular to the Ebbinghaus size perception illusion in which the size of a target figure is made to appear larger or smaller by surrounding it with smaller or larger figures respectively. Happé's evidence for a reduction in this illusion in autism is therefore evidence for reduced context-sensitivity in autism. There have been failures to replicate this finding, however, so its status is not yet clear (e.g., Ropar & Mitchell 1999).

As deficiencies in theory-of-mind tests are also prominent in autism and can also be related to impaired coordination (Brock et al. 2002), Uhlhaas (2003) studied the performance of schizophrenic patients on theory-of-mind tasks and on a psychophysical test of context-sensitivity based on the Ebbinghaus size perception illusion. He found a clear relation between the two in that poor performance on a particular theory-of-mind task (the hinting test) was associated with reduced context-sensitivity (and thus better performance) on the size perception task. Others (e.g., Safarti et al. 1999) have also found that disorganized schizophrenics have deficits in theory-of-mind tasks. This strengthens the grounds for assuming that a useful analogy can be drawn between cognitive impairments in schizophrenia and autism.

Brock et al. (2002) have proposed an "impaired temporal binding" hypothesis of autism that is very similar to our hypothesis of impaired cognitive coordination in schizophrenia. From a psychological perspective the hypothesis of a cognitive coordination deficit in autism has much in common with the far better known theory of reduced "central coherence" (Frith 2003). However, the cognitive coordination hypothesis has the great advantage that the fundamental concepts are given a precise formal specification and are related in detail to physiological mechanisms. The psychological concepts can therefore be developed and tested in a far more principled way.

R3.2. The pathophysiology of impaired cognitive coordination in autism

Bertone et al. suggest that as the clinical symptomatology in autism differs from that in schizophrenia their underlying pathophysiologies must also differ. We agree. We must note at the outset, however, that although section 6 of the target article did suggest that genetically specified variations in the strength of coordinating neuronal interactions may play an important role in autism, this does not necessarily imply a primary deficit in NMDA-receptors, and certainly not one that is the same as any associated with schizophrenia. This in no way implies that they cannot both involve NMDA-receptor malfunctions, however. As outlined in section R2.2, coordination within the glutamatergic system via the various subtypes of NMDA-receptor and their modulators provides a rich source of possibilities for many different malfunctions. It remains to be discovered which malfunctions produce which disorders, but even at this stage it seems likely that there is not only one kind of NMDA-receptor malfunction, but many.

Another point requiring clarification here is that we do not assume that NMDA-receptor malfunction necessarily produces a hypoglutamatergic state. Our working hypothesis is that it produces dysregulation of glutamatergic activity. In some conditions this will lead to an overall excess of activity, in others to an overall decrease, and perhaps in others to little or no net change in overall activity. However, in all cases this dysregulation will produce activity that is less internally coherent and less relevant to the current stimulus and task conditions.

Is there any evidence for NMDA-receptor malfunction in autism? Very little is known about its pathophysiology, but two main neurotransmitter systems have been implicated: the serotonergic and the glutamatergic. Genetic linkage studies indicate that one of the susceptibility genes for autism encodes a serotonin receptor protein, and increased serotonin (5HT) levels have been found in both blood and urine (reviewed in Gerlai & Gerlai 2003). Risperidone is a potent 5HT-2A receptor antagonist and has been reported to ameliorate some autistic symptoms (Hunsinger et al. 2000). In mice, serotonin 5HT-2A receptor antagonists are effective in counteracting the psychotomimetic effects of NMDA antagonists (Carlsson et al. 1999). Based in part on the similarity of these psychotomimetic effects to autism, Carlsson (1998) hypothesized that autism is a hypoglutamatergic disorder that involves the underactivity of NMDA-receptors and that may therefore be treatable with agents acting on the glycine site that modulates their activity, just as Javitt (2003) proposed for schizophrenia. Though still speculative, Carlsson's hypothesis clearly merits further investigation and development.

Any similarities between the neurochemical disorders in autism and schizophrenia must not be allowed to obscure their clear differences, however. The remitting and relapsing time course of schizophrenia and its good response to neuroleptics contrasts with the enduring and treatment-resistant character of autism, indicating that the underlying malfunction in autism has more profound and lasting effects on brain development. Furthermore, the above suggests that serotonin-NMDA interactions may be particularly important for autism. This contrasts with schizophrenia, where dopamine-NMDA interactions seem more important. Any such contrast is not absolute, however, as both classes of interaction are probably relevant to both disorders to some extent.

R4. The importance of individual differences

In the above we have referred to aging, autism, and schizophrenia as though they were essentially homogeneous, with no important internal variation. This may be misleading. It is better to think of each subject at any time as impaired to a greater or lesser extent on each of a number of basic aspects of mental function. From this perspective the goal is to discover the physiological bases for each of those aspects and their malfunctions. This way of looking at the problem of heterogeneity can be related to the notion of subtypes but is not equivalent to it.

There is clear evidence for distinct dimensions of variation within each of the disorders. The distinct dimensions of reality distortion, negativity, and cognitive disorganization in schizophrenia were outlined in section 1 of the target article, where we made clear that we were primarily concerned with the latter. In relation to aging, the evidence clearly shows that variance both within and between sub-

jects increases with age, and to account for this Rabbitt (1993) concluded that there are several different patterns of cognitive aging. In relation to the balance between local and global processing, Massman et al. (1993) found pronounced dissociations in performance in a global-local task among Alzheimer's disease subgroups. Those with greater impairment in verbal than spatial skills had particular difficulties in processing the local forms, whereas patients who had greater spatial than verbal impairment exhibited deficits in processing the configural (global) forms.

As knowledge of the various forms of autism has increased they have become known as autistic spectrum conditions. This suggests that it is only severity on a single dimension that varies, however, and there are at least three distinct areas of mental function on which severity of impairment can vary: social interaction, communication, and cognitive coherence. Emphasis on this multidimensionality may help explain puzzling and unpublished findings from five studies of the context-sensitivity of size perception in autism that have been conducted at Stirling. The studies have used various tests based on the Ebbinghaus illusion, and include rigorous psychophysical paradigms that unequivocally provide sensitive and specific measures of context-sensitivity (Phillips et al. 2003). The first three of these studies showed that, in accord with Happé (1997), autistic subjects as a group are less context-sensitive, and thus they performed significantly better than controls. When parents of the autistic subjects were also studied, they too showed significantly reduced context-sensitivity. The last two studies found no such differences, however. One of these studied university students who scored either high or low on the Autistic Quotient questionnaire (Baron-Cohen et al. 2001). There was no sign of low context-sensitivity in those with high autistic quotient scores, even though those subjects did have relative lengths of the second and fourth fingers indicative of high prenatal testosterone. Furthermore, a subject diagnosed with Asperger's syndrome, and who clearly has difficulties with social interaction, showed significantly greater context-sensitivity than the mean for students as a whole. Further analysis of the Stirling studies that did find reduced context-sensitivity in autism clearly shows that the group difference was due to just a subset of autistic subjects, with the remainder showing normal effects of context. Our current working hypothesis is therefore that impairments of social interaction, and possibly also of communication, can occur independently of any impairments in cognitive coordination, even though impairments in all three aspects of mental function often co-occur. One possibility is that malfunctions of a "mind-reading" module can occur independently of any general deficit in cognitive coordination, but widespread deficits in cognitive coordination can also occur, and have particularly strong effects on "mind reading" processes because they tend to rely strongly on coordinating interactions.

R5. Conclusion

In brief, we can build on the title of **Bertone et al.**'s commentary to state our conclusion: Cognitive decline in aging, autism, and schizophrenia have similar but different perceptual consequences, and similar but different pathophysiological bases.

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The letter "r" before author's initials stands for Authors' response to CC references

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