Disrupted development and imbalanced function in the global neuronal workspace: A positive-feedback mechanism for the emergence of ASD in early infancy

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Abstract: Autism Spectrum Disorder (ASD) is increasingly being conceptualized as a spectrum disorder of connectome development. We review evidence suggesting that ASD is characterized by a positive feedback loop that amplifies small functional variations in early-developing sensory-processing pathways into structural and functional imbalances in the global neuronal workspace (GNW). Using vision as an example, we discuss how early functional variants in visual processing may be feedback-amplified to produce variant object categories and disrupted top-down expectations, atypically large expectation-to-perception mismatches, problems re-identifying individual people and objects, socially inappropriate, generally aversive emotional responses and disrupted sensory-motor coordination. Viewing ASD in terms of feedback amplification of small functional variants allows a number of recent models of ASD to be integrated with neuroanatomical, neurofunctional and genetic data.

Keywords: Categorization; Connectome; Predictive coding; Prenatal development; Resting-state networks; Small-world networks

Introduction

Autism Spectrum Disorders (ASD) are early-onset conditions characterized by deficits or delays in social interaction and language, repetitive, stereotypical behaviors and restricted interests (DSM-5; American Psychiatric Association, 2013). They have high (> 1%) prevalence with an approximately 4:1 bias toward males, varying severity, and unknown, apparently heterogeneous etiology (reviewed by Volkmar, Chawarska and Klin, 2005; Geschwind, 2009; Leonard *et al*., 2010; Matson and Kozlowski, 2011) and are often comorbid with other psychiatric conditions ranging from Fragile X syndrome to epilepsy (reviewed by Jeste, 2011; Peca and Feng, 2012). Dozens of genes representing multiple functional families have been associated with ASD (reviewed by Geschwind, 2008; Betancur, 2011; Miles, 2011; Geschwind and Flint, 2015). Heritability is high (40% - 80%; Geschwind and Flint, 2015, Fig. 1), but *de novo* mutations including *de novo* copy-number variants are also common. Functional-network analysis confirms that the products of many ASD-associated genes are involved in neuronal growth and synaptic regulation (Chow *et al*., 2012; Parikshak *et al*., 2013; Pinto *et al*., 2014); in some cases, ASD-relevant phenotypes have been directly confirmed in animal models (e.g. Vaccarino, Grigorenko, Smith and Stevens, 2009). Gene expression studies indicate that at least some ASD-related gene products are active in early- to mid-fetal development (Parikshak *et al*., 2013; Willsey *et al*., 2013). A wide variety of dietary and other environmental factors expected to affect nervous-system development have also been associated, either prenatally or postnatally, with ASD (reviewed by Currenti, 2010; Gardener, Spiegelman and Buka, 2011). Functional connectivity studies in both children and adults with ASD have reported both under-connectivity, particularly between hemispheres, and over-connectivity, especially locally; however, the blanket statement that ASD is characterized in general by local overconnectivity and global underconnectivity is increasingly not supported (reviewed by Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Minshew and Williams, 2007; Rippon *et al*., 2007; Müller et al., 2011; Wass, 2011; Vissers, Cohen and Geurts, 2012; Maximo, Cadena and Kana, 2014; Tyszka, Kennedy, Paul and Adolphs, 2014; Picci, Gotts and Scherf, 2016). A recent study of high-functioning ASD adults, for example, demonstrated both significant differences in the spatial patterns of inter-hemispheric functional connections in ASD compared to typical subjects and significantly greater functional connection heterogeneity among the ASD group, leading to the suggestion that functional connectivity patterns in ASD are idiosyncratic, not stereotypical (Hahamy, Behrmann and Malach, 2015).

Early models of ASD tended to focus on one or more of the primary symptomatic presentations (for an extensive historical review, see Rajendran and Mitchell, 2007). Examples include models organized around deficits in social cognition (Baron-Cohen, 2002), aversion to novelty (Markram, Rinaldi and Markram, 2007) or weak central coherence, i.e. a relative inability to grasp overall gestalt features of a scene or situation (Happé and Frith, 2006). The explosion of data on the functional neuroscience of ASD since the early 2000's has motivated a second generation of models that focus not on overt symptoms but on proposed developmental and neurocognitive mechanisms. An early example is the proposal of Williams, Whiten, Suddendorf and Perrett (2001), later elaborated by Iacoboni and Dapretto (2006) and Oberman and Ramachandran (2007), that the social-cognition deficits typical of ASD are the result of mirror-system dysfunctions. Along similar lines, Pelphrey, Shultz, Hudac and Vander Wyk (2011) proposed that early dysfunction in posterior superior temporal sulcus (STS), a component of the mirror system, induced dysfunction throughout the “social brain” network and hence dysfunctions in social cognition. More recently, a number of authors have proposed second-generation models of ASD as primarily disorders of perceptual categorization and/or the generation and evaluation

of perceptual expectations, and have shown that the social interaction, language, and other typical presentations of ASD can be explained on this basis (Fields, 2012a; Pellicano and Burr, 2012; Lawson, Rees and Friston, 2014; Van de Cruys *et al.*, 2014; Hellendoorn, Wijnroks and Leseman, 2015). These models suggest a number of different underlying mechanisms: Fields (2012a) attributes ASD to disrupted category learning, Pellicano and Burr (2012) to attenuated top-down perceptual expectations, Lawson, Rees and Friston (2014) and Van de Cruys *et al.* (2014) to overly-precise representations of differences between expectations and perceptions, and Hellendoorn, Wijnroks and Leseman (2015) to deficits in the detection of perceptual invariances.

While existing second-generation models have viewed ASD in primarily cognitive or cognitive-affective terms, both developmental and clinical perspectives suggest an expanded and more fully integrated view of ASD that explicitly recognizes the role of variant experiences of the world, beginning in earliest infancy, in generating variant behavioral responses that, in turn, provide variant contexts for further experiences. Such an expanded view suggests a focus not on particular processes or modules but on the coordination of neural activity across multiple functional networks. Overall functional coordination of both experience and behavior is generally attributed to the global neuronal workspace, henceforth abbreviated to GNW (Dehaene and Naccache, 2001; Dehaene and Changeux, 2004; Dehaene and Changeux, 2011; Dehaene, Charles, King and Marti, 2014), also referred to as the global workspace (Baars, 1998; Baars and Franklin, 2003; Baars, 2005; Baars, Franklin and Ramsoy, 2013), connective core (Shanahan, 2012) or “rich club” (Sporns, 2013), a network of long-distance cortico-cortical and cortico-thalamic pathways. Normal GNW function depends critically on how the total connectivity of the network is allocated between typically shorter-range connections within networks subserving particular functions and typically longer-range connections between such networks. As suggested by Belmonte and Baron-Cohen (2004), disruptions of this balance between within- and between-network connectivity can be expected to present symptomatically as cognitive and/or emotional disorders including ASD (Just *et al.*, 2012; Peters *et al*., 2013; Glazebrook and Wallace, 2015). New data on the functional organization and connectivity of the GNW prenatally through the first two years (reviewed by Di Martino *et al.*, 2014; Dehaene-Lambertz and Spelke, 2015; Vértes and Bullmore, 2015) provide a basis for examining a potential role for such GNW imbalances in the critical early-developmental stage of ASD.

Motivated by these new data and theoretical approaches, we here review theoretical, computational and experimental studies which together suggest that ASD is characterized, beginning in earliest infancy, by a positive feedback loop that amplifies small functional variations in early-developing sensory processing and sensory-motor pathways into structural and functional imbalances in the developing GNW. This suggestion is consistent with the functional development of the nervous system being fundamentally interactive (reviewed by Johnson, 2011) and with the emerging view of developmental neuropsychiatric disorders in general as disruptions of typical “connectome” development (Di Martino *et al.*, 2014; Dehaene-Lambertz and Spelke, 2015; Vértes and Bullmore, 2015). Using the well-established graph-theoretic model of the GNW as a small-world network, henceforth abbreviated to SWN (Sporns, Tononi and Edelman, 2002; Sporns and Zwi, 2004; Achard *et al*., 2006; Bassett and Bullmore, 2006; Sporns and Honey, 2006; Glazebrook and Wallace, 2009; reviewed by Rubinov and Sporns, 2010; Sporns, 2013), we show how small variations in the relative probabilities of forming stable within- and between-network connections can have dramatic outcomes for overall GNW function. The broad perspective obtained by considering the effects of local functional perturbations on the GNW as a whole allow us to integrate the mechanistic and etiological proposals of multiple, *prima facie* competing models within a single developmental framework. Within this feedback-amplification

framework, both structural and functional heterogeneity of outcomes is to be expected; we consider this to be a major contribution of the proposed approach.

While it is increasingly clear that multiple sensory systems as well as multi-sensory integration are affected in ASD (reviewed by Baum, Stevenson and Wallace, 2015), both typical and variant visual processing, including the cognitive and affective interpretation of visual input, are the most well-characterized and recent models mainly reference these processes. We therefore focus on early-developmental interactions between visuomotor, medial visual/categorization, dorsal and ventral attention, and affective/reward networks, which together implement both the cognitive and affective interpretation of visual input and the use of visual input to control object-directed behavior, and the interaction of these networks with later-developing (Casey, Tottenham, Liston and Durstan, 2005) executive and default (i.e. self and self-other representation, see Andrews-Hanna, Smallwood and Spreng, 2014 for review) systems. We examine the expected effects of imbalancing the coordination of these networks by the relative over- or under-production or enhanced or reduced strength of stable within- or between-network connections. We describe how multiple distinct GNW imbalances can be expected to result, given exposure to a typical infant environment, in cognitive-affective outcomes typical of ASD. We then show that the functional disruptions proposed to be associated with ASD by Fields (2012a), Pellicano and Burr (2012), Lawson, Rees and Friston (2014), Van de Cruys *et al.* (2014) and Hellendoorn, Wijnroks and Leseman (2015) can be characterized within this integrative framework. Finally, we comment on further extensions of the model and the possibility of direct experimental tests.

The next section, “Background: The GNW as an SWN of SWNs” briefly reviews the common structure of small-world networks, evidence that the GNW is an SWN, and caveats that must be borne in mind when describing the GNW as an SWN. The following section, “Development of the GNW” briefly reviews the cognitive, affective and behavioral phenomenology with which models of GNW development must be consistent, and considers how new data, primarily on the functional integration between resting-state networks (RSNs) from the prenatal period through late infancy, further constrain such models. A formal framework is then developed that allows the representation of both typical and variant GNW development. The fourth section, “Perturbations of GNW development” distinguishes global from localized disruptions of GNW function, focusing on those that can be expected to be amplified in the typical infant environment. The fifth section, “Five recent models of ASD from a GNW perspective” discusses the functional disruptions advanced by specific recent models within the GNW framework. The paper concludes with the hypothesis that multiple localized and possibly relatively minor perturbations of GNW function could be amplified, in the typical infant environment, to symptomatic ASD.

Background: The GNW as an SWN of SWNs

The mathematical concepts and tools of complex network analysis are increasingly being applied to anatomical, comparative and functional connectome data (Rubinov and Sporns, 2010; Sporns, 2013). A key concept of such analysis is the SWN (Watts and Strogatz, 1998; see also Barabasi and Albert, 1999; Newman, 2003), defined as a network with both a small average distance between nodes (formally, an average distance logarithmic in the number of nodes) and a high clustering coefficient (formally, higher than the clustering coefficient expected for a random graph). Informally, SWNs are characterized by clusters of locally-connected nodes (also called “communities” e.g. in Sporns, 2013)

surrounding a relatively small number of mutually-connected hubs, as shown in Fig. 1. However, not all networks containing hubs are SWNs; networks containing no closed triangles, in particular, have clustering coefficients of zero and are therefore not SWNs (Fig. 1b). Reducing modularity by adding redundant paths between clusters render an SWN more robust, i.e. less prone to disconnection by the removal of a single node or connection (Fig. 1c).

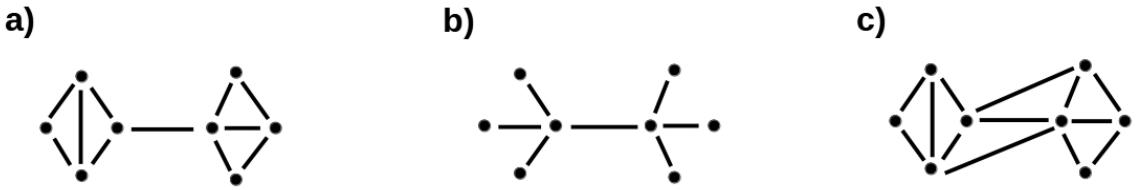

Fig. 1: a) A simple SWN with high modularity, i.e. clearly distinct "communities" of nodes. "Hubs" are nodes through which connections between modules pass. Note that each module contains two triangles. b) A modular network with no triangles and hence a clustering coefficient of zero; this network is not an SWN. c) A less-modular SWN with more triangles and hence a higher clustering coefficient than the network in a).

Networks with the characteristics of SWNs can clearly be sought and found at many different scales in nervous systems (Sporns and Honey, 2006). Examining connectivity across the entire brain either anatomically by tracing white-matter tracts or functionally by measuring correlated activity yields an SWN in which the nodes are anatomical regions with relatively well-defined, coherent functions (e.g. primary visual cortex, medial-temporal area or thalamus) and the connections link these areas into large-scale functional networks (e.g. dorsal and ventral attention systems, default and task networks, memory and affective/reward systems; reviewed by Park and Friston, 2013; Rugg and Vilberg, 2013; Sporns, 2013; Andrews-Hanna, Smallwood and Spreng, 2014; Rolls, 2015; Vossel, Geng and Fink, 2014). Taken together, these large-scale functional networks constitute the GNW (Shanahan, 2012; Baars, Franklin and Ramsoy, 2013; Dehaene, Charles, King and Marti, 2014), with the most highly mutually-connected hubs within the GNW forming the "rich club" or connective core of the human connectome (van den Heuvel and Sporns, 2011; Shanahan, 2012; Sporns, 2013). The GNW concept was originally introduced to explain both the apparent unity of and the requirement for serial processing in ordinary, waking consciousness (Baars, 1998; Dehaene and Naccache, 2001; Baars and Franklin, 2003; Dehaene and Changeaux, 2004; Wallace, 2005). Functional studies have now largely confirmed the correlation between coordinated patterns of GNW activity and waking consciousness (Baars, Franklin and Ramsoy, 2013; Dehaene, Charles, King and Marti, 2014), although the implementation of conscious awareness and consciously-directed activity is by no means settled (e.g. Block *et al.*, 2014; Graziano, 2014; Hoffman and Prakash, 2014; Tononi and Koch, 2015; van Leeuwen, 2015).

While it is standard to conceptualize the GNW as a network of functionally-coherent anatomical regions connected by white-matter tracts (e.g. Park and Friston, 2013, Fig. 2B; Sporns, 2013, Fig. 3b), doing so can obscure two important facts. First, each functional region is itself a complex network and

possibly an SWN. Second and more importantly, inter-regional fiber tracts comprise many parallel connections between individual neurons, many if not most of which implement unique functional outcomes at the whole-network scale. Such complexity is evident at the voxel scale from which regional networks are constructed experimentally (e.g. Park and Friston, 2013, Fig. 2D; Sporns, 2013, Fig. 3a). Network "hubs" do not, therefore, exchange functionally-uniform signals and the "connection strength" between hubs cannot be regarded as a measure of the strength of any given signal transmitted between functional regions. The situation may instead be as illustrated in Fig. 2, with as least as many functionally-distinct connections between hubs as there are nodes within a hub.

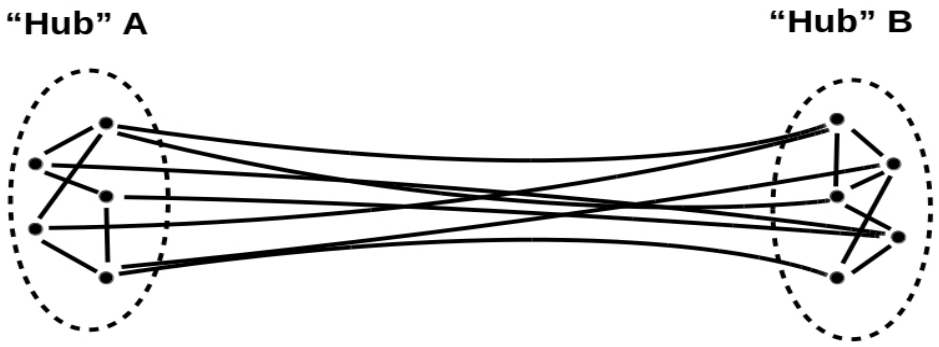

Fig. 2: "Hubs" in the GNW are themselves complex networks that may be connected by many parallel, functionally-distinct pathways. The "strength" of connection between hubs is not, therefore, a measure of the strength of any given functional connection.

As an example, consider the relation between visual object categorization and motor plans for object manipulation, a relationship that has been extensively studied in the case of tool identification and tool use (reviewed by Vingerhoets, 2014; Gallivan and Culham, 2015; see also Brandi, Wohlschläger, Sorg and Hermsdörfer, 2014). In typical adults, the medial visual system is able to recognize dozens to hundreds of tools suitable for a broad array of applications, while the frontal-parietal action network is able to plan actions using these tools in multiple orientations to accomplish many different goals (reviewed by Lewis, 2006; Brandi, Wohlschläger, Sorg and Hermsdörfer, 2014; Ishibashi, Pobric, Saito and Lambon Ralph, 2016). Tools, tool-related actions and tool-use goals are each elements of complex, at least quasi-hierarchical categories with many semantic and logical relationships between elements. Hammers and screwdrivers, for example, generally serve different functions, and may have similar or quite different sizes, shapes, weights, and locations in the toolbox. A large, heavy screwdriver may substitute functionally for a hammer in some applications, while a hammer being useful as a screwdriver is unlikely. Most people are far more familiar and competent with some tools than others, indicating that connection strengths are highly variable across representations. The robust human ability to improvise tools, invent new tools and adapt existing tools to novel applications shows, moreover, that the entire tool-use network is highly adaptable. The connections between medial-visual representations of tools as meaningful objects and frontal-parietal representations of tool-use goals and actions appear, therefore, to implement many-to-many mappings between complex, at least quasi-

hierarchical, and highly-plastic representational domains. How these many-to-many mappings function in contexts involving multiple tools and multiple goals, whether they are better conceptualized in terms of memory or problem-solving and how they degrade in tool-use apraxias remain subject to considerable debate (e.g. Osiurak *et al*., 2013; Sunderland, Wilkins, Dineen and Dawson, 2013; Buxbaum, Shapiro and Coslett, 2014).

Three other issues complicate any simple representation of large-scale networks in general and the GNW in particular as SWNs. First, both within-region and inter-regional connections may be either excitatory or inhibitory. Second, the information transmitted along either excitatory or inhibitory inter-regional connections may be complicated functions of local activity. Information-theoretic considerations, for example, suggest that nervous systems capable of flexible behavior in changing environments would ubiquitously employ predictive coding schemes in which model-based expectations are transmitted top-down and prediction errors, i.e. perception – expectation differences, are transmitted bottom-up (reviewed by Friston, 2010). Both local and inter-regional functional network analysis provide evidence that mammalian nervous systems are in fact organized in this way (reviewed by Gómez and Flores, 2011; Bastos *et al*., 2012; Shipp, Adams and Friston, 2013; Adams, Friston and Bastos, 2015). Third, local integration of either excitatory or inhibitory signals requires signal synchrony or, at a finer scale, temporal coding. Activity in the GNW, in particular, involves global coordination in time of activity across all contributing components of the network (Baars, Franklin and Ramsoy, 2013). Analytic measures that consider only a single path between network components, such as the widely-employed "efficiency" measure of Latora and Marchiori (2001), cannot capture this temporal coordination requirement and may therefore yield spurious or misleading results. However, including connection strengths as well as path lengths (Rubinov and Sporns, 2010) in the analysis may compensate, if only implicitly, for this weakness, as suggested by both the heritability of some network efficiency variants reported by Fornito *et al.* (2011) and the correlations between connection efficiency and ASD severity reported by Lewis *et al.* (2014; see also below).

With these caveats and complications in mind, we follow Shanahan (2012) in conceptualizing the GNW as an SWN in which all or at least most of the contributing "communities" are themselves SWNs, the connections between communities are many-to-many as shown in Fig. 2, predictive coding is employed at multiple scales, and signal synchrony is critical to coherent functioning. McCall and Franklin (2013) have shown this conceptual approach is computationally feasible within the Learning Intelligent Distribution Agent (LIDA) architecture, a hybrid computing architecture that models the GNW (Franklin *et al*., 2007); Grossberg and Seidman (2006) have obtained similar results using the Adaptive Resonance Theory (ART) architecture, which models networks of neurons with feedback modulation. The next section reviews recent data on GWN development during infancy, focusing on the growth and subsequent activity-dependent pruning of long-range connections between the co-developing visuomotor, medial visual/categorization, attention and affective/reward networks. Perturbations of this process and their expected phenotypic presentations are then considered.

Development of the GNW

Phenomenology of the infant world

Like any developmental process, the development of the GNW can be expected to be sensitive to genetics, to the pre-, peri- and postnatal physical, chemical and biochemical environments, and to pre-,

peri- and postnatal experience. As the GNW is a global functional network, its development can be expected to be particularly sensitive to the interplay between bottom-up effects originating in its "input" components, including proprioception and interoception, and top-down effects originating in more "central" components. The general Hebbian heuristic that synchronous activity enhances connectivity while asynchronous activity inhibits it can be expected to describe the functional integration of both the GNW itself and its component networks. At the level of individual cells, synchrony and asynchrony between even temporary synaptic partners can be expected to influence axonal branching and exploration, as recently demonstrated in non-mammalian systems (Munz *et al*., 2014; Kita, Scott and Goodhill, 2015).

Any successful model of GNW development must be consistent with the basic phenomenology of neonate and early-infant behavior. Human neonates are aware of and responsive to their environments and are particularly sensitive to motion, novelty, faces and sensations from within their own bodies (reviewed by Rochat, 2012). They exhibit object-directed exploratory and aversive behaviors and rapidly develop gaze following, attention sharing and goal-directed object manipulation (reviewed by von Hofsten, 2007). In the absence of other salient input, they provide themselves with sensory-motor feedback through motor and verbal babbling. The phenomenal world of the infant resolves itself only gradually, however, into the shared adult world of spatially-bounded, located, persistent objects with more or less stable collections of features (Colombo, Brez and Curtindale, 2012 provide a general review of infant cognition). Neonates can segregate moving objects from the background, for example, and are sensitive to features such as shape of static objects (Rakison and Yermoleva, 2010). By 4 months old, infants can recognize moving objects as persistent following brief occlusion (e.g. Bremner *et al*., 2005). However, 4-month-olds may not segregate unfamiliar static objects from each other or from the background until their individual manipulability has been demonstrated (e.g. Needham, Dueker and Lockhead, 2005). An ability to see features and an ability to see objects, in other words, does not automatically imply an ability to bind features to objects in a way that enables object segregation. Feature visibility does not, moreover, imply feature salience, which develops gradually and in a predictable order (e.g. shape and size before color) over the first year (reviewed by Baillargeon, Li, Gertner and Wu, 2011). The extent to which neonates and young infants experience segregated objects localized in space, as older infants, children and adults do, remains poorly understood (reviewed by Fields, 2013).

The extent to which the early infant's social world matches that of late infancy or childhood is also unclear. Both the feature clusters that indicate faces and the trajectory components that indicate animacy appear to be innate and available from birth (reviewed by Simion *et al.*, 2011; Hoelh and Peykarjou, 2012). Infants can identify and attribute goals to agents by as early as 3 months, with indicators of animacy serving as indicators of agency (reviewed by Luo and Baillargeon, 2010; see also Luo, 2011). It is, however, not clear whether young infants treat agency as a persistent feature of objects seen to act as agents, or whether "agent" is a category that generates specific expectations about behavior.

While parenting and other social interactions provide extrinsic motivations to correctly identify, categorize and associate expectations with objects, theoretical considerations (e.g. Friston, 2010; Gottlieb, Oudeyer, Lopes and Baranes, 2013), experiments using developmental robotics (reviewed by Oudeyer, Baranes and Kaplan, 2013; Cangelosi and Schlesinger, 2015) and observational and experimental studies of infant behavior (e.g. von Hofsten, 2007; Gopnik, 2012; Rochat, 2012) all suggest that a powerful intrinsic motivation to increase the predictability of the phenomenal world

drives this transition. It is important to bear in mind that both the particular static features and the particular motion characteristics of each of the identifiable objects comprising the infant's world must be learned from observation. Infants must, for example, learn not just the specific facial features of family members and any others they recognize as familiar, but also their general visual features, voice, gait, other typical motions or gestures, smell, etc. These features, generated by multiple sensory pathways, must be integrated into a single object token (reviewed by Zimmer and Ecker, 2010) maintained in memory as a stable, temporally-persistent individual that is permanently distinguished from all other individual objects. This representation must, moreover, be stable across periods of non-observation and against changes in location and minor changes in features. Infants must, for example, learn that changes in clothing – which may be highly visually salient – do not indicate changes in the identity of an individual person (reviewed by Fields, 2012b); failures to recognize perceptual invariants that indicate object identity have, indeed, been proposed as an underlying functional correlate of ASD (Hellendoorn, Wijnroks and Leseman, 2015). Typically-developing infants achieve this level of object-token integration and stability for dozens if not hundreds of individual objects within the first year. There is every reason to believe that successful recognition of persistent objects generates significant affective rewards that encourage further exploration of both social and non-social components of the world.

Functional connectivity in the infant GNW

It has long been known that cortical functions develop in a roughly caudal-to-rostral direction, with sensory-motor networks maturing several years before prefrontal executive systems (reviewed by Casey, Tottenham, Liston and Durstan, 2005). Several recent longitudinal resting-state fMRI or diffusion tensor MRI (DTI) studies of pre-term or full-term neonates, one- and two-year-olds (Doria *et al*., 2010; Yap *et al*., 2011; Gao *et al.*, 2013; Alcauter *et al.*, 2014; Ball *et al*., 2014; Gao *et al.*, 2015; Huang *et al.*, 2015; Toulmin *et al.*, 2015; see also Di Martino *et al.*, 2014; Dehaene-Lambertz and Spelke, 2015; Vértes and Bullmore, 2015 for supporting results) now allow following the early stages of large-scale functional network development at high resolution. These studies reveal robust connectivity within, and to varying extents between, major RSNs defined in adults (e.g. Damoiseaux *et al.*, 2006; Yeo *et al.*, 2011), including in particular the visuomotor, medial visual/categorization, dorsal and ventral attention, and affective/reward networks of primary interest here. Distinct RSNs including sensory, motor, attention and affective networks embedded in an SWN architecture with evident “rich club” nodes including frontal, parietal and superior temporal areas as well as hippocampus and amygdala are identifiable over 2 months pre-term (Doria *et al*., 2010; Ball *et al*., 2014). Adult-like cortico-cortico (Yap *et al*., 2011; Gao *et al.*, 2015; Huang *et al.*, 2015) and thalamo-cortical (Alcauter *et al.*, 2014; Toulmin *et al.*, 2015) RSN connection topology is evident in term neonates, with some departures from normal connectivity in early pre-term infants of an equivalent age (Doria *et al*., 2010; Ball *et al*., 2014).

The studies of Yap *et al*. (2011) and Gao *et al*. (2015) each examined neonates, 1- and 2-year-olds, using DTI and fMRI methods, respectively. On average, within-network connectivity increases rapidly during the first year and more slowly during the second year, with the exceptions of the sensory-motor network in which connectivity declines in both years and the language network which continues steady growth (Gao *et al.*, 2015). Early postnatal increases in between-network connectivity are followed by connectivity decreases as between-network functional activity is refined by experience. As expected, sensory and sensory-motor networks develop earlier and faster than executive and default networks (see also Doria, 2011 for evidence that the same is true prenatally). The functional decoupling of the

default and dorsal attention networks by 2 years (Gao *et al.*, 2013) is particularly striking. The more rapid functional integration of frontal-parietal attention networks bilaterally in boys compared to girls demonstrated by Gao *et al.* (2015) is also particularly interesting given the atypical allocation of attention in ASD, the greater prevalence of ASD in males (e.g. Baron-Cohen, 2002; Crespi and Badcock, 2008), and recent demonstrations of reduced frontal-parietal connectivity at 12 months in high ASD-risk infants (Keehn, Wagner, Tager-Flusberg and Nelson, 2013; Righi, Tierney, Tager-Flusberg and Nelson, 2014; though see Uddin, Supekar and Menon, 2013 and Picci, Gotts and Scherf, 2016 for cautions regarding the extrapolation of connectivity results across the lifespan).

While these studies of typically-developing neonates and infants do not explicitly discuss the experiential or behavioral correlates of their network-level observations, from a GNW perspective it is useful to consider the relation between increasing within- and between-network functionality and the phenomenology of perceiving and acting in the world. As noted earlier, neonates are capable of basic sensory-motor integration, consistent with the observation of Gao *et al.* (2015) that bilateral medial visual and sensory-motor networks have essentially adult-like connection topology at birth. Sensory-motor coordination increases rapidly as motor babbling gives way to more intentional and object-oriented activity; the comparatively early decreases in sensory-motor within-network connectivity observed by Gao *et al.* (2015) may reflect the early functional refinement of this system. The visuomotor (Lateral Visual/Parietal in Gao *et al.*, 2015) network is heavily involved in visual object segregation, motion tracking and the targeting and coordination of reaching behaviors; its continued growth during this period may reflect the increasing complexity of position, shape and motion information that infants are able to process as their behavioral capabilities mature. Early development of thalamo-cortical connections (Alcauter *et al.*, 2014; Toulmin *et al.*, 2015) is consistent with early emergence of multi-sensory integration as well as the robust awareness of their surroundings exhibited even by neonates. Robust connections between the reward (components of Salience in Gao *et al.*, 2015), sensory, sensory-motor and attention networks are consistent with the assignment of strong affective valences to some objects – e.g. caregivers, strangers or favorite toys – as well as the presence of intrinsic motivations to explore the local environment and experiment with the objects it contains.

These behavioral and architectural observations, together with general neurodevelopmental considerations, suggest the qualitative picture of GNW development shown in Fig. 3. Regions within both cortex and subcortical areas are defined by some combination of genetic and spatial or other physical constraints during early embryogenesis. Within-region connectivity increases rapidly in the late 2nd to early 3rd trimester (reviewed by Andersen, 2003). Long-range connectivity at this time is sparse and functionally incoherent (Fig. 3a). As the results of Doria *et al*. (2010) and Ball *et al*. (2014) indicate, both within-region and long-range connectivity increase significantly during the 3rd trimester, reaching sufficient long-range coherence to enable pre-term infants to exhibit object discrimination, exploratory behavior and social interactions (Fig. 3b). Regions with strong genetic determinants such as the fusiform face area or having early exposure to coherent input such as auditory cortex are sufficiently functional to enable individual recognition. By normal term, multi-regional functional networks are robustly connected, between-network connectivity has increased, and “rich club” hubs are apparent (Fig. 3c). By this stage, experiences processed primarily by one network can affect the perceptual expectations generated by a different network.

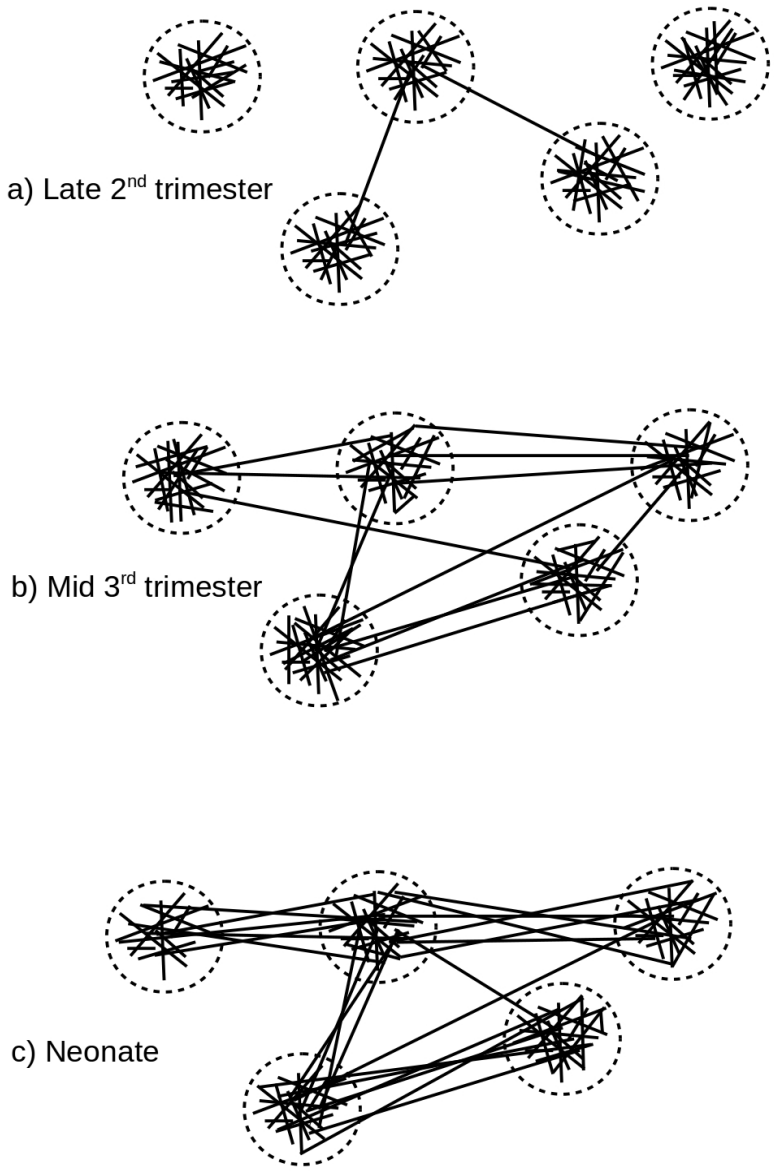

Fig. 3: Schematic representation of GNW development to from mid-fetal development to birth. a) Genetically or physically demarcated regions (dashed circles) develop within-region connections by late 2nd trimester. b) Multi-regional functional networks are sufficiently developed by early 3rd trimester to support pre-term cognitive abilities, but between-network connections are under-developed. c) By normal-term birth, within-network connections are robust and "rich club" hubs through which networks are mainly linked have formed (cf. Gao *et al*., 2015).

By the end of the first postnatal year, increases in connectivity are counterbalanced by experience-dependent synaptic pruning (Andersen, 2003), as reflected in the slower growth in within-network connectivity during the second year observed for most RSNs by Gao *et al.* (2015). This process is effectively Hebbian and hence highly dependent on the coherence, consistency, and hence predictability of the experienced world. A higher probability of pruning for relatively short, within-region connections is indicated by the increases in longer within-network or between-network connections compared to shorter within-network connections during the second year noted by both Yap *et al*. (2011) and Gao *et al*. (2015).

A graphic notation for visualizing typical and variant GNW development

As shown by RSN imaging (Doria *et al*., 2010; Yap *et al*., 2011; Gao *et al.*, 2013; Alcauter *et al.*, 2014; Ball *et al*., 2014; Gao *et al.*, 2015; Huang *et al.*, 2015; Toulmin *et al.*, 2015) and illustrated in Fig. 3, the connection probabilities within and between functionally-characterized regions are functions of both developmental time and the identities of the regions being connected. Even within-region connectivity increases and decreases at different times and rates in different regions, and both between-region connectivity within a given RSN and between-network connectivity vary significantly among individual RSNs and between pairs of RSNs, respectively. Within an RSN, the existence of a "rich club" of highly mutually-connected hubs even prenatally (Doria *et al*., 2010; Ball *et al*., 2014) indicates that connection probabilities exhibit preferential attachment (Barabasi and Albert, 1999), a special case of assortative connectivity (Newman, 2003) in which well-connected nodes have a higher probability of acquiring additional connections than poorly-connected nodes. Hebbian learning requires, moreover, that connection probabilities depend on synchrony of activity between new and existing connections. The probability $\mathbf{P}_{ij}(t)$ of a new connection between functional regions i and j at time t can, therefore, be expected to depend, at minimum, on genetically-established cell-surface or other markers identifying i and j as functional regions, the number of i-j connections already established, the correlation at t between the overall activities of regions i and j, and particularly for intra-regional (i.e. $i = j$) connections, the extent to which the new connection increases the temporal coherence of regional activity. While reciprocal connection probabilities may be expected to be similar (i.e. $\mathbf{P}_{ij}(t) \sim \mathbf{P}_{ji}(t)$), they need not be identical. Similar dependencies can be expected for connection probabilities between multi-regional RSNs, which themselves form a rich-club network (Sporns and Honey, 2006; Shanahan, 2012). It is difficult, given this level of complexity, to frame questions about the results of developmental shifts in the probabilities of particular region-to-region or network-to-network connections or about changes in the magnitudes of particular connection probabilities (e.g. Di Martino *et al*., 2014, Fig. 1) in this representation.

For the purposes of characterizing variants in GNW development, however, the time-dependent ratios $\mathbf{P}_{ij}^{\mathrm{Var}}(t)/\mathbf{P}_{ij}^{\mathrm{Typ}}(t)$ of variant (Var) to typical (Typ) connection probabilities either within or between RSNs are more relevant than the connection probabilities themselves. Following Rubinov and Sporns (2010), we consider these probability ratios to incorporate information on the strength of connectivity as a function of time, i.e. we interpret $\mathbf{P}_{ij}^{\mathrm{Var}}(t)/\mathbf{P}_{ij}^{\mathrm{Typ}}(t)$ as a measure of the time-dependent *effective* connectivity (Friston, 2011) of a variant network compared to that of a typical network. As we do not assume that $\mathbf{P}_{ij} = \mathbf{P}_{ji}$ for all i and j, these effective connectivity ratios are directional. Such ratios are amenable to a simple graphic representation, as shown in Fig. 4. At each fixed time t, the graph of directed connections between any given set of either N regions or N multi-region networks can be drawn as a complete directed graph (i.e. digraph) on N nodes, with symmetry under $2\pi/N$ rotations

indicating typical connectivity (i.e. $\mathbf{P}_{ij}^{\mathrm{Typ}}(t)/\mathbf{P}_{ij}^{\mathrm{Typ}}(t) = 1$). Equal normalized effective connectivity between nodes is indicated by drawing equal-width connections. In graphs in which each node represents a network, e.g. an RSN, each of the N nodes is represented by superposed solid and open symbols, indicating that the ratio of short (i.e. within-region) connections in the network to long (i.e. between-region) connections within the network is typical. As "typical" connectivity is by definition typical at all developmental times, a typically-developing network will have the same graph for all *t*. With this graphic convention, any differences from the graph structure shown in Fig. 4a, including the unaligned solid and open node symbols, unequal connection widths and geometric asymmetries shown in Fig. 4b, represent differences from typicality.

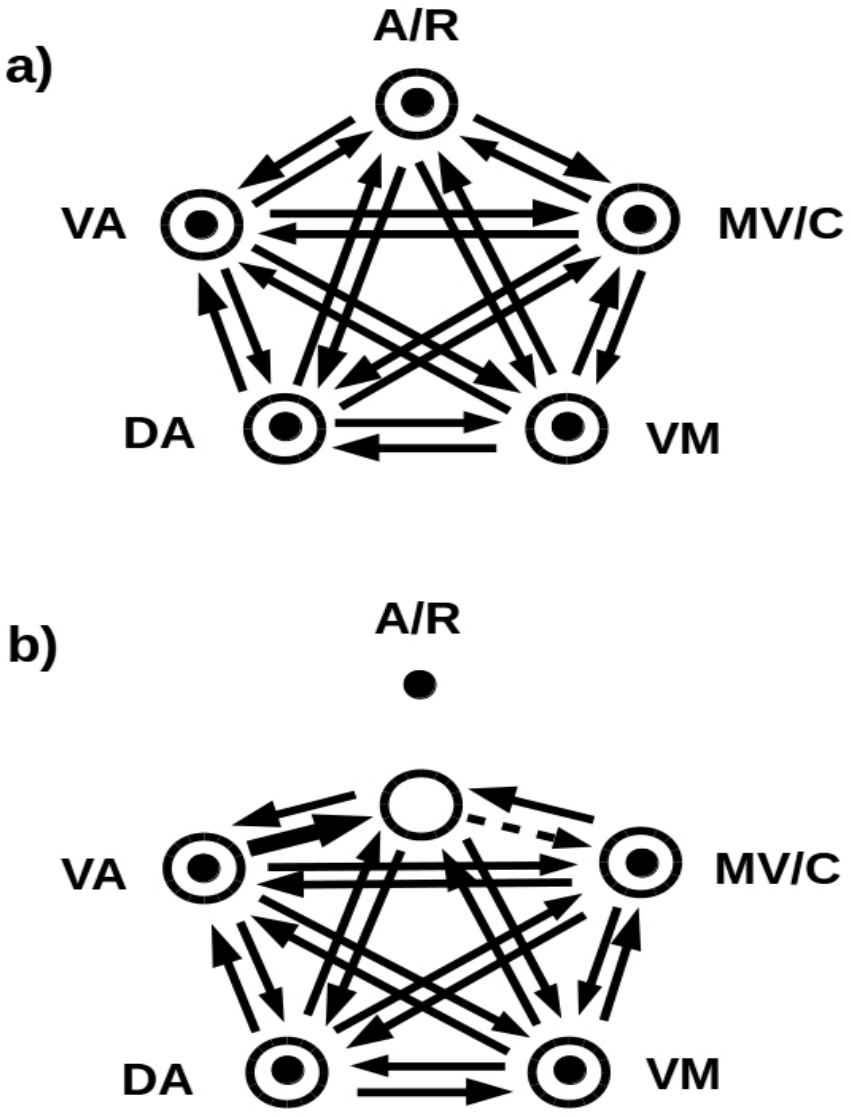

Fig. 4: a) A typically-developing network may be represented by a symmetrically-drawn complete digraph. Here the network of long-range connections between affective/reward (A/R), medial visual/categorization (MV/C), visuo-motor (VM),

dorsal attention (DA) and ventral attention (VA) RSNs is shown (cf. Gao et al., 2013); additional networks (e.g. default, language, higher-order executive) could clearly be included also. Open circles represent long-range (i.e. between-region) within-network connections while dots represent short-range (i.e. within-region) within-network connections; superposing these symbols indicates typical ratios of long-range to short-range within-network connections. Typical ratios of between-network connections are indicated by equal-width lines between nodes. b) A variant network in which one component (here A/R) has an atypically-large ratio of short to long within-network connections (or short to long within-network connection strengths), and has larger-than-typical connectivity from one other network (VA) and small-than-typical connectivity to another (MV/C). Between-network connections are drawn to the open symbols to emphasize that "rich club" nodes tend to receive long-range within- and between-network connections.

Geometric distortions may be used to symbolize differences from typicality in the ratios between connection probabilities, as shown in Fig. 4b. Moving the open and solid symbols for each node apart indicates a larger (dot farther from center than circle) or smaller (circle farther from center than dot) ratio of short- to long-range connections within a network; moving both symbols outward or inward provides a representation for whole-network over- or under-development, respectively. Thicker lines between networks indicate higher-than-typical between-network connectivity; thinner (i.e. dashed) lines indicate lower-than-typical between-network connectivity. At such variations may occur at different developmental times, the graph of a variant network may have different geometry at different times.

In the next section, we consider the consequences that may be expected from early-developmental perturbations of GNW organization, focusing on the subnetwork of the GNW comprising the affective/reward, medial visual/categorization, visuo-motor, and dorsal and ventral attention systems. We then employ the graphic representation developed above to examine the functional disruptions proposed in recent second-generation models of ASD (Fields, 2012a; Pellicano and Burr, 2012; Lawson, Rees and Friston, 2014; Van de Cruys *et al.*, 2014; Hellendoorn, Wijnroks and Leseman, 2015), showing that in each case they can be described as consequences of each connectivity perturbations.

Perturbations of GNW development

General versus localized developmental GNW disruptions

By placing the emergence of an SWN architecture linking functionally-specialized cortical and subcortical regions in the early third trimester at the latest, the results of Doria *et al*. (2010) and Ball *et al*. (2014), in particular, render the association of genes acting to regulate neural differentiation and connectivity in early- to mid-fetal development (Parikshak *et al*., 2013; Willsey *et al*., 2013) and maternal dietary deficiencies or toxin exposure (Currenti, 2010; Gardener, Spiegelman and Buka, 2011) with ASD less surprising. The results of Chow *et al.* (2012) indicate, moreover, that such genes continue to act through early childhood, as expected on the basis of gross anatomical and functional changes (Andersen, 2003; Casey, Tottenham, Liston and Durstan, 2005), but are replaced as potential

markers of pathology by maintenance-associated genes in adulthood. Symptoms attributable to GNW disruption would, therefore, be expected to arise no later than early childhood, and to be detectable, at least as prodromes, either neo- or peri-natally.

Early neuron over-growth followed by delayed functional maturation and reduced white-matter connectivity, particularly in frontal and temporal cortex and amygdala, was the first well-documented neurological correlate of ASD (reviewed by Courchesne and Pierce, 2005; Courchesne *et al.*, 2005; Courchesne *et al.*, 2007; for recent evidence that head size *per se* is not an information marker, see e.g. Zwaigenbaum *et al*., 2014). Uniform enhancement of short-range at the expense of long-range connectivity in these areas would be expected to disrupt function in all RSNs of interest here except the visuo-motor system, as well as in the language, default, and higher-level executive systems. Such extensive functional disruption would be expected to correlate with severe social, language, and attentional symptoms, consistent with the generally-recognized (e.g. Geschwind, 2009) tendency to diagnose only severe cases as ASD until relatively recently. An over-responsive amygdala and dysregulated ventral attention system could, in particular, be expected to generate the "intense world" symptoms discussed by Markram, Rinaldi and Markram (2007), while general frontal hypofunctionality could explain the learning disabilities and general intelligence deficits of severe autism, as proposed in theories of autism that focus on executive dysfunction as the primary cognitive phenotype (Rajendran and Mitchell, 2007).

The recent genetic dissociation of ASD and general intellectual disability (Parikshak *et al*., 2013), the varied symptomology of less-severe ASD and the diversity of ASD-associated genes and expression profiles all suggest that more localized and subtle disruptions of either regional or network-level function may be involved in most cases of ASD. While any significant departure from typicality in the GNW components shown in Fig. 4a, for example, can be expected to yield variant experience and behavior, the question of interest for pathology is whether such variation will be self-correcting in a typical infant environment, or will progress to diagnosable symptoms within the first 2 – 3 years. Using DTI and a connection-strength weighted efficiency measure, Lewis et al. (2014) have shown that RSN connection efficiency correlated with ASD severity at 2 years, noting that the networks most affected are those traversing ventral occipital and temporal cortex. This result indicates that at least some variants do not self-correct, among them variants associated with ASD. Relatively small variants in the pattern of connectivity that may be amplified, in a typical infant environment, into significant disruptions of function are of particular interest. Before discussing specific recent models of ASD, it is useful to review two kinds of variants that may be expected, on the basis of general neurocognitive considerations, to undergo such amplification: perturbations of salience and attention, and perturbations of category learning, including perturbations of category – reward associations. When viewed from the perspective of predictive coding and the Free Energy Principle (Friston 2010), these kinds of variants could be expected to affect expectation generation, error detection and coding, and precision estimates, as described in the models of Lawson, Rees and Friston (2014) and Van de Cruys *et al*. (2014) discussed below. We also briefly review expected effects of such variants on the default and executive systems, as it is these consequential effects that would be expected to generate the deficits in theory of mind and central coherence typical of ASD.

Perturbations of salience

As noted earlier, motion, faces, bodily sensations and novelty are particularly salient to infants. The relatively high salience of novel stimuli provides the basis for the widely-used looking time paradigm

in studies of infant cognition (reviewed by Aslin, 2007). Most available data on the relative salience of different classes of visual features (e.g. shapes, sizes, colors) and events (e.g. apparent violations of object permanence or solidity, inanimate objects acting as agents) have been provided by looking-time studies (see Luo and Baillargeon, 2010; Baillargeon, Li, Gertner and Wu, 2011; Aslin, 2014 for relevant reviews); hence there is significant ambiguity between "salience" and "novelty" in the early-development literature. As expected from considerations of learning efficiency (e.g. Oudeyer, Baranes and Kaplan, 2013), infants learn more effectively in the presence of novelty (Stahl and Feigenson, 2015; see Gopnik, 2012 for a review of supporting data), but divert attention away from overly-complex stimuli from which coherent regularities cannot be extracted (Kidd, Piantadosi and Aslin, 2012; see Aslin, 2014 for a review of supporting data). Both intrinsic motivation and learning context are, therefore, also potential confounds in salience studies with infants. One can, however, ask how disruptions in the typical development of object and event salience would affect an infant's experience of the world while taking these various caveats into account.

Both faces and motions indicative of animacy are key indicators of agency, and hence of the potential for social interactions, from earliest infancy onwards (Simion *et al.*, 2011). Specific deficits in either face perception (e.g. under-connectivity of fusiform face area) or the detection of biological motion (e.g. under-connectivity of STS) would, therefore, be expected to disrupt the perception of agency and hence the ability to engage in and learn from social interactions. Deficit social interaction can be expected to impact social learning in general and language learning in particular; hence both face and biological motion perception deficits can be expected to amplify into generalized cognitive-affective deficits in a typical infant environment. Deficits in face recognition and the inference of emotion from facial expressions correlate with severity in ASD (reviewed by Harms, Martin and Wallace, 2010; Weigelt, Koldewyn and Kanwisher, 2012), with considerable but not all evidence suggesting that emotional information conveyed by the eyes is specifically neglected (reviewed by Tanaka and Sung, 2013). Deficits in coherent motion perception in general (Robertson *et al*., 2014) and biological motion perception in particular (reviewed by Kaiser and Pelphrey, 2012) are associated with ASD, and are attributable to deficit higher-order processing, e.g. in STS, not deficit lower-level motion detection.

Salience controls the reactive ventral attention system and is controlled, at least in part, by the voluntary dorsal attention system (reviewed by Corbetta and Shulman, 2002; Vossel, Geng and Fink, 2014; Uddin, 2015). Disrupting the balance between these two competing systems in favor of reactivity, e.g. by over-activation of the amygdala in response to detected motion, would be expected to negatively impact attention sharing and hence social learning in addition to generating inappropriate negative affect. Disrupting the balance in favor of voluntary attention, e.g. by over-activation of motion-tracking areas in intraparietal sulcus, would be expected to negatively impact attention switching, again rendering attention sharing and social learning more difficult. Environments rich in unpredictable motion stimuli would be expected to amplify the former condition, while environments rich in predictable motion stimuli would amplify the latter. High distractability with inappropriate negative affect (e.g. Markram, Rinaldi and Markram, 2007) and low distractability with deficit attention switching (e.g. Elsabbagh *et al*., 2013) are both described in ASD, suggesting that both of these mechanisms may contribute to ASD symptomology.

The existence of multiple, possibly opposing mechanisms capable of generating cognitive, affective and behavioral symptoms meeting diagnostic criteria for ASD may also explain apparently-conflicting connectivity results. Hyper-connectivity within the salience network, and specifically between insular and anterior cingulate cortices, has been demonstrated in pre-adolescent children with ASD (Uddin *et*

al., 2013). In a study of primarily older children and adolescents, however, Abbott *et al.* (2015) demonstrated hypo-connectivity between insular and anterior cingulate cortices. A similar situation exists regarding the potential role in ASD of von Economo neurons (VENs), large spindle-shaped cells with long projections found in both insular and cingulate cortices . Postmortem studies of small numbers of subjects have reported fewer (Simms, Kemper, Timbie, Bauman and Blatt, 2009, 6 of 9 subjects), the same number (Kennedy, Semendeferi and Courchesne, 2007) and more (Simms, Kemper, Timbie, Bauman and Blatt, 2009, 3 of 9 subjects; Santos *et al*., 2011) VENs relative to pyramidal cells in ASD subjects that in controls (see Allman *et al.*, 2011; Butti, Santos, Uppal and Hof, 2013 for reviews). As in the case of general salience network connectivity, the apparent conflict between these results may be resolvable by considering a broader functional context that takes the potential effects of small local changes on other networks into account. Such ”knock-on” effects determine what kinds of internal or external stimuli have reduced or enhanced salience, and hence determine the cognitive, affective and behavioral consequences of local variants in neuron numbers or connectivity. Over a developmental time scale, small differences in the response of other networks to increases or decreases in salience can lead to dramatically different outcomes; for example, whether an increase in the salience of motion stimuli is associated with an increased fear response may determine the difference between an “intense world” (Markram, Rinaldi and Markram, 2007) outcome and a more benign hypersystemizing (Fields, 2012a) outcome.

Perturbations of categorization

Again as noted earlier, the grouping of objects into categories with which appropriate expectations can be associated is a key requirement for achieving predictability of and some level of control over the environment. It is also a pre-requisite for language learning (reviewed by Westermann and Mareschal, 2012). In adults, object categories or “concepts” are implemented as associations between modally-represented object features and behaviors (reviewed by Kiefer and Pulvermüller, 2012; see also Fernandino *et al*., 2015) and typically point to multiple episodic-memory resident object tokens representing individual exemplars (Fields, 2012b). The implementation of categories in infants is not well characterized, even in the canonical case of human faces (reviewed by Hoehl, 2015). The results of Gao *et al*. (2015) indicate that connectivity of the medial-visual network is adult-like in neonates; however, they provide no information on higher-order categorization areas (e.g. anterior temporal pole) or processes (e.g. abstraction or the organization of inter-category relations). The rapid development of categorization capabilities after language capabilities have developed suggests that categorization may be not just rudimentary but possibly also fluid in pre-linguistic infants.

At least four kinds of categorization disruption can be expected to be amplified into significant dysfunction in a typical infant environment. First, categorizing objects correctly whether they are currently moving or not requires the suppression of motion information relative to feature information during both category learning and subsequent object categorization (Fields, 2011). Insufficient suppression of motion information during category learning can be expected to result in aberrant, motion-emphasizing or even motion-dominated categories, with deleterious consequences for object identification and language learning (Fields, 2012a; see also below). Second, the animate-inanimate distinction is fundamental to normal category formation and may indeed be innate (Simion et al., 2011). Disruptions of this distinction can be expected to result in aberrant agency judgments and either too-broad or too-narrow social interactions. Third, many categories incorporate affective valences; either enhancing or suppressing interactions between the categorization and reward systems can be expected to lead to inappropriate approach or avoidance behaviors and either over- or under-expression

of affect. Finally, many categories incorporate manipulability information or even specific motor plans. Suppression of such connections would be expected to lead to category-specific apraxias as noted earlier, while enhancements may lead to inappropriate attempts to manipulate objects or styles of manipulation. Motor-planning deficits and dyspraxias are common in ASD (Jeste, 2011), although a connection with categorization deficits has not been established. Inappropriate manipulative and other motor behavior is also common in ASD.

Deficit categorization or the deployment of robust but aberrant categories can be expected to lead to the generation of either deficit or aberrant expectations about the behavior of objects in the world, including other people. Considerable evidence supports an association between deficit or aberrant expectation generation and hence deficit or aberrant action planning with ASD (reviewed by Gomot and Wicker, 2012; see also discussions of Pellicano and Burr, 2012 and Van de Cruys *et al.*, 2014 below). Deficits or significant variants in the detection and processing of salience as discussed above would, moreover, be expected to generate or at least correlate with deficit or variant categorization. The medial-visual/categorization network (MV/C in Fig. 4) comprising the static-feature detecting ventral visual processing stream, feature-cluster detectors in fusiform and lingual gyrus, hippocampal and parahippocampal areas associated with binding, object recognition and episodic-memory encoding, and high-level "concept" areas in the anterior temporal pole would be expected to be "ground zero" for such deficits or variants. The network connection inefficiencies correlated with ASD in 2-year-olds by Lewis *et al.* (2014) are, interestingly, concentrated in these areas.

Consequences of salience and categorization perturbations for the default and executive systems

As noted earlier, the executive and default networks develop later and mature more slowly than the sensory processing, sensory-motor control networks of primary interest here. From a cognitive-behavioral standpoint, major milestones in the development of these networks include, respectively, reasoning about mechanical causation and theory-of-mind (ToM), both of which are typically achieved in the pre-school years (reviewed by Fields, 2014), and abstract (e.g. mathematical or mechanical) and personally-relevant planning, which are typically achieved by adolescence (Casey, Tottenham, Liston and Durstan, 2005; for the default network in particular, Fair *et al.*, 2008). First-generation models of ASD centered around deficits in central coherence (e.g. Happé and Frith, 2006) or ToM (e.g. Baron-Cohen, 2002) focused attention on deficits in or disruptions of the executive or default networks, respectively, while functional and connectivity studies supporting disconnection of prefrontal cortex in ASD relative to typical development (e.g. Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Wass, 2011) suggested an etiological focus on these networks. However, recent studies suggest a more complicated picture. Shih et al. (2010) and Abbott et al. (2015), for example, both report overconnectivity between executive and default networks together with underconnectivity between specific components of each network; Elton, Di Martino, Hazlett and Gao (2016) similarly report enhanced default-to-executive connectivity combined with disrupted connectivity between components of the executive network. Such results are consistent with the more nuanced view of connectivity variations in ASD that has emerged as larger subject populations and refined methods have become available (Müller et al., 2011; Vissers, Cohen and Geurts, 2012; Maximo, Cadena and Kana, 2014; Picci, Gotts and Scherf, 2016).

Within the current, GNW-based framework, variant functional connectivity within and between the executive and default networks, as well as between these networks and the categorization, salience and attention systems, is expected to result, at least in large part, from disrupted or variant functional

connectivity within and between earlier-developing networks. Disruptions of ToM or self-representation, for example, can be expected to result from disruptions of the categorization and salience systems, as discussed further below. A categorization network biased toward similarities in kinematic or dynamic properties of objects and against similarities in static properties would, similarly, be expected to facilitate planning and abstract problem solving in formal and mechanical domains while inhibiting planning and problem solving in the social domain (Fields, 2012a; 2012b). Substantial individual variation in executive and default network functions are, moreover, to be expected if disruptions in these networks are developmental consequences of disruptions or variations in functionally antecedent networks with which these later-developing systems have bidirectional connectivity. Such a scenario is consistent with both the heterogeneity of connectivity variations (Hahamy, Behrmann and Malach, 2015) and symptomatic presentations observed in ASD adults.

Five recent models of ASD from a GNW perspective

As noted earlier, disruptions of functional connectivity in ASD have been intensively investigated since the early 2000s (Courchesne and Pierce, 2005; Geschwind and Levitt, 2007; Minshew and Williams, 2007; Rippon *et al*., 2007; Müller et al., 2011; Wass, 2011; Vissers, Cohen and Geurts, 2012; Maximo, Cadena and Kana, 2014; Tyszka, Kennedy, Paul and Adolphs, 2014; Picci, Gotts and Scherf, 2016) and ASD is now widely considered to be a connectome-scale developmental disorder (Di Martino *et al.*, 2014; Dehaene-Lambertz and Spelke, 2015; Vértes and Bullmore, 2015). While the vast majority of studies have examined connectivity in older children, adolescents or adults with ASD, significant departures for typical connectivity have been observed, albeit at relatively low spatial resolution, even in high ASD-risk infants (Keehn, Wagner, Tager-Flusberg and Nelson, 2013; Righi, Tierney, Tager-Flusberg and Nelson, 2014). As the GNW is the "network of networks" that coordinates conscious activity (Dehaene and Changeux, 2011; Dehaene, Charles, King and Marti, 2014), it is reasonable to ask how changes in connectivity might affect GNW function and hence experience of and interaction with the world. It is, in particular, reasonable to ask how such changes might affect the functions of the early-developing sub-network of the GNW represented in Fig. 4a.

Even second-generation, neurocognitive models of ASD have focused on mechanisms that might underlie typical cognitive and behavioral manifestations of ASD post-diagnosis, i.e. beginning in early childhood. The considerations outlined in the previous two sections suggest, however, that post-diagnosis symptoms may have their source in very early, possibly prenatal alterations in functional connectivity. Our goals in this section are 1) to show that the neurocognitive outcomes proposed by the models of Fields (2012a), Pellicano and Burr (2012), Lawson, Rees and Friston (2014), Van de Cruys *et al. (*2014) and Hellendoorn, Wijnroks and Leseman (2015) can be represented within the graphical framework of Fig. 4 and 2) to suggest that in every case, these outcomes may result from relatively small, localized, and early perturbations of connectivity within the medial-visual/categorization network. We review each model briefly, outlining in particular the symptoms or typical characteristics of ASD it seeks to explain; we then reformulate each model in the graphical framework of Fig. 4 and use this reformulation to highlight connectivity perturbations that could produce the initial conditions assumed by the model.

As noted earlier, perturbations of MV/C network can be expected to manifest as disruptions of categorization. Early connectivity perturbations of this or other networks are consistent with the mid-gestation action of many ASD-associated genes (Parikshak *et al*., 2013; Willsey *et al*., 2013). As the developmental consequences of small, localized and early connectivity perturbations can be expected

to be highly dependent on interactions both with unperturbed components of the neurocognitive network and with the external environment, including the prenatal environment, considerable variation in phenotypic presentation by the age of typical diagnosis can be expected within this GNW-based framework.

Motion-based categories (Fields, 2012a)

Fields (2012a) suggested that insufficient suppression of inputs from the dorsal visual processing (i.e. visuo-motor) stream relative to inputs from the ventral (i.e. static feature recognition) stream during category learning could lead to the generation of categories that grouped objects by their motion patterns, not by their static features. Such motion-based categories would, in the extreme case, be orthogonal to typical human feature-based categories; a family member, for example, might be assigned to different categories depending on how he or she was moving at the time of observation, and hence might never be recognized to be a single, situation-invariant individual. Fields (2012a) argued that deploying such motion-based categories instead of feature-based categories in infancy would broadly interfere with typical object-directed behaviors, social interactions and language learning, leading to cognitive and behavioral symptoms typical of ASD.

Both the initial perturbation postulated by this model and its amplified outcome are represented in Fig. 5 using the visualization scheme developed earlier (cf. Fig. 4). The initial perturbation is an increase in input connectivity from the visuo-motor network to the medial visual/categorization network, with an accompanying decrease in feature- or category-driven inhibition of motion information. Continued activation of motion-based categories would be expected to further decrease the effective contribution of static features to the categorization process, and hence to further decrease effective connectivity from the medial visual system to higher-level medial and anterior temporal areas involved in category learning and memory. Enhanced correlation between visuo-motor and category inputs to other networks together with decreased correlation between medial visual (i.e. feature-encoding) inputs and category inputs to these same networks would tend to increase outgoing visuo-motor connectivity while decreasing outgoing medial visual connectivity as indicated in Fig. 5. As objects would be recognized primarily by their motion patterns, dorsal attention system interactions with the visuo-motor system would be strengthened.

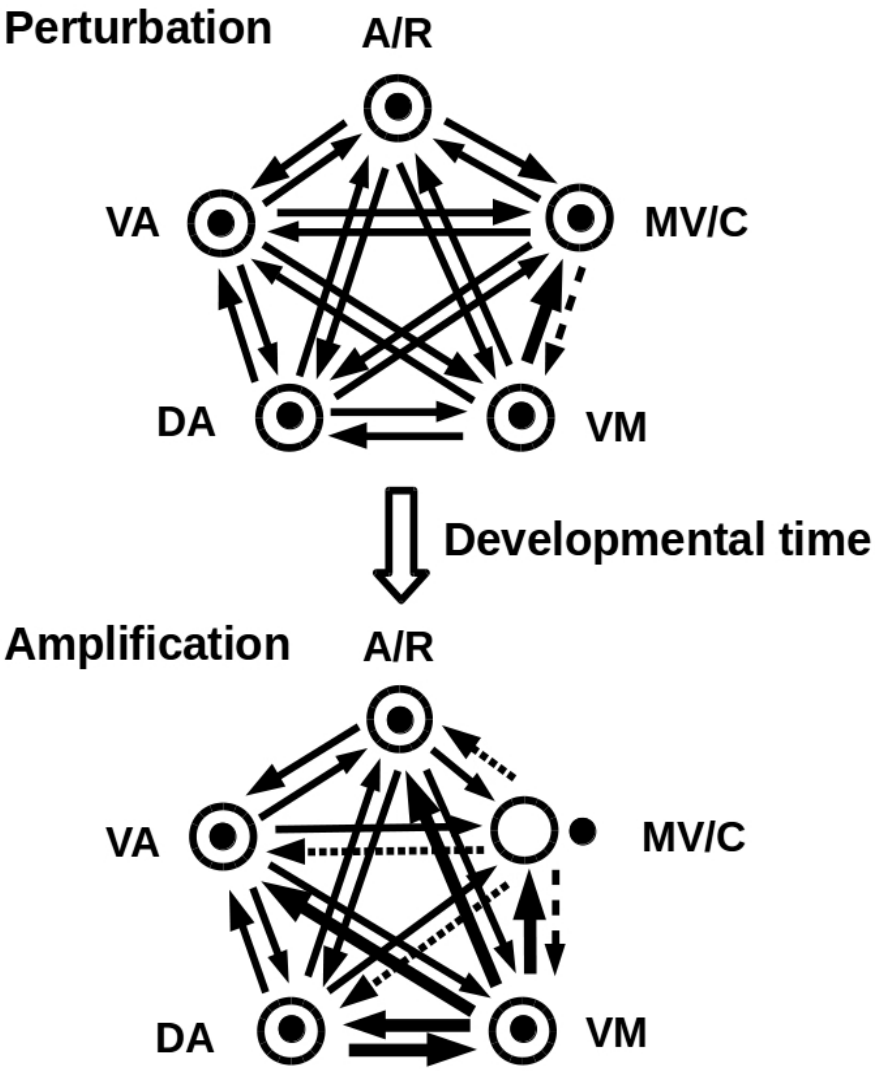

Fig. 5: The model of Fields (2012a) represented using the graphic visualization method of Fig. 4. The initial perturbation in this model is a relative increase in visuo-motor (VM) input to the object categorization process (upper part of figure). Amplifying this perturbation over developmental time decreases connectivity between medial visual (MV) and categorization (C) network components (lower part of figure). Functional correlation and hence connectivity are consequently increased from VM to other GNW components and decreased from MV/C to other GNW components.

While they are broadly consistent with ASD phenomenology, the connectivity changes predicted in Fig. 5 have not been directly tested. Enhanced visuo-motor connectivity relative to medial visual connectivity is, however, suggested by results of Zmigrod *et al*. (2013), who shows that older ASD children were both faster than typical children in a spatial response task and less accurate than typical

children in adjusting a spatial response given a featural (shape or color) cue. Using an object identification and location task monitored with fMRI, DeRamus, Black, Pennick and Kana (2014) showed both that older ASD children are marginally deficient in object identification but not object location compared to typicals, and that temporal – parietal functional connectivity is reduced in ASD children relative to typicals, in both cases consistent with the model.

Attenuated expectations (Pellicano and Burr, 2012)

Pellicano and Burr (2012) introduced the idea that an overall attenuation of top-down expectations could explain the enhanced sensitivity to perceptual detail, decreased sensitivity to gestalt features of scenes, and variant emotional responses typical of ASD. When formulated in the terms of a Bayesian analysis of perception as an inverse inference of features of a stimulus from features of its image, top-down expectations become experience-based prior probabilities of stimulus features; a uniform prior probability distribution corresponds to no expectations about what is contained in a scene (e.g. Knill and Pouget, 2004). Reducing the relative strength of expectations by flattening the prior probability distribution allows image features to determine the perceived stimulus features with minimal expectation-based interpretation. Pellicano and Burr (2012) suggest that relatively flat prior probability distributions for most stimulus features would lead to excessively "literal" and detail-oriented perceptions, relative immunity to perceptual illusions, preference for exactly-repeated stimuli, and aversion to perceptual noise and rapid changes of scene.

As shown by Bastos *et al*. (2012) and Adams, Friston and Bastos (2015), fine-scale predictions about typical activity patterns and hence prior probabilities in the Bayesian sense are encoded even by the local-circuit architecture of cortical minicolumns. In principle, therefore, all cortical processing can be viewed as Bayesian inference. For the present purposes, however, it is useful to focus on the encoding of prior probabilities for perceived scenes by the categorization system. Category learning during infancy and childhood can be viewed as the progressive elaboration of experience-based prior probabilities for perceptible features within each category (e.g. Gopnik and Wellman, 2012). Developing the expectation that dogs have fur, for example, is incorporating the feature `has-fur' into the category `dogs' or, in Bayesian terms, increasing the prior probability P(fur) for objects already classified as dogs or, more generally, increasing the prior conditional probability P(fur|dog). Relatively uniform probability distributions for features correspond, in this case, to relatively open-ended and uninformative categories. Extending the relatively uniform probability distribution for the number of limbs appropriate to the `animals' category to the subcategory `mammals', for example, leads to a significant decrease in predictive power; not including as an essential feature that mammals have faces similarly decreases the power of the category. Unlike in the model of Fields (2012a), the attenuation of prior probabilities and hence perceptual expectations proposed by Pellicano and Burr (2012) applies equally to all features, including features specifying motion patterns. The model of Pellicano and Burr (2012) does not predict that individuals with ASD will categorize individuals by their motion patterns, but rather that motion patterns, like static features, will be incorporated only weakly into categories.

Encoding a rich category structure incorporating probabilities for large numbers of features within each category as well as conditional probabilities relating features to each other requires high coding capacity and hence a wealth of short-range connections within the categorization system. The general attenuation of perceptual expectations and hence of categorization proposed by Pellicano and Burr (2012) could be expected, therefore, to result from an early-developmental perturbation of GNW architecture that decreased short-range connectivity and hence information encoding capacity within

the medial-to-anterior temporal-lobe network that implements the categorization system, as shown in Fig. 6. Decreased top-down categorization feedback would be expected to decrease both top-down and bottom-up connectivity between both the dorsal and ventral visual processing streams and the categorization system, with concomitant decreases in ventral-stream connectivity to the attention and affective/reward systems. Attention and affective feedback would, in this case, be expected to be captured mainly by motion stimuli via the fast, categorization-independent, visuo-motor to limbic system pathways that enable reflexive responses to dangerous stimuli prior to conscious perception. Sensitivity to perceptual noise and change would be expected to be more severe on this model, for a given level of static-feature based categorization dysfunction, than on the model of Fields (2012a). However, the inappropriate behaviors based on inappropriate motion-based categories, i.e. behaving in the same way toward all entities that moved in the same way, expected from the model of Fields (2012a) would not be expected on this model. Pellicano and Burr (2012) make no specific claims about the severity of attenuation of expectations in their model, consistent with the graded dysfunctions seen in ASD.

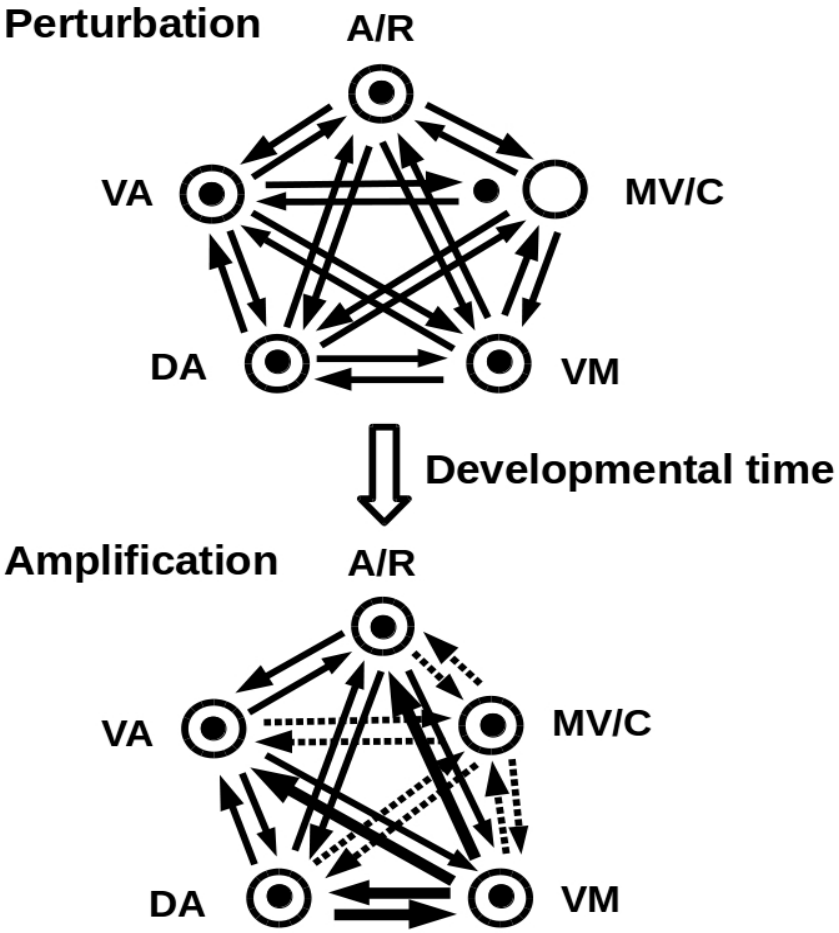

Fig. 6: The model of Pellicano and Burr (2012) represented using the graphic visualization method of Fig. 4. The initial perturbation in this model is a relative decrease in short-range connectivity in the categorization (C) system. The main developmental consequence of attenuated categorization capability is attenuated feedback from the categorization system to sensory systems generally, and to visual processing streams in particular. This lack of feedback drives reconfiguration of the GNW toward an emphasis on visuo-motor as opposed to static-feature based processing.

As seen in Fig. 6, the long-term effects that could be expected to result from the attenuation of expectations proposed by Pellicano and Burr (2012) are not dissimilar to those predicted by Fields (2012a). Both models, in particular, predict over-development or over-activation of connections between the visuo-motor and dorsal attention system in ASD compared to typical development. The models are, however, distinguished by the deficit local connectivity within the categorization system predicted by the above reconstruction of the model of Pellicano and Burr (2012). While this prediction has not been tested directly, Keehn, Wagner, Tager-Flusberg and Nelson (2013) reported marginally enhanced left-hemisphere anterior-to-posterior connectivity in high compared to low ASD risk 3 month-old infants, followed by decreased intrahemispheric connectivity in high-risk infants at 12 months; Righi, Tierney, Tager-Flusberg and Nelson (2014) similarly reported decreased intrahemispheric connectivity in high-risk infants at 12 months. Additional support for reduced temporal-lobe connectivity in late infancy is provided by Lombardo et al. (2015), who demonstrated reductions in temporal lobe activity in response to speech in 1- to 4-year-olds with ASD and poor language development compared to age-matched controls or ASD with good language development, and by Dinstein *et al*. (2011), who demonstrated reduced interhemispheric synchronization in superior temporal gyrus, an area implicated in language processing, in 1- to 3.5-year-olds with ASD compared to controls.

Overly-precise perceptions (Lawson, Rees and Friston, 2014, Van de Cruys et al., 2014)

As noted earlier, considerable evidence supports the ubiquitous use of predictive coding in mammalian cortical processing. In a predictive coding context, “correct” top-down expectation signals are insufficient to assure correct processing of perceptual inputs; the process of comparing perceptual inputs with expectations must also work correctly. Lawson, Rees and Friston (2014) and Van de Cruys *et al*. (2014) suggest that it is not an attenuation of expectations *per se* that generates the typical perceptual and categorization symptoms of ASD, but rather a dysfunction in the process of generating the “error” signals that represent differences between perceptions and expectations. The magnitude of the error signal depends not only on the strengths but also on the estimated precisions of both the bottom-up perceptual signal and the top-down expectation or prior-probability signal; imprecise percepts are easier to match to expectations and vice versa, while very precise percepts are harder to match to expectations and vice versa. Precision is itself context-dependent and must be estimated based on experience; one has to learn, for example, when to regard either percepts or expectations with near certainty and when to be open to the possibility that one's expectations are only weakly supported by insufficient knowledge or one's visual interpretation of a scene is incorrect. As Friston, Lawson and Frith (2012) point out in a Commentary on Pellicano and Burr (2012), estimating precision is effectively a metacognitive process, as it requires inferences about the functional adequacy of already-complex cognitive representations.

The models of Lawson, Rees and Friston (2014) and Van de Cruys *et al*. (2014) both focus on disrupted estimates of precision, but differ in the specificity of the assumed dysfunction. Lawson, Rees and Friston (2014) suggest that in ASD sensory precision is in general set too high, while pointing out that "overly precise estimates of sensory precision and under-precise estimates of prior precision would produce the same functional consequences; i.e., perception/interaction that lies closer to the sensory input and is insensitive to context" (p. 6). Insufficiently-precise priors are, on this model, an expected side-effect (*cf.* van Boxtel and Lu, 2013). Van de Cruys *et al*. (2014) locate the dysfunction not in the representation of percepts or priors *per se*, but in the atypical weighting of prediction errors and in the precision assigned to the percept-expectation error signal. This "high, inflexible precision of prediction errors in autism" (p. 4) or HIPPEA model is, at least in principle, independent of the precisions assigned to either percepts or expectations individually. Its emphasis on inflexibility, moreover, suggests that the assumed dysfunction cannot be overcome by learning.

Like the model of Pellicano and Burr (2012), the models of Lawson, Rees and Friston (2014) and Van de Cruys *et al*. (2014) are intended to characterize ASD in children, adolescents and adults, i.e. in neurocognitive systems that have already developed robust, hierarchical categories. For the present purposes, the question of interest is how a categorization system characterized by overly-precise percepts and weak, imprecise priors or by inflexibility in precision assignments could develop during early infancy. Like perceptual expectations themselves, appropriate estimates of both perceptual and categorization precision must be learned from experience. Connectivity disruptions that impair such learning can be expected to impair estimates of precision. An insufficiently-developed categorization system, as shown in Fig. 6, would be expected to produce poorly-defined and hence imprecise expectations across the board. If all expectations are equally imprecise, accurate precision estimates cannot be learned. Alternatively, a failure to develop sufficient top-down connectivity from a normally-developing categorization system to normally-developing dorsal and ventral visual-processing streams, as shown in Fig. 7, could also be expected to disrupt precision estimates and hence precision-estimate learning. As insufficient or inaccurate feed-forward error signals would be expected to further disrupt category learning, the outcome of this perturbation could be essentially indistinguishable from the outcome of the Pellicano and Burr (2012) mechanism shown in Fig. 6.

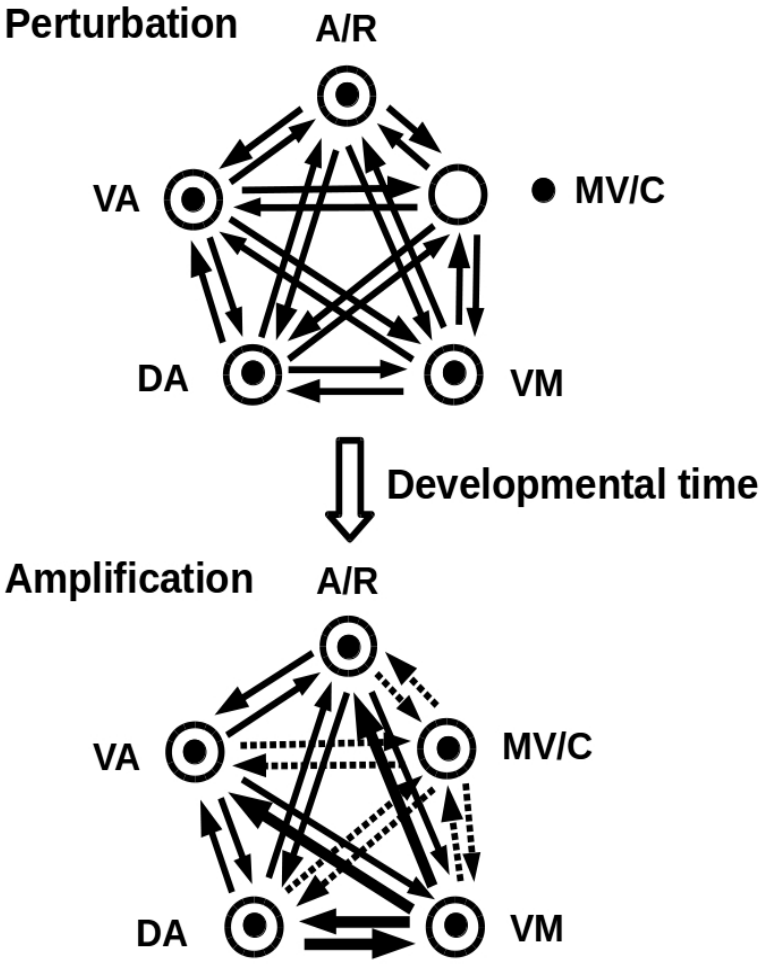

Fig. 7: Deficit top-down feedback of expectations to visual processing streams would be expected to result in categorization deficits similar to those expected from deficit categorization-system development (cf. Fig. 6).

The possibility that multiple initial perturbations of GNW development could produce functionally equivalent or at least very similar outcomes after exposure to typical infant and early-childhood environments is consistent with the idea that ASD is a syndrome with possibly quite-diverse etiologies. Disrupted connectivity within the MV/C system or between this system and the functionally very closely related VM system (i.e. the dorsal visual processing stream) appear, however, to be plausible candidates for the initial disruption across a broad range of models. It is interesting in this regard that connection efficiency within lingual gyrus, an MV/C component involved in complex-feature detection

and binding, is both highly sensitive to prenatal genetic variability (Fornito *et al*., 2011) and highly correlated with ASD as an outcome (Lewis *et al.,* 2014). These results suggest that lingual gyrus may be a plausible locus for the initial disruptions of MV/C connectivity represented in Figs. 5 – 7.

Disrupted invariance detection (Hellendoorn et al., 2015)

Hellendoorn, Wijnroks and Leseman (2015) offer a variation on the model of Pellicano and Burr (2012) in which what is attenuated in ASD is not perceptual expectations *per se* but the detection of perceptual invariants, where these are viewed in Gibson's (1979) terms as affordance-specifying properties of the environment, including (for vision) the ambient photon field. The core of the model is the proposal that categorization ASD is based on comparisons between percepts and individual exemplars as opposed to abstracted categories; contrasting their model with that of Pellicano and Burr (2012), Hellendoorn, Wijnroks and Leseman (2015) "do not suggest that people with ASD have weak priors, but *different* priors. Because of their invariance detection impairments, we hypothesize that the priors of people with ASD also include variant aspects of the environment and are more exemplar-based instead of prototype-based" (p. 9, emphasis in original). People with ASD would, in other words, expect to encounter the same individual entity in the same environmental context, as opposed to expecting a "typical" entity in a "typical" context. From a developmental perspective, one would expect purely exemplar-based categorization in childhood or adulthood to result from a systematic failure of abstraction in infancy and hence from early dysfunction in the categorization system, although how such a process would be described in Gibsonian terms, which require all information about category membership to be encoded by the stimulus, is unclear.

As Hellendoorn, Wijnroks and Leseman (2015) point out, expectations and hence priors based on individual exemplars cannot distinguish invariant from accidental and hence variant features of a category member; hence the substitution of exemplars for abstract categories would be expected to impair invariance detection. However, it is unclear how exemplars are associated with categories – in the example employed by Hellendoorn, Wijnroks and Leseman (2015), how exemplars of factories are represented as exemplars of a common category `factory' – in the model, especially given the Gibsonian rejection of representation as a function of cognitive systems. However this association is implemented, however, it must be learned; hence the deficit in invariance detection postulated by Hellendoorn, Wijnroks and Leseman (2015) may result developmentally from a deficit in invariance learning. The model of Hellendoorn, Wijnroks and Leseman (2015) can, therefore, be reconstructed along the lines of either Fig. 6 or Fig. 7, i.e. as an outcome of either deficit categorization *per se* or of deficit category learning.

Conclusion

The second-generation models briefly reviewed here are all consistent with the emerging idea that "sensory processing is not only an additional piece of the puzzle, but rather a critical cornerstone for characterizing and understanding ASD" (Baum, Stevenson and Wallace, 2015, p. 140). As discussed in detail by Fields (2012a), Pellicano and Burr (2012), Lawson, Rees and Friston (2014), Van de Cruys *et al.* (2014) and Hellendoorn, Wijnroks and Leseman (2015), these perception and categorization focused models are able to explain the deficits in social interaction, affect and executive function on which the earlier generation of models tended to focus as consequences of disruptions in the processing and interpretation, in context, of perceptual input. What has been suggested here is that the specific sensory

processing, or in the case of Hellendoorn, Wijnroks and Leseman (2015), sensory detection deficits or variants proposed these models can be understood as developmental outcomes of perturbations of GNW organization and function in early infancy, possibly prenatally. In particular, both the models considered here individually and the integrative framework we have proposed to understand them from a GNW perspective locate the etiology of ASD in the interactions between early-developing sensory processing, sensory-motor and attention systems, and regard functional disruptions in the "higher" executive and default networks as consequences, not causes. An early-developmental etiology of ASD is consistent with the early activity of ASD-associated genes (Parikshak *et al*., 2013; Willsey *et al*., 2013; see also Geschwind and Flint, 2015) as well as the association between ASD and prenatal toxicity (Currenti, 2010; Gardener, Spiegelman and Buka, 2011). Functional disruption of GNW development is also consistent with the emerging view that ASD is a connectome-level developmental disorder (Di Martino *et al*., 2014; Dehaene-Lambertz and Spelke, 2015; Vértes and Bullmore, 2015).

The models discussed here have yet to be directly tested by high-resolution connectivity studies in infants, and they are supported at present only by low-resolution, indirect or circumstantial evidence as discussed above and in their respective original publications. High-resolution functional connectivity analysis of infant ASD (or high ASD risk) populations compared to typical controls, especially of pre-term infants followed longitudinally as performed by Doria *et al*. (2010) and Ball *et al*. (2014), may in principle be capable of distinguishing the mechanisms proposed by these models. As noted earlier, underconnectivity or functional disruptions in lingual gyrus may be an attractive target for such studies. At least two kinds of formal studies may also contribute. First, the developmental robotics methods employed by Schlesinger *et al*. (2012) to replicate typical infant performance on a perceptual completion task could, in principle, be extended to investigate the representational and algorithmic assumptions necessary to replicate typical and ASD infant performance on perceptual categorization tasks (see also Cangelosi and Schlesinger, 2015 for a more general discussion of such methods). Second, network-growth methods such as those of Jarman *et al*. (2014), if extended to include position-dependent connection probabilities between functional regions as discussed above, may be sufficiently powerful to model the early development of the GNW in a way that provides new insights into network parameters that may be affected by genes, particularly axonal growth-cone guidance genes (e.g. McFadden and Minshew, 2013), acting in mid- to late-fetal development.

Setting the differences between these models aside, however, they all suggest that early-developing deficits or disruption in the medial-visual/categorization network underlie ASD. They therefore suggest that therapeutic interventions that facilitate learning both feature-based categories and motion-feature correlations in early infancy may be useful for ameliorating the functional deficits of ASD.

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