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Failures of Dynamic Coordination in Disease States and Their Implications for Normal Brain Function

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Abstract

Dynamic coordination may become compromised due to several nonindependent factors, including a reduced ability to generate oscillations and synchrony, neurotransmitter and receptor excesses and reductions, anatomical and cellular changes that impair connectivity at local and global scales, and changes in gene expression that stem from primary genetic or environmental causes. This chapter presents a review of disorders in which dynamic coordination failures have been identified. It compares and contrasts the forms and severity levels of the impairments in each disorder and links these to biological causes, as far as is currently known. Questions are posed regarding the implications of data on coordination failures for increasing our understanding of normal coordination and the possibility of its enhancement.

Overview and Issues

Dynamic coordination refers to the ongoing combination and recombination of neural signals to form higher-level, adaptive patterns of activity that retain the identity of the original signals yet are nonlinear due to feedback and recurrent processing. This can be contrasted with driving (or feedforward) input, which refers to the signals whose timing, salience, and relative contributions to emergent patterns of activation are modulated by coordinating processes. Dynamic coordination of neural activity allows for rapid and effective adaptation to changing conditions. However, the nearly infinite combination of potential networks that can be formed by local and long-range connectivity and the complex timing requirements—both within and across frequency bands—that are

needed to support them result in a complex system in which even small errors can have significant, large-scale consequences. In this chapter, I address the nature of these errors and their consequences.

Because dynamic coordination at the neural level—via synchronization of firing activity or other proposed mechanisms—is thought to support a range of cognitive functions—including visual perception, working memory, language, and self-representation—it is reasonable to ask whether reduced coordination is the mechanism underlying the dysfunctions in these processes found in certain neurological and psychiatric conditions. If this were to be the case, information on dynamic coordination could provide a unifying framework for understanding the core pathology underlying specific disease states. This knowledge could also foster cross-disorder comparisons, thereby clarifying genetic and neurodevelopmental contributions common to multiple diseases. By increasing our understanding of how disordered coordination leads to abnormal mental activity, we may be able to shed light on how normal coordination supports effective mental functioning and how coordination can be enhanced.

I begin by reviewing the evidence for failures of dynamic coordination in several illnesses: amblyopia, schizophrenia, Williams syndrome, autism, epilepsy, and Alzheimer's disease. Here the focus is on paradigmatic examples of coordination failures as demonstrated in studies of visual perceptual organization. Behavioral, functional magnetic resonance imaging (fMRI), and electrophysiological data are presented to clarify the similarities and differences in the severity, valence, and scope of coordination failures in these disorders. Discussion in the next section is more speculative, focusing on evidence for other forms of cognitive impairment in these and other disorders and addressing the question of whether these phenomena can also be seen as evidence of reduced coordination capacity. Thereafter, I address the issue of whether coordination failures are due primarily to reductions in a coordinating function, versus an increase in the strength of driving input, or a local attentional bias, or whether evidence for all of these exist. Following this discussion, I address neurotransmitter systems and their interactions, as well as neuronal and genetic abnormalities that may be involved in coordination changes. The final section poses questions regarding what abnormal dynamic coordination and its effects can teach us about normal brain and cognitive functioning.

Paradigmatic Evidence for Impaired Dynamic Coordination in Brain Diseases

Perceptual organization in vision is a paradigmatic example of dynamic coordination in that features are grouped together into an emergent holistic representation based upon their relationships to each other, while the signal for each individual feature remains intact. This process can be seen clearly in the case of contour integration (Figure 17.1), which has been studied extensively

in healthy and clinical populations. In a typical contour integration task, the conditions under which integration can occur, and the mechanisms responsible for it, are determined by employing stimuli with a continuous path of Gabor signals embedded in noise. Gabor signals closely model the receptive field properties of orientation-selective simple cells in primary visual cortex (V1) and are therefore ideal for the examination of these small spatial filters and their integration and interactions. Embedded contours cannot be detected by purely local filters or by the known types of orientation-tuned neurons with large receptive fields. The long-range orientation correlations along the path of the contour can only be found by the integration of local orientation measurements, and this can be seen as a classic example of dynamic coordination (Figure 17.1). Therefore, evidence of contour integration impairment associated with a brain disorder would be *prima facie* evidence of abnormal dynamic coordination in that condition. In the following subsections, this evidence is reviewed. Evidence for dynamic coordination failures using other measures of perceptual organization will also be noted.
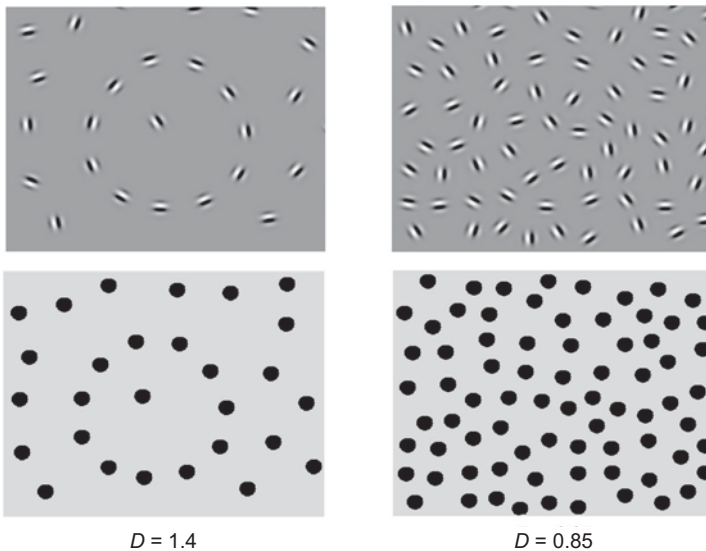

$D = 1.4$ $D = 0.85$

Figure 17.1 Examples of Gabor-defined contours with different D values (left: $D = 1.4$, right: $D = 0.85$). D is the ratio of the average distance between adjacent background elements to the average distance between adjacent contour elements; this is equivalent to the actual signal-to-noise ratio. In the bottom panels, Gabor elements were replaced by disks. Without orientation cues, the contour remains invisible at $D < 1$. This is the range where perceptual organization depends on long-range, horizontal, excitatory interactions between feature detectors based on relationships present in the input (in this case, correlations between orientations of adjacent contour elements) and represents a paradigmatic example of dynamic coordination. At $D > 1$ the contour can be perceived simply via density cues. Figure designed by Ilona Kovács; reprinted from Silverstein et al. (2000), with permission from Elsevier.

Amblyopia

Amblyopia is a condition characterized by abnormal binocular input due to problems with a single eye, leading to suppression of input from that eye. This can occur because of muscle weakness in one eye (e.g., "lazy eye"; strabismic amblyopia), or to one eye having significantly greater refractive error than the other (anisometropic amblyopia). Amblyopia has been associated with reduced contour-integration performance (Kovács et al. 2000), especially when contours must be linked within background noise and when there is positional uncertainty. These impairments have been found in both strabismic and anisometropic amblyopia, although less consistently in the latter condition. Findings of amblyopia-related reduced contour integration have been replicated in animal studies (Kiorpes 2006). The findings cannot be attributed to reduced contrast sensitivity or other low-level visual factors. In humans, contour-integration performance varies as a function of the degree to which binocular input was restored in childhood via treatment (Kovács et al. 2000).

Because all studies to date of contour integration in amblyopia have solely used behavioral measures, there is a relative lack of direct physiological evidence on biological mechanisms involved in the impairment. Research in cats indicates that visual processing of high frequency gratings by the amblyopic eye is associated with significantly reduced neural synchrony compared to that observed in the fellow eye, suggesting that altered synchrony and its associated excitatory and inhibitory mechanisms may be involved in human amblyopia (Roelfsema et al. 1994). A recent structural MRI study found reduced gray matter in visual processing areas (Mendola et al. 2005), suggesting a link between abnormal contour integration and gray matter loss. Interestingly, of all the disorders reviewed in this section, amblyopia has the most limited form of dynamic coordination failure (limited only to vision), and has been associated with only gray matter reduction. In contrast, other disorders have more widespread coordination failures, and this greater degree of impairment has often been associated with both gray and white matter reductions (see below). This supports the hypothesis that white matter tracts are critical for inter-regional coordination, whereas they are less critical for intra-regional coordination, of which contour integration may be an example.

Williams Syndrome

Williams syndrome is a genetic and neurodevelopmental disorder characterized by cardiac anomalies, overdeveloped expressive language skills, normal to superior memory abilities, a strong desire to talk but often poor social understanding, and poor motor and visuospatial skills. Many, but not all, studies demonstrate that perceptual organization, including contour integration, is impaired in Williams syndrome (Martens et al. 2008). Some of the discrepancies may be accounted for by evidence that grouping by some features (e.g.,

luminance, closure, alignment) is intact, whereas grouping by others (e.g., shape, orientation, proximity) is impaired (Farran 2005). A recent fMRI study indicated reduced activation in visual and parietal cortices in Williams syndrome patients during a processing of global forms made up of local features (Mobbs et al. 2007). Evidence of reduced functional connectivity between cortical regions during object processing has also been found (Martens et al. 2008). Evidence of both gray and white matter reduction has been found in Williams syndrome. To a large extent, these findings parallel those found in schizophrenia (see below), although the clinical features of the syndromes are very different. This is an important consideration as attempts are made to determine the role of coordination failures in the overall pathophysiology of each disorder.

Schizophrenia

In contrast to amblyopia, schizophrenia is a condition in which dynamic coordination appears to be impaired throughout the cortex, as evidenced by multiple cognitive impairments. All studies of contour integration in schizophrenia indicate impaired performance. Performance is also significantly, and inversely, correlated with scores on the Ebbinghaus illusion task (see Figure 17.2), in which schizophrenia patients are more accurate in size judgments secondary to reduced effects of contextual integration (Uhlhaas, Phillips et al. 2006). A recent fMRI study indicated that impaired contour integration was associated with reduced activation in V2–V4 in schizophrenia patients, areas where
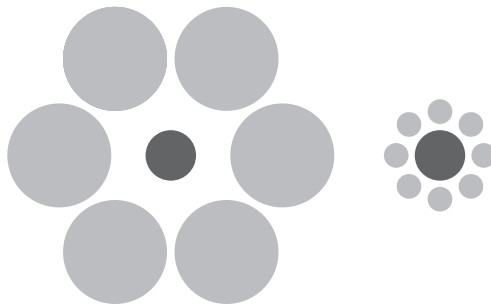

Figure 17.2   Examples of the Ebbinghaus illusion. The two inner circles are the same diameter. When the inner circle is surrounded by smaller circles, most observers perceive it as larger than its actual size. In contrast, when surrounded by larger circles, most observers perceive it as smaller than its actual size. People with schizophrenia have been found to be less susceptible to this illusion. In most laboratory tasks incorporating this phenomenon, the size of the inner circle is compared to a no-surround circle, or two circles with surrounds (one larger, one smaller) are shown and the subject is required to determine which inner circle is larger/smaller. By manipulating the actual sizes of the inner circles, the sizes of the outer circles, and/or the distance between inner and outer circles, a parametric determination of context sensitivity can be obtained.

integration of features into wholes occurs (Silverstein et al. 2009). These data are consistent with findings from human (nonclinical) and monkey fMRI studies that identified cortical regions involved in contour integration (e.g., Kourtzi et al. 2003).

Studies of perceptual organization using paradigms other than contour integration also consistently indicate that integration of noncontiguous elements is impaired in schizophrenia (for a review, see Uhlhaas and Silverstein 2005). In contrast, processing of textons, continuous contour, and features such as symmetry are intact. This suggests that in schizophrenia, coordination via pre-specified feature hierarchies is not affected, whereas dynamic coordination is impaired. As further evidence of this, studies that specifically studied top-down effects on grouping indicate that performance is especially poor under these conditions.

A consistent problem in schizophrenia research is the generalized deficit, or the tendency of patients to perform poorly on nearly every measure, for reasons that may have nothing to do with the process purportedly being measured (e.g., sedation from medications, poor motivation) (Silverstein 2008). However, in ten of the studies of perceptual organization in schizophrenia, the reduced ability to integrate information and the subsequent reduced influence of visual context led to superior performance, compared to controls, in terms of either making decisions about individual features or reduced susceptibility to illusions. Therefore, evidence for impairments in visual integration has been convincingly demonstrated independent of a generalized deficit. These impairments also cannot be accounted for by medication, as they have been demonstrated in nonmedicated patients, and task performance is not correlated with medication dose in medicated patients. This extensive experimental literature is consistent with earlier clinical descriptions and first-hand subjective patient accounts of fragmented face, object, and scene perception in schizophrenia (see Carr and Wale 1986).

Electrophysiological studies of perceptual organization in schizophrenia have identified reduced P100 amplitude when patients viewed fragmented pictures (e.g., Foxe et al. 2001). A recent study found reduced N150 amplitude to global fragmented targets in a global-local task in schizophrenia (Johnson et al. 2005), and the source of that waveform has been localized to V3/V3a within the lateral occipital complex, an area in which feature integration occurs (Di Russo et al. 2001). Especially relevant to the issue of dynamic coordination are studies of synchronized neural activity during performance of perceptual organization tasks. In nonpatients, synchronization of oscillatory activity has been identified within the gamma (reflecting binding of activity at shorter cortical distances, often within-region) and beta (reflecting longer-distances, often between regions) bands (von Stein et al. 1999). Uhlhaas, Phillips et al. (2006) demonstrated smaller increases in beta-band synchrony among patients viewing degraded facial images, evidence consistent with earlier data on smaller increases in gamma-band synchrony during processing of illusory contours

(Spencer et al. 2004). Further evidence for abnormal dynamic coordination in schizophrenia comes from findings of reduced stimulus-locked power within the beta and gamma bands, reduced evoked stimulus-locked oscillatory activity within the gamma band, and reduced non-stimulus-locked oscillations within the gamma band during visual or auditory processing tasks (Uhlhaas, Haenschel et al. 2008; Uhlhaas and Singer 2006). Abnormal oscillatory activity is present at least as early as the first illness episode (Symond et al. 2005).

In contrast with findings of reduced synchrony in first episode patients, behavioral evidence for perceptual organization dysfunction has not been found among either high risk or first episode patients (Silverstein et al. 2006; Parnas et al. 2001), except in one study, in which it was only found among subjects with increased symptoms (Uhlhaas et al. 2004). In contrast, perceptual organization dysfunction has been consistently identified in older patients with a chronic disease course. This parallels diffusion tensor imaging data, which indicate smaller white matter changes at first episode compared to patients with chronic illness (Friedman et al. 2008), supporting a link between white matter integrity (and corticocortical connectivity) and dynamic coordination. Taken together, these data suggest both a core illness-related impairment and a progressive process. Further evidence for this is that perceptual organization impairments in schizophrenia are most reliably found in individuals with histories of poor premorbid social functioning (Knight and Silverstein 1998), suggesting that the impairment is associated with a core illness subtype with neurodevelopmental disturbances: the subgroup of patients with histories of good functioning before the initial psychotic episode generally demonstrate normal perceptual organization. Even among the poor premorbid functioning subgroup, however, the severity of the impairment correlates with degree of symptomatology, especially disorganized thinking.

Autism

Autism is a neurodevelopmental disorder characterized by severe cognitive and social functioning deficits. Studies have demonstrated that autism is associated with reduced context sensitivity and an increased ability to recognize or make decisions about individual elements embedded within visual displays (Happe and Frith 2006). Studies specifically investigating integration of spatially separated stimuli reveal conflicting findings; some show reduced integration whereas others show normal integration (e.g., Del Viva et al. 2006). As with schizophrenia, it appears as if a determinant of integration impairment in autism is illness severity. Deficits in autism are most reliably found in persons with comorbid mental retardation, a frequent aspect of the disorder. People with autism with normal IQs and people with autism spectrum disorders are more likely to demonstrate normal perceptual organization of both static and moving displays. As reviewed by Uhlhaas and Singer (2006), converging evidence from EEG and fMRI studies indicates reduced functional connectivity

and smaller increases in gamma-band synchrony compared to controls during cognitive tasks. The biological bases of these abnormalities are less clear, but it has been proposed that autism may be characterized by excess excitation and unstable cortical networks. White matter abnormalities have also been identified in autism, although these have not been specifically linked to task performance.

The apparent similarities between schizophrenia and autism suggest that each should have significant comorbidity of features from the other disorder. Indeed, this has been found (Rapoport et al. 2009; Sprong et al. 2008), raising the possibility that genetic and neurobiological studies exploring the boundaries and overlap between these conditions may help identify the core pathology caused by coordination failures.

Alzheimer's Disease

In contrast to amblyopia, in which coordination failures are caused by abnormal sensory input, and schizophrenia, in which they are caused by an interaction between neurodevelopmental abnormalities and progressive illness effects, in Alzheimer's disease, dynamic coordination failures are due to late life neurodegeneration. At least six studies to date (reviewed in Uhlhaas, Pantel et al. 2008) have documented impaired perceptual organization in Alzheimer's disease. Patients with white matter atrophy demonstrated the poorest contour integration ability.

Parkinson's Disease

Parkinson's disease involves massive loss of dopaminergic neurons in the substantia nigra, leading to akinesia, tremor, and cognitive deficits. Unlike other disorders reviewed here, Parkinson's disease is characterized by increases in relative synchrony. This evidence is largely physiological and has thus far been seen only in the motor domain. It is not yet known whether Parkinson's disease is characterized by nonmotor manifestations of impaired coordination. Uhlhaas and Singer (2006) reviewed evidence that increased beta-band synchronization in cortical motor areas is related to akinesia in Parkinson's disease. There is also evidence for abnormal oscillatory activity that is coherent with the frequency of limb tremor, and data showing that tremor is associated with abnormal synchronization of motor neurons. Parkinson's disease offers an interesting contrast to amblyopia. Both involve focal abnormalities of synchronized activity: the former is characterized by increased patterned motor activity, the latter by a reduced ability to generate patterned visual representations. The focal activity in Parkinson's disease can also be viewed as an analog to the focal activity in schizophrenia (see next section) and epilepsy (discussed below). In all cases, there is heightened self-organized activity that is relatively impermeable to mental or environmental influences.

Epilepsy

Epilepsy is a heterogeneous category that includes conditions involving restricted seizure activity as well as seizures involving the spread of activity throughout the cortex. Because it is not possible to conduct behavioral testing during seizure activity, the evidence on dynamic coordination in epilepsy comes solely from physiological recording. Evidence for both increased and decreased synchronization of activity has been found. A synthesis of the evidence (Uhlhaas and Singer 2006) suggests that synchronization between distant cortical regions is reduced, whereas it is increased in the epileptic focus (i.e., the site of seizure origin). Moreover, reduction in synchrony may play a causal role in seizure formation by allowing for the formation of the epileptic focus, whose self-sustaining activity is relatively uninfluenced by other cortical activity. In general, the setting of reduced synchrony—along with isolated areas of increased synchrony—that is hypothesized to characterize seizure proneness has also been suggested to exist in schizophrenia (see next section). Interestingly, there is an increased risk of schizophrenia in people with epilepsy, and NMDA receptor antagonists (used to model schizophrenia; see below) lead to EEG changes similar to those seen in some forms of epilepsy (Lisman et al. 2008).

Putative Evidence for Impaired Dynamic Coordination in Brain Diseases

Phillips and Singer (1997) hypothesized that the cortical algorithm and cortical circuitry involved in dynamic coordination are implemented throughout the cortex and are operative for multiple cognitive functions, including perceptual organization, attention, working memory, long-term memory, language, and consciousness. Implementation of this algorithm modulates the timing and strength of driving input and creates the higher-order representations that emerge from it, based on contextual relationships that can be established in both the input itself and information about past experience with similar stimuli. The neural circuitry necessary to produce the contextual fields supporting dynamic coordination is thought to rely heavily on NMDA receptor (excitatory, pyramidal cell) and GABAergic (inhibitory, interneuron) activity. A similar proposal, in terms of an isomorphism in neural network activity underlying multiple forms of cognition, was advanced by Fuster (2003). Evidence in support of the Phillips and Singer (1997) and Fuster (2003) theories includes similar modulatory circuitry in all areas of the cortex, the role of interneurons and neural networks in generating synchronized oscillations, and the role of gamma-, beta-, and theta-band synchrony in implementing all of the cognitive functions hypothesized to be based on this circuitry. Models based on principles of perceptual organization have also been applied to binding of social information in

social cognition (e.g., theory of mind; Blakemore and Decety 2001) as well as to segregation of information in observed behavior and relationships between unit size and attributions for behaviors (Baldwin et al. 2001). These functions, however, have not yet been linked to biological processes.

Regarding brain diseases, support for the above models would come from evidence of impairment in nonperceptual cognitive functions, as well as evidence that these impairments involve reduced coordination and abnormal synchronization. The latter is critical, because while there is much evidence for cognitive deficits in attention, memory, and language in psychiatric and neurologic disorders, this evidence has typically not been understood in terms of integrative and coordinating processes. A summary of the evidence, which suggests that disorders with multiple cognitive deficits can be understood within the framework of widespread dynamic coordination failure, is presented below. To date, this has largely come from studies of schizophrenia.

Amblyopia

As noted above, in amblyopia, deficits in dynamic coordination appear to be limited to visual processing, secondary to impaired input early in development.

Williams Syndrome

The hypothesis of multiple examples of dynamic coordination failure in Williams syndrome has not yet been investigated. Evidence of fine motor-sequencing difficulties, attentional problems (especially at younger ages), and impaired social inference are areas worthy of further study. It is also possible that the specific genetic factors involved in Williams syndrome produce a relatively circumscribed deficit in the area of visuospatial processing that is unrelated to other illness features.

Schizophrenia

Three sources of evidence support the hypothesis of widespread dynamic coordination failure: (a) behavioral studies indicating reduced binding in nonperceptual cognitive impairments, (b) involvement of abnormal oscillatory or synchronized activity in these impairments, and (c) significant correlations between indices of these impairments. Regarding the first, a recent study indicated that reduced perceptual organization was associated with attentional disengagement (i.e., reduced ability to maintain attentional focus within groups of stimuli) in an attention task (van Assche and Giersch 2009). Another recent study (Lefèbvre et al. 2009) indicated reduced binding of features during encoding of both spatial and temporal information in a working memory task, suggesting that the binding impairment is not limited to spatial information. These data are consistent with poor performance on tasks of coherent motion

detection (Tschacher et al. 2008), which involve both spatial and temporal processing. It has also been shown that schizophrenia is characterized by reduced context-based binding of cues in episodic memory (Waters et al. 2004) and reduced relational memory organization (Titone et al. 2004). Regarding the second point, Uhlhaas, Haenschel et al. (2008) reviewed evidence for abnormal oscillatory activity and synchrony during a range of cognitive tasks in schizophrenia.

Evidence from several studies indicates that impairments on multiple indices of reduced dynamic coordination are related in schizophrenia. For example, severity of impairment on tests of perceptual organization is significantly correlated with the level of thought disorganization (Knight and Silverstein 1998; Uhlhaas and Silverstein 2005). Test scores are also significantly correlated with scores on theory of mind tasks, supporting views of similar integrative mechanisms underlying both perception and aspects of social cognition involving inferential or propositional reasoning (Uhlhaas, Linden et al. 2006). These data support the hypotheses of Carr and Wale (1986) and Phillips and Silverstein (2003) that schizophrenia is characterized by multiple variants of the same basic dysfunction, leading to widespread failures in binding related information together into coherent representations to support effective thought and behavior. This impairment is present in pre-attentive and post-attentive as well as spatial and temporal processing. It has also been observed in functions as high level as autobiographical memory, the disturbance of which has been attributed to a reduced binding of self-representations with observed actions during encoding of episodic memories (Danion et al. 1999).

Overall, evidence from studies of schizophrenia suggests failures of perceptual organization and associated widespread reductions in oscillatory and synchronized neural activity. However, there are also suggestions of excessive synchronization. For example, Hoffman and McGlashan (2001) suggested that symptoms such as delusional ideas or hallucinations might reflect "parasitic foci." This refers to self-perpetuating attractor states, which, although reflecting abnormally strong connectivity themselves, are thought to be formed within a context of reduced connectivity (i.e., functional fragmentation) in which nonreality-based combinations of representations are more likely to occur. This hypothesis is consistent with evidence of abnormal neural coactivation secondary to white matter abnormalities in patients with auditory hallucinations (Hubl et al. 2004). On a more global scale, there is evidence that the smaller post-stimulus increases in gamma-band synchrony in schizophrenia reflect an abnormally high baseline level of synchrony, against which only small relative increases are possible (Flynn et al. 2008). This could, as does the hypothesis of reduced coordination, also account for the reduced ability of emergent feature properties (e.g., gestalts) to take precedence in conscious awareness over background information. Such data are consistent with recent findings of network hyperactivity in patients who experience an exaggerated self-awareness during conditions when self-awareness is normally suppressed, and findings that

this hyper-connectivity is present even at rest (Whitfield-Gabrieli et al. 2009). The latter may be the neural signature of the symptom of "hyper-reflexivity" discussed by Sass and Parnas (2003). To resolve the competing positions of hyper- and hypo-connectivity, it was suggested that for relatively inflexible networks, such as parasitic foci (and associated stable symptoms such as delusional ideas and hallucinations), to form, there must be a reduction in functional connectivity in surrounding areas (similar to that proposed for seizures, see below), whereas symptoms such as rapid shifts in perspective, and disorganized thinking and speech, are characterized by states of transient, hyper-plastic connectivity (Guterman 2007). An important unresolved issue here is the extent to which heterogeneity in coordination abnormalities in schizophrenia is related to heterogeneity in autonomic arousal abnormalities, which are also observed in schizophrenia.

Much research in schizophrenia has implicated dysfunction of the prefrontal cortex (PFC), and has noted the control functions of this region in domains such as temporal context processing, working memory, relational encoding in memory, and action planning. Recent evidence (Barbalat et al. 2009) suggests, however, that information is hierarchically organized in the PFC in part based on the temporal framing of action and events, that activity in the caudal lateral PFC varies as a function of episodic and contextual signals, and that activity is reduced in this region in schizophrenia. Therefore, rather than viewing the PFC as a monolithic control center that is responsible for imposing order on the output of operations from other cortical areas, it, as do other regions, may operate via dynamic coordination, with, in this case, the coordinating algorithm generating the typical "gestalts" of the PFC (e.g., action plans, anticipated behavior–consequence links, and temporal context). To what extent then can the evidence for PFC abnormalities in schizophrenia be accounted for by coordination failures within this region? Conversely, to what extent does the evidence that the frontal cortex is involved in grouping of distant, but not closely separated, visual elements (Ciaramelli et al. 2007) and that in schizophrenia, perceptual organization deficits are most pronounced when top-down feedback is required for effective performance, implicate a specific role for the PFC in dynamic coordination in this and other illnesses with coordination failures, and also in healthy individuals?

Autism

Uhlhaas and Singer (2006) review evidence that in autism, a reduced ability to group stimuli is found in auditory processing, linguistic context processing, and social cognition, in addition to vision. To date, there have been few studies of physiological processes associated with impairment on these tasks, but one study (Grice et al. 2001) found reduced gamma-band synchrony during a face perception task.

Alzheimer's Disease

Despite behavioral evidence for reduced perceptual organization and profound memory deficits, and resting physiological evidence for reduced neural synchrony, there has been only one task-related study, and this indicated reduced synchrony during a cognitive (working memory) task. Uhlhaas and Singer (2006) concluded that in addition to loss of neurons, phenomena found in this disease also reflect impairments in the coordination of distributed neural activity, which could be due to gray and white matter reduction.

Other Conditions

Studies in other conditions (e.g., epilepsy, Parkinson's disease) could clarify the extent to which *multiple* impairments reflect reduced dynamic coordination, but have yet to be done. Interestingly, recent findings of reduced synchrony in response to steady state auditory stimulation in multiple sclerosis (Arrondo et al. 2009), a disorder characterized by white matter degeneration, support the hypothesis that these tracts are involved in dynamic coordination, and therefore that abnormalities therein could produce a range of coordination failures in disorders with this feature.

Issues that Arise

Can Life Experience Cause Reduced Dynamic Coordination?

Evidence concerning the disorders reviewed above suggests that abnormal dynamic coordination can occur in the context of abnormal sensory input (e.g., amblyopia), neurodevelopment (e.g., Williams syndrome, autism), neurodevelopmental abnormalities interacting with stress and neurotransmitter/receptor changes (e.g., schizophrenia), degenerative processes (Alzheimer's disease, Parkinson's disease), or developmental, injury-related, or idiopathic causes (epilepsy). It remains to be determined whether, and to what extent, these different etiologies produce qualitatively different forms of coordination abnormalities. Another relatively unexplored issue is whether dynamic coordination failures can occur due primarily to neurobiological changes caused by abnormal life experience.

As an example of this, it has been hypothesized that auditory hallucinations in posttraumatic stress disorder and schizophrenia may consist of sensory components of memories of traumatic incidents (e.g., sexual abuse) that are decontextualized from the majority of the episodic memory trace and its associated affect (Read et al. 2005). This is similar to the model for dissociative symptoms postulated long ago by Breuer and Freud (1895), in which the affect associated with the traumatic experience is split off from ideation related to the experience. This is also similar to the ideas of Janet (1889), who proposed

two core phenomena in mental functioning: one that preserves and recreates the past, and one that involves integration (van der Hart and Friedman 1989). The latter "reunites more or less numerous given phenomena into a new phenomenon different from its elements. At every moment of life, this activity effectuates new combinations which are necessary to maintain the organism in equilibrium with the changes of the surroundings" (Janet 1889, cited in van der Hart and Friedman 1989:5)—a view similar to Phillips and Singer's (1997) concept of dynamic coordination. In Janet's view, in schizophrenia and other mental disorders involving cognitive fragmentation there is reduced integration, such that components (e.g., memory traces) are unmodulated and appear magnified relative to ongoing events in the person's life.

Evidence in support of a link between trauma and reduced coordination of mental activity comes from a class of mental disorders known as dissociative disorders, which are characterized by losses of conscious awareness of aspects of experience. This can involve identity (psychogenic fugue states), aspects of remembered experience (psychogenic amnesia), or aspects of self (e.g., dissociative identity—multiple personality—disorder). Dissociative identity disorder is commonly associated with histories of childhood physical and/or sexual abuse, and psychogenic fugue and psychogenic amnesia are often associated with intolerable stress in adulthood. While no studies have yet examined dynamic coordination in these disorders, clarification of the extent to which dissociation involves reduced coordination is provided by studies of hypnosis, in which dissociation of consciousness (e.g., the non-experience of pain), and phenomena such as hallucinations can be temporarily induced, especially in highly hypnotizable subjects (Silverstein 1993). Preliminary evidence from hypnosis research indeed suggests that splitting apart of normally integrated representations does involve reduced coordination. For example, Fingelkurts et al. (2007), in a case study, demonstrated reduced functional connectivity, across multiple frequency bands, after hypnotic induction compared to baseline. The authors concluded that, in highly hypnotizable subjects, cognitive modules and subsystems may be temporarily incapable of communicating with each other. In a controlled study, Croft et al. (2002) found that prior to hypnosis, gamma synchrony predicted pain ratings for both high- and low-hypnotizable subjects. However, during hypnosis, while this relationship was again observed for low-hypnotizable subjects, it was eliminated for high-hypnotizable subjects. These data suggested that hypnosis involves a functional disconnection between the frontal cortex and other areas, and thus that the symptoms of dissociative disorders may reflect functional and/or anatomical disconnections.

Interestingly, increasing evidence suggests that people with schizophrenia have high rates of childhood trauma, and one study has found links between trauma history in schizophrenia, more severe illness, and more impaired contour integration (Schenkel et al. 2005). Trauma is rarely examined as a correlate of cognitive or biological functioning. However, it could be a common factor in dissociation and impaired dynamic coordination across a range of

mental disorders that develop after childhood. Relatedly, factors such as being bullied in childhood, racial discrimination, and chronic social defeat have also been linked to the later development of psychosis, all raising the possibility that chronic profound stress alters dynamic coordination (the biological basis of this possibility will be discussed below).

Is Reduced Dynamic Coordination Involved in Emotion-processing Abnormalities?

To date, nearly all research on dynamic coordination in mental disorders has focused on cognitive phenomena (e.g., perceptual organization, working memory, hallucinations). However, a hallmark of several of the disorders considered is altered emotion processing and expression. To what extent is altered dynamic coordination involved in these abnormalities, and/or in the apparent decoupling between ideation and emotional experience that can be found in these disorders?

Intriguing evidence comes from studies of alexithymia, a personality trait characterized by a reduced ability to identify and verbally label emotional experiences. A recent study (Matsumoto et al. 2006) found that whereas in healthy controls gamma-band power and phase synchronization were increased when processing emotionally negative stimuli, individuals with alexithymia did not demonstrate either increase. This suggests that people with alexithymia may be characterized by a reduction in communication between brain regions and a related reduction in the integration of mnemonic and/or emotional information during processing of emotional stimuli. These data also support the hypothesis that altered gamma-band synchronization is involved in the splitting of ideation and affect that has been hypothesized to occur in people with histories of trauma, as noted above.

In contrast to alexithymia, a disorder that is characterized by excessive emotional activity (and often a history of childhood trauma) is borderline personality disorder (BPD). BPD is characterized by emotional dysregulation, including anger outbursts and intense sadness, feelings of loneliness and emptiness, transient psychotic symptoms, and an unstable sense of identity (and unstable relationships). In a recent study (Williams et al. 2006), during a tone discrimination task, patients with BPD demonstrated a delay in the generation of gamma synchrony over posterior cortical sites and a reduction in gamma synchrony over right hemisphere sites. Moreover, the delay in posterior synchrony was associated with ideational distortions involving self and others, and reduced right hemisphere synchrony was associated with behavioral impulsivity. Williams et al. (2006) suggest that the data indicate reduced functional connectivity between posterior and frontal networks, and that this is a mechanism in the abnormal evaluation of stimulus significance and dyscoordinated emotional responses seen in BPD.

Taken together, the preliminary data from studies of alexithymia and BPD—conditions at the extremes of emotional experience—suggest that there is an optimal degree of synchronization necessary for adaptive integration of emotional and cognitive experience. Abnormalities in networks involved in emotion–cognition integration can lead either to reduced emotional experience and expression or to unmodulated expression. This perspective on coordination and emotions can be seen as analogous to the difference between, for example, amblyopia (reduced coordination) and Parkinson's disease (increased coordination).

The research presented in the last two subsections suggests that manifestations of dynamic coordination failures may extend beyond the cognitive and motor phenomena that have been studied thus far. Specifically, it is suggested that dysregulated emotional experience and behavior may also be manifestations of impaired dynamic coordination. Neuroscience research techniques have only begun to be applied to these important aspects of brain disease. Nonetheless, theories have appeared in which (a) mood regulation; (b) coordination of feelings, thoughts, and behavior; and (c) balance between thought and instinctual drives are seen as three core dimensions of brain function, with all of these rooted in synchronized oscillations. In this view, a range of mental disorders (e.g., mood disorders, schizophrenia, obsessive-compulsive disorder, phobias, BPD) reflects brain region-specific variation in the neurodevelopment of the capacity for coordinated activity (Pediaditakis 2006).

Similarly, the extent to which the apparent splitting between mental contents, and/or between mental and emotional content following traumatic or other chronically stressful life experiences, involves reduced dynamic coordination requires further study. Preliminary evidence from a number of psychiatric conditions suggests that a history of trauma may lead to selective areas of reduced coordination, and that this can account for commonality of symptoms across a variety of disorders including dissociative, borderline personality, and psychotic disorders—most of which were once grouped together as either "hysteria" or "schizophrenia" where similarities in the core integrative psychic dysfunction were suggested long ago (e.g., Jung 1907). Questions arising are whether corrective emotional experiences (e.g., dynamic psychotherapy, cognitive behavior therapy, healing relationships) can reduce or eliminate manifestations of altered dynamic coordination, and if so, whether this is a mechanism by which psychotherapy is effective.

Overall, the research reviewed above suggests that dynamic coordination abnormalities can manifest in multiple ways, causing a variety of pathological phenomena depending on their scope (i.e., extent and loci of distribution in the cortex), valence (excessive or reduced), and severity. An unresolved issue is the extent to which differences on these three dimensions can parsimoniously account for the clinical presentations in each condition. What is needed, therefore, are (a) additional biomarkers of cognitive coordination that are separable from generalized performance difficulties and symptom severity, and (b) more

sophisticated models that explain and clarify the mechanisms whereby differences in scope, valence, and severity of coordination failures specifically account for individual symptoms and syndromes, and their differences.

Is Apparent Dynamic Coordination Failure Caused by Too Little Integration or Too Much Feature Processing?

The data cited in the first section provide consistent evidence for reduced performance on tests of perceptual organization in specific brain diseases. This literature generally assumes that this reflects reduced integrative or modulatory ability (except where noted, e.g., Parkinson's disease) in the presence of normal intensity of driving input. However, it is also possible that these findings reflect (a) excessive feature processing even in the face of normal integrative functions or (b) an attentional bias toward local stimuli in the presence of normal global processing. Studies of perceptual organization typically have not been able to distinguish between these explanations; however, some evidence suggests that this issue is worth exploring. For example, studies of global and local processing with compound stimuli have demonstrated that adopting a focus on one level or the other (i.e., an attentional bias) can change which level appears to take precedence, raising the possibility that an illness-related attentional bias could produce what looks like a dynamic coordination failure. In Williams syndrome and autism, there is evidence of attentional bias toward local processing (Porter and Coltheart 2006), although not in all studies. This contrasts with the excessive global bias found in Down's syndrome, and thus it is possible that illness-related and illness-specific attentional biases exist, in addition to, or rather than, the hypothesized illness related integration deficit. In schizophrenia, a long history of findings of sensory gating disturbance and subjective reports of increased subjective intensity of sensory stimuli are consistent with the hypothesis of excessive feature processing. Further, in autism, there is some evidence for excessive processing of the meaning of words (Uhlhaas and Singer 2006). Questions that arise from these considerations include:

- Are the findings of increased baseline synchrony (Flynn et al. 2008) and hyperactivity in cortical networks (Whitfield-Gabrieli et al. 2009) in schizophrenia compatible with excessive levels of driving input?
- Can explanations involving excessive driving input or local attentional bias account for reduced organization in other cognitive functions (e.g., memory, language, social cognition) in schizophrenia, autism, and Williams syndrome?
- To what extent do attentional biases to local or global levels reflect coordination impairments (see Engel et al., this volume)?
- Is it possible to have both excessive processing of features and reduced integration? This is consistent with the conclusions of an fMRI study

demonstrating excessive left-right frontal connectivity and reduced anterior-posterior connectivity in schizophrenia (Foucher et al. 2005).

- Can the problem of apparent similarities in dynamic coordination failures in disorders with different clinical presentations be, at least in part, resolved by attributing the deficits to different causes (e.g., integration deficit, excessive feature processing, attentional bias)?
- Alternatively, to what extent are the differences in coordination failures and/or clinical presentations in the different disorders a function of variation in the spatial distances (and corresponding differences in frequency bands) over which coordination can and cannot be implemented?

Neurobiological Candidate Mechanisms for Abnormal Dynamic Coordination

Biological explanations for impaired dynamic coordination have generally focused on three levels of analysis: (a) coordination within and between brain systems (e.g., electrophysiology), (b) anatomy (e.g., gray and white matter reductions and other cellular abnormalities), and (c) neurotransmitters. Representative evidence for the first of these was presented above. Anatomical findings related to impaired dynamic coordination include:

- gray matter reductions in amblyopia, schizophrenia, and possibly in autism;
- white matter reductions in schizophrenia, Alzheimer's disease, Williams syndrome, and possibly in autism;
- increased neuronal cell packing density in visual cortical regions (consistent with reduced connectivity and decreased synaptic signalling) in schizophrenia (Selemon 2001); and
- decreased dendritic field size in schizophrenia.

Hypotheses and data regarding neurotransmitter-related abnormalities in dynamic coordination failures have generally focused on:

- NMDA-receptor hypofunction as a basis for impaired excitatory binding of relevant features (Phillips and Silverstein 2003), as well as for changes in GABA-related inhibitory function (Roopun, Cunningham et al. 2008);
- abnormal regulation of NMDA receptor-dependent synaptic plasticity by neurotransmitters such as dopamine, acetylcholine, and serotonin (Stephan et al. 2009);
- a primary impairment in GABAergic (inhibitory) activity including reduced generation of oscillations via inhibitory interneurons (Gonzalez-Burgos and Lewis 2008);

- alterations in acetylcholine receptors, which must be active for cortical networks to engage in synchronized, high frequency oscillations (Uhlhaas, Haenschel et al. 2008); and
- excessive activity at cannabinoid receptors, which leads to both diminished oscillatory activity and impaired sensory gating (Hajós et al. 2008).

Genetic factors related to neurotransmitters and neuroplasticity may also play a role in illness-related dynamic coordination failures (Lisman et al. 2008). There is little research on this specific issue to date, although evidence is accumulating regarding genetic contributions to (a) neurotransmitter function and expression of different types within the same class of (e.g., NMDA) receptor, (b) neurotransmitter abnormalities in schizophrenia, and (c) the development of autism, Williams syndrome, epilepsy, and other relevant disorders. For example, decreased expression of genes related to synaptic function has been found in schizophrenia (Mirnics et al. 2001). Recently, an increase in NOS1AP has been found in postmortem samples in schizophrenia, and this has been hypothesized to lead to decreased signaling at NMDA receptors and reduced dendritic field size (Brzustowicz 2008). A question suggested by these findings is whether—if disorders differ in their type of dynamic coordination failure—these differences can be accounted for by differences in neuroanatomical, neurotransmitter, or genetic factors.

A rarely addressed issue concerns the extent to which the biological basis of dynamic coordination can be affected by factors such as reduced social interaction, poor diet, lack of exercise, poor maternal care, or physical or sexual abuse. For example, it was recently proposed that reduced gray matter in schizophrenia may be secondary to reduced cardiovascular functioning and related reduction in neuronal growth, which in turn may be related to lack of physical activity and related reduction in brain-derived neurotrophic factor (BDNF) expression, overweight status and poor diet (Ward 2009). Diet has been demonstrated to affect gene expression related to brain plasticity (McGowan et al. 2008). It has also been demonstrated that, in rats, poor maternal care is associated with reduced NMDA receptor levels, reduced BDNF expression, and impaired spatial learning (Liu et al. 2000). Moreover, in humans, child abuse alters expression of genes that control stress responsiveness later in life; this can lead to the sequence of chronically increased cortisol, hypothalamus–pituitary–adrenal axis dysregulation, and hippocampal cell death, thereby reducing the hippocampus's ability to integrate contextual features during recall of episodic memories (McGowan et al. 2009). As noted above, this phenomenon has been suggested to be a cause of auditory hallucinations. All of these findings are relevant for models of reduced dynamic coordination in disorders associated with trauma and/or unhealthy lifestyles (e.g., schizophrenia, BPD, dissociative disorders, as reviewed above).

Questions Regarding Normal Brain Functioning

To what extent can data on dynamic coordination abnormalities inform our understanding of normality? For example, to what extent can findings of changes in disorders with genetic contributions allow us eventually to understand the genetic factors associated with normal coordinating processes? How would this add significantly to our understanding of coordinating functions beyond what is known about neurotransmitters and neuroanatomy? Also, to what extent can increases or decreases in coordination result from self-generated changes in mood or thought? The extent of downward causation from mental activity has yet to be explored.

Phillips and Singer (1997) suggest a distinction between prespecified feature hierarchies and dynamic coordination. This is supported by evidence from schizophrenia, in which grouping based on principles consistent with the former is intact, whereas performance deficits appear on tasks involving the latter. Does this suggest that these two processes are separable? Relatedly, do the relationships between neuronal loss, abnormal synchrony, and binding disturbances, as well as the correlations between indices of dynamic coordination failure in disorders such as schizophrenia, support Phillips and Singer's (1997) hypothesis that "the cortical algorithm everywhere is the same?" Do such data provide disconfirmatory evidence for Rolls' (2006) hypothesis that synchronization is most relevant for binding in feature hierarchy networks in early cortical areas (e.g., V2–V4) whereas information representation in higher areas is conveyed nearly completely by spike rates?

Data from schizophrenia and epilepsy suggest that reduced synchrony is the mechanism by which attractor states form that are relatively isolated from other cortical functioning. The data overall agree with Uhlhaas and Singer's (2006) contention that a trade-off between correlated and decorrelated activity is critical for normal brain function. Is it possible to quantify this trade-off and, if so (e.g., via neurofeedback), to enhance performance at various job functions or in life in general?

Phillips et al. (this volume) suggest that in addition to dynamic grouping and contextual disambiguation, concepts such as dynamic embedding, dynamic linking, and dynamic routing are relevant to understanding cognition. For example, they suggest that thoughts about thoughts (i.e., metacognition) may require dynamically embedded groupings. This suggests that disorders such as schizophrenia and autism, both characterized by disturbances in metacognition and theory of mind, may involve failures in dynamic embedding. In addition, data on autobiographical memory support a form of dynamic embedding involving grouping by causation, temporal proximity, and similarity in content (Brown and Schopflocher 1998). Can the concept of dynamic embedding guide the development of techniques to improve metacognition, social cognition, and memory function in both healthy and ill persons?

A potential criticism of the construct of dynamic coordination is that if it can explain nearly all aspects of normal and abnormal mental functioning, then it is too broad and simply too general a term for what the brain does. What are the implications of the data from illness states for determining how the construct of dynamic coordination adds to or conflicts with views such as Hebb's (1949) seminal theory of cell assemblies, Hemsley's (2005) theory of the role of the hippocampus in integrating sensory input with memory traces, and Andreasen's (2008) view that cerebellar activity is a primary determinant of cognitive coordination? Engel et al. (this volume) have made a first pass at clarifying which aspects of cognition do, and do not, involve cognitive coordination. In addition, they highlight the theoretical perspectives on cognitive coordination that can help differentiate it from other theories.

Do the differences in type and severity of dynamic coordination changes across disorders have implications for understanding individual differences? For example, can the tendency to bind normally uncorrelated representations, as found to an extreme in schizophrenia, be the basis for creativity? Is context sensitivity, which is reduced to an extreme degree in schizophrenia and autism—two conditions with social functioning deficits—the basis for social skill in the "neurotypical" population?

The questions posed here are but a sample of those that could be generated from a reading of the data laid out in this chapter. We may be far from an answer to these and other questions at present, but the relative ease with which they can be generated suggests that understanding failures of dynamic coordination has the potential to increase our understanding of normal brain function, and possibly to lead to the development of techniques to improve the cognitive and emotional functioning of healthy people as well.

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