The gap between intention and action: altered connectivity and GABA-mediated synchrony in autism

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Autism is a "spectrum" condition defined symptomatically and observationally, based on marked qualitative differences in two central domains:

1) Social communication and interaction, including reciprocity, use of non-verbal cues, and the initiation and maintenance of relationships;

2) Restricted or repetitive patterns of behavior, including echolalia, unusual object use, inflexibility of routines, circumscribed interests and altered response to sensory aspects of the environment.[1]

While significant and observable challenges in these core domains may be assigned the specific diagnosis of autism, it does not follow that the diagnosis of autism reflects a specific neurobiological mechanism. Large-scale population studies indicate that the majority of autism risk is rooted in genetic factors, but there is significant heterogeneity across individuals, with common, rare, inherited, and de-novo variants in hundreds of individual genes contributing to liability for autism[2]. Similarly, functional MRI studies have demonstrated significant differences in cortical activation patterns in autism, compared with neurotypical controls, but these patterns are also characterized by greater "noise" – a tendency toward individualized variations in functional connectivity that may not be shared across individuals[3].

As a result, the question "What causes autism?" is ill-posed, as numerous distinct etiologies may produce the same broadly observable phenotype. Still, given that individuals on the autism spectrum demonstrate identifiable disruptions in the domains of social communication, interaction, and behavior, many of these etiologies may exert their effect through common pathways. For this reason, identifying common molecular functions among autism-related genes, and common neurobiological correlates of autism-related behaviors, is essential to understanding the nature of autism.

This chapter focuses on two such mechanisms that are suggested by a broad range of genetic, neuroanatomical, and clinical evidence in autism:

1) Altered connectivity, at both anatomical and functional levels, and;

2) Altered excitatory/inhibitory balance, particularly affecting the properties of GABAergic circuits that regulate temporal synchrony and feedback.

These mechanisms contribute to an understanding of observed features in autism, as well as common features that are not well-captured by current diagnostic criteria – particularly difficulties in motor initiation and praxis. Both mechanisms play a role in the integration of signals that are distributed across spatially distinct processing hubs involved in cognition, communication, social behavior, sensory processing, and motor function. This integration, in turn, has an impact on the ability to link intention to action, ideation to execution, and the ability to demonstrate internal states through external behavior.

Diagnostic Considerations

The original characterization of autism by Kanner[4] in 1943 was quite severe in comparison to current use of the same label. Kanner described individuals with autism as differing "markedly and uniquely

from anything reported so far," "not responding to anything that comes to them from the outside world," and characterized by "extreme autism, obsessiveness, stereotypy, and echolalia." Prior to 1980, the estimated prevalence of autism was consistently reported below 1 in 2000.[5] In 1980, the third edition of the Diagnostic and Statistical Manual of the American Psychiatric Association included autism as a subset of "pervasive developmental disorders" (PDD)[6]. In 2013, the DSM-5 definition of "autism spectrum disorder" (ASD) created a single umbrella to include conditions previously classified as Autistic Disorder, Asperger's Syndrome, and all pervasive developmental disorders "not otherwise specified" by a distinct diagnosis (PDD-NOS). By 2016, the U.S. Centers for Disease Control and Prevention estimated that 1 in 68 school-aged children were on the autism spectrum[7]. Most of the upward trend in autism diagnosis can be accounted for by such changes in diagnostic criteria, as well as greater service availability, public awareness, and ascertainment[8].

Because the diagnostic threshold has become notably less extreme over time, the term "autism spectrum condition" (ASC) (or simply "autism") is used here, rather than "autism spectrum disorder" (ASD). Baron-Cohen (2009) favors this term not only because it is less stigmatizing, but also because autism-related traits appear to be continuously distributed in the general population, with the diagnosis based on a clinical judgment about the point where these traits are significant enough to interfere with daily life functioning[9]. From this perspective, the 1 in 2000 prevalence associated with Kanner's original characterization of autism can be heuristically viewed as equivalent to setting the diagnostic threshold 3.29 standard deviations away from the mean of a normal distribution. By contrast, more recent CDC prevalence estimates of 1 in 88 (2012) and 1 in 68 (2016) correspond to thresholds of 2.28 and 2.18 standard deviations from the mean, respectively.

External Behavior versus Internal States of Mind

Although ASC is defined observationally, the classification of symptoms relating to communication, social interaction, and behavior is often paired with inferences relating to intelligence and states of mind. Such inferences are problematic because the ability to *demonstrate* intelligence or thought may be directly affected by the symptoms of autism. For example, if speech and execution of intentional movement is affected by autism, tests of intelligence that rely on speech and movement will produce invalid results even in measures that may be valid among neurotypical individuals.

This distinction between observable features of autism and internal states of mind is consistently described by non-verbal or limited-verbal individuals with autism that later developed the ability to communicate independently using alternative and augmentative communication (AAC) methods:

"When I was growing up, speaking was so frustrating. I could see the words in my brain, but then I realized that making my mouth move [was needed to] get those letters to come alive, they died as soon as they were born. What made me feel angry was to know that I knew exactly what I was to say and my brain was retreating in defeat." - Jamie Burke[10]

"One of the biggest misunderstandings you have about us is your belief that our feelings aren't as subtle and complex as yours. Because how we behave can appear so childish in your eyes, you tend to assume that we're childish on the inside too. Stuck here inside these unresponsive bodies of ours, with feelings we can't properly express, it's always a struggle just to survive." – Naoki Higashida[11]

Self-descriptions such as these indicate a perceived gap in autism between intention and action; between the ideation of speech and movement and its execution through motor plans. This concern is particularly relevant because motor difficulties are often the earliest observable signs of autism[12] [13] [14]. Motor skills at age 2 are highly correlated with later outcome measures[15], and a robust correlation is observed between measures of motor function and measures of intelligence on standard tests[16] [17] [18] [19], which necessarily rely on verbal and motor skills.

While this correlation could be driven by some underlying feature of autism that jointly affects both intelligence and motor ability, individuals with ASC show discrepantly higher performance on non-verbal tests of intelligence[20], processing speed[21], and inspection time[22] compared with performance on standard intelligence tests. These alternate measures capture fundamental aspects of "fluid intelligence" (thinking, reasoning, and processing), but are poorly correlated with "crystallized intelligence," which is based on the accumulation of facts and experience[23]. Thus, standard measures of intelligence in autism may be confounded by challenges in verbal and motor ability, as well as restricted exposure to age-level curriculum, but may not be indicative of more general thinking, reasoning or processing skills.

With respect to motor function, it is important to distinguish basic motor skill from praxis. Basic motor skill is assessed based on execution of straightforward axial and limb movements, including gait, balance, pointing, and repetitive tapping. Praxis, in contrast, relies on the translation of internal "action models" into the performance of skilled, multi-step, goal-directed motor behaviors[24]. Thus, praxis requires not only basic motor skill, but also knowledge of representations of the movement, and translation of these representations into movement plans.
Individuals with autism demonstrate significant challenges in praxis, even after controlling for age, IQ, basic motor skill, and postural knowledge [25]. Notably, praxis in children with autism is a strong predictor of social, communicative and behavioral characteristics; significantly correlated with these features, as measured using the Autism Diagnostic Observation Schedule. This correlation with praxis remains significant even after controlling for basic motor skill, suggesting that dyspraxia may represent a core feature of autism[26].

Connectivity and GABA-mediated Synchrony

Convergent evidence in genomics, histology, neuroimaging, and electrophysiology suggests two related neurobiological mechanisms – connectivity and GABA-mediated synchrony – that can account for many of the observed features of autism. A central feature of both is the coordination of signals across multiple, spatially distinct processing hubs.

Altered Connectivity in Autism

The hypothesis of altered connectivity in autism was first proposed by Just, et al. (2004[27], 2007[28]) based on findings using functional magnetic resonance imaging (fMRI, which measures the synchronization of activation across brain regions), as well as anatomical morphometry. This hypothesis views the difficulties observed in autism as non-localized: an "emergent property of the collaboration among brain centers" rather than a single "core deficit." From this perspective, difficulties are most likely to arise when a task requires the coordination and integration of multiple processing centers, including regions responsible for motor function, as well as the perceptual and affective processing of social stimuli. Social interaction, language and behavior are viewed as particularly vulnerable to altered connectivity, because these are the domains that are most dependent on the synchronized integration of information from spatially discrete processing hubs[29].

Convergent lines of evidence support the hypothesis of altered connectivity and circuit formation in autism. Applying noise-reduction techniques to large-scale genome wide association data, Hussman et al. (2011) demonstrated that high-confidence genes associated with autism show significant functional enrichment in processes governing regulation of the neuronal cytoskeleton and the outgrowth and guidance of axons and dendrites, with secondary enrichment in pathways related excitatory/inhibitory neurotransmission[30]. Conversely, the set of genes most correlated to neuroanatomic connectivity, which is enriched for genes involved in neuronal development and axon guidance, shows a significant overlap with genes implicated in autism[31].

Anatomically, a reduction of long-range fiber tracts is observed in autism, with more exuberant short-range connectivity potentially compensating for this reduction. Individuals with ASC show increased volume of radiate white matter[32], particularly comprised of abundant short fibers in the primary motor cortex. This difference has a robust correlation with deficits in motor skill[33]. There is an observed reduction in the largest axons that communicate over long distances, with more abundant connections between neighboring areas[34]. An abundance of short connective fibers is also observed in frontal and temporal regions, relative to long-range connections[35].

Evidence from fMRI studies demonstrate that individuals with ASC exhibit reduced long-range functional connectivity between frontal and posterior parietal brain regions[36] [37] [38]. High-resolution (dynamic) coherence also shows reduced long-range connections in ASC in frontal-occipital connections, and increased short-range connections in lateral-frontal connections, with differences correlated with the severity of observed symptoms[39]. By contrast, individuals who spontaneously recover language after stroke show increased frontal-parietal integration[40].

Both imitation and praxis depend on frontal-parietal circuits for the execution of "action models." Specifically, skilled execution relies on connectivity between premotor regions responsible for selecting and sequencing intended motor programs, and posterior parietal regions that form and store these programs as spatial representations of movement[41].

Take a moment to execute the following action: reach forward, pick up an imaginary grape, and place it into a bowl. Now, reach forward, pick up an imaginary grape, and bring it to your mouth to eat. Repeated execution of such action chains results in two distinct representations in the parietal lobe; one corresponding to the complete "bowl" sequence, and the other corresponding to the complete "mouth" sequence. Conceptually, the choice of the desired sequence occurs in frontal areas responsible for executive control, and the associated motor plan is retrieved from parietal areas. Once a given sequence is chosen, frontal-parietal circuits typically trigger muscle activation related to the entire sequence, at the very outset of the action. For example, when grasping to eat, activation of mouth-opening muscles is typically evident even during the grasping action. In ASC individuals, however, no activation of mouth-opening muscles is observed when grasping to eat until the food immediately approaches the mouth[42].

Similarly, when several actions are combined to produce a single goal-directed motor plan, the kinematics of individual component movements are affected by the context and final goal of the sequence. However, in autism, this modulation does not occur, suggesting that individuals with autism experience difficulty chaining discrete motor acts into a global action[43]. Indeed, children with ASC show less activation in the cerebellum, with relatively greater fronto-striatal activation; a shift in activation patterns that is associated with increased need for conscious execution of planned movements[44].

This increased reliance on sequential execution of component movements is echoed in self-reports by individuals with autism describing their subjective experience[45]:

"To learn the technique of moving my right hand needed control over the ball and socket joint of the shoulder and then the hinge joint of my elbow and finally fold the other fingers and keep the point finger out. After that, focusing on the object which matched the word." – Tito Mukhopadhyay

"It is hot; we should open the window… I can describe the action: I must push the button with my finger. But my hesitation grows while I try to put the sequences to go through the action. I mentally review the necessary steps, but the first one simply doesn't come out. I'm trapped. To help the child with autism, verbally give me the sequences and facilitate me while I try to organize myself." - Alberto Frugone

Altered GABA-mediated Synchrony in Autism

In 2001, Hussman first proposed the hypothesis that autism may reflect dysfunction in a single factor shared in common by many neural circuits: GABAergic inhibition, and corresponding regulation of glutamate-induced excitation. Suppressed inhibitory tone was proposed to result in excitatory over-stimulation of glutamate receptors on neurons, resulting in excessive neural activity and difficulties in "gating" sensory information. This loss of inhibitory control would then result in deterioration in the quality of sensory information due to the failure to suppress competing 'noise.' The ability to process sensory information and learning tasks could then be overwhelmed[46]. Rubenstein & Merzenich later restated this hypothesis in 2003 in terms of an increased ratio of excitation to inhibition in autism[47].

Loss of GABAergic influence (e.g. ketamine antagonism of NMDA-receptor bearing GABAergic neurons) and excessive stimulation of non-NMDA glutamate receptors generate pathology and neuroanatomical features that mirror what is observed in autism. Loss of inhibitory control can result in hyperexcitation of target neurons, with preferential damage to large and medium-sized pyramidal and multipolar neurons[48]. Consistent with this mechanism, loss of Purkinje cells, multipolar GABAergic neurons located in the cerebellar cortex, remains one of the most consistent neuroanatomical findings in autism[49]. Individuals with autism also show significant alterations in GABAergic architecture of neocortical minicolumns[50]. Blatt et al. (2001) provided the first direct evidence that the GABAergic system is altered in autism, reporting a significant reduction in benzodiazepine and GABA-A receptor density in the hippocampus, predominantly in the region of the pyramidal cell layer[51].

Importantly, the role of GABAergic circuitry extends beyond the general inhibition of excitatory impulses. GABAergic circuitry is indispensable in mediating "temporal binding" or "synchrony" – the time-sensitive coordination of disperse signals across multiple regions of the brain into coherent percepts. Social interaction, communication, and complex movements are all dependent on such coordinated activity. Reduced temporal binding has been suggested to contribute to symptoms observed in autism[52]. Wallace and Stevenson (2014) provide a useful review of temporal binding and its relevance to developmental disabilities[53].

In addition to local connections among neurons, large numbers of cells are linked by a smaller set of "hub" neurons that orchestrate synchronization across the network. Analysis of network dynamics and physiology reveals that these hubs represent a subpopulation of GABAergic interneurons[54]. These interneurons regulate alternating periods of excitatory and inhibitory activity, which generate wave-like oscillations in local field potential that can be measured by EEG.

Time-sensitive integration of cognitive, sensory and motor information is achieved by binding action potentials that occur within the same "temporal binding window," much like passengers entering a train car, or pedestrians entering segments of a revolving door. Singer (1999) first proposed that neuronal oscillations in the gamma frequency band between 30-90 cycles per second (Hz) could enable temporal binding[55]. When groups of neurons are entrained in synchronized oscillations, their joint signal is amplified, and "noise" is reduced. High frequency oscillations appear well-suited to the rapid, time-sensitive integration of sensory inputs. Neuronal oscillations in the gamma frequency band have widespread evidence of importance in feature integration, selective attention, associative learning, lexical processing, and other forms of perception[56].

Temporal binding of sensory inputs is well-illustrated by the sound-induced flash illusion[57]. When a single visual flash is accompanied by multiple auditory beeps, the single flash is perceived as multiple flashes. When beeps are separated by 57ms, the strength of gamma band responses discriminates between trials where the illusion is perceived by neurotypical observers and those where it is not perceived[58]. The sound-induced flash illusion is not discriminated by children with autism, and less precise temporal processing is observed with increasing stimulus complexity[59].

Optimal gamma oscillations are produced by delayed feedback and shunting inhibition by fast-spiking, soma-inhibiting, GABAergic basket cells expressing parvalbumin (PV), a robust marker for interneurons, and specialized for GABA-A mediated conductance[60]. Notably, multiple mouse models of autism show a common circuit disruption in PV-positive GABAergic inhibitory interneurons[61].

Children and adolescents with autism demonstrate decreased gamma-band activity as measured by EEG[62]. Gamma-band oscillations are suggested to link structural connectivity with network synchronization, serving as a fundamental basis for the integration of cortical information flows[63]. Disruptions of network synchronization in autism, identified by EEG analysis, are consistent with deficient GABAergic inhibition, and suggest a reduction in the number and/or strength of thalamo-cortical connections. Moreover, the specific pattern of phase disruptions – reduced phase-shift duration and increased phase-lock duration in the occipital-parietal regions – is consistent with repetitive behavior and language difficulties observed in autism[64].

The superior temporal sulcus (STS) provides an informative model for the integration of information from spatially discrete processing hubs. The STS runs along the length of each temporal lobe, and is attuned to socially meaningful stimuli, for example, showing preferential activation to voices versus other sounds. This activation is less evident in autism, based on fMRI. When communication between STS across cortical hemispheres is required, neurotypical individuals show enhanced gamma band coherence, which is not observed in individuals with ASC[65]. Perhaps not surprisingly, GABA concentration in the STS predicts gamma power and perception in sound-induced flash illusion[66].

Motor function is another domain that relies on the coherent integration of spatially discrete inputs in order to link intended movement to skilled execution. Motor control can be conceptualized as a feedback process whereby outgoing (efferent) motor commands are accompanied by an efference copy or "internal motor model." This copy provides an estimate of the sensory feedback or "corollary discharge" that is expected from the proper execution of the desired movement. In response to motor activation, the sensory system sends actual feedback, which is then compared with the estimate, and any discrepancy between these is accompanied by corrective responses to align the actual movement with the intended trajectory[67].

Notably, GABA-mediated gamma band synchrony appears to facilitate the integration of sensorimotor feedback during motor execution. Specifically, post-movement cortical potentials (reafferent feedback signals) during movement execution are associated with highly-focused gamma synchronization in the 40-60Hz band, which always occurs in contacts located in the primary sensorimotor areas. This suggests that gamma event-related synchronization facilitates post-movement reafferent feedback from muscles and joints to the primary sensorimotor cortex, enabling the accuracy and ongoing control of movement[68].

Perspectives

The foregoing results indicate that the observed features of autism are consistent with altered connectivity, at both anatomical and functional levels, and altered excitatory/inhibitory balance, particularly affecting the properties of GABAergic circuits that regulate temporal synchrony and feedback. Both mechanisms are central to the integration of signals that are distributed across spatially distinct processing hubs involved in cognition, communication, social behavior, sensory processing, and motor function. They also offer useful perspectives relating to instructional strategies, as well as the "presumption of competence" toward individuals with autism.

Instructional strategies: playing to strengths

As noted previously, circuit formation in autism appears to compensate for reduced long-range connectivity with more exuberant short-range connectivity between adjacent processing regions. This

suggests instructional strategies that leverage local connectivity (proprioceptive input for motor tasks, visualization for comprehension) to partially substitute for long-range connectivity.

For example, during sentence comprehension, individuals with ASC activate parietal and occipital brain areas (adjacent to Wernicke's area) for both low- and high-imagery sentences, suggesting they engage mental imagery in both conditions[69]. However, when performing motor tasks, individuals with autism are less reliant on visual feedback than neurotypical individuals. Instead, learning novel movements is more strongly reliant on proprioceptive feedback[70]. The formation of action models through proprioceptive feedback evidently plays to the strengths of individuals with autism, by placing greater reliance on abundant short-range connections between the adjacent somatosensory and motor cortices[71].

Similarly, haptic feedback engages the sense of touch by applying force, resistance or other motion to provide proprioceptive feedback to the individual. Importantly, such feedback is not equivalent to guidance, which provides support in the same direction as the intended movement, and may include impedance that alters task dynamics, as motor execution may be enhanced by error learning[72 73]. Haptic feedback appears to facilitate the decoding of motor imagery, "closing the sensorimotor loop"[74] between intended and actual motor behaviors. In conjunction with visual feedback, haptic training may be an effective tool for teaching sensorimotor skills that have a force-sensitive component to them[75].

In many cases, even passive touch may enable individuals with autism to bridge the gap between intention and action. This observation is supported by self-reports of individuals with autism[76]:

"Touch is always a big help when an activity is new for me. Only through practice and through the gradual fading of touch the activity can be done independently. I needed to be touched on my right shoulder for doing any new skill. So I consider that the touch method is a vital step to speed up my learning skill." - Tito Mukhopadhyay

"I take mechanical steps alone, but if taken by the hand or the arm, I walk regularly." - Alberto Frugone

Touch given prior to action affects the integration of visual and proprioceptive body location information. The brain uses cues from passive touch and vision to update its own position and to experience self-location[77]. Passive tactile input can also improve stability. If passive input about posture is available, postural control adapts to this input, producing stabilizing reactions[78].

Presuming competence

Increasing evidence of altered connectivity and synchrony in autism suggests great caution against inferring internal states of mind from observed symptoms and behaviors. There may be a significant mismatch between thought, ideation, and intention, and the ability to *demonstrate* these internal states through behavior, which requires the ability to recruit and coordinate multiple systems necessary for their execution.

This potential mismatch between internal states and external behavior in autism has important implications in both social and intellectual domains. Difficulty demonstrating competence can easily result in the restriction of educational content to simplistic or "functional" curriculum. Individuals with autism may also be deprived of social interaction on their own terms, as difficulty navigating social interaction may be misinterpreted as a lack of interest in human relationships:

"I can't believe that anyone born as a human being really wants to be left all on their own, not really. The truth is, we'd love to be with other people. But because things never, ever go right, we end up

getting used to being alone, without even noticing this is happening. Whenever I overhear someone remark how much I prefer being on my own, it makes me feel desperately lonely." – Naoki Higashida[79]

Donnellan (1984) has proposed the concept of the "least dangerous assumption" with respect to individuals with autism and other developmental conditions: in the absence of conclusive data, decisions should be based on assumptions which, if incorrect, will have the least harmful effect on the individual[80]. This criterion suggests that access to age-level curriculum, social and educational inclusion, engagement in community, and the dignity to be regarded as an equal human being should not be conditioned on measures of "readiness" or the ability to pass a test that relies on verbal or motor ability. This view does not imply the abandonment of "functional" daily living skills as part of the information set provided to individuals with autism, but strongly questions common practices that lower the level of instruction to the level of comprehension demonstrated by testing, and that isolate individuals to segregated settings on the basis of assumed "low function."

Arguably, the least dangerous assumption toward individuals with autism is to adopt a presumption of competence with respect to internal states, including the capacity to learn, understand, enjoy social relationships, appreciate knowledge, and benefit from inclusion in school, family and community life. Accordingly, the static labels "high functioning" and "low functioning" could be usefully replaced by first presuming competence, and focusing instead on creating opportunities, expanding abilities, and identifying ways for these individuals to *demonstrate* that competence.

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