PAPER

The over-pruning hypothesis of autism

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Abstract

This article outlines the over-pruning hypothesis of autism. The hypothesis originates in a neurocomputational model of the regressive sub-type (Thomas, Knowland & Karmiloff-Smith, 2011a, 2011b). Here we develop a more general version of the over-pruning hypothesis to address heterogeneity in the timing of manifestation of ASD, including new computer simulations which reconcile the different observed developmental trajectories (early onset, late onset, regression) via a single underlying atypical mechanism; and which show how unaffected siblings of individuals with ASD may differ from controls either by inheriting a milder version of the pathological mechanism or by co-inheriting the risk factors without the pathological mechanism. The proposed atypical mechanism involves overly aggressive synaptic pruning in infancy and early childhood, an exaggeration of a normal phase of brain development. We show how the hypothesis generates novel predictions that differ from existing theories of ASD including that (1) the first few months of development in ASD will be indistinguishable from typical, and (2) the earliest atypicalities in ASD will be sensory and motor rather than social. Both predictions gain cautious support from emerging longitudinal studies of infants at-risk of ASD. We review evidence consistent with the over-pruning hypothesis, its relation to other current theories (including C. Frith's under-pruning proposal; C. Frith, 2003, 2004), as well as inconsistent data and current limitations. The hypothesis situates causal accounts of ASD within a framework of protective and risk factors (Newschaffer et al., 2012); clarifies different versions of the broader autism phenotype (i.e. the implication of observed similarities between individuals with autism and their family members); and integrates data from multiple disciplines, including behavioural studies, neuroscience studies, genetics, and intervention studies.

Research highlights

- We present a new hypothesis of the underlying cause of autistic spectrum disorders (ASD) that explains the lack of observed differences from typical development in early infancy and heterogeneity in the timing of manifestation of the disorder
- The over-pruning hypothesis proposes that ASD results from over-pruning of brain connectivity early in development, particularly impacting long-range connections; we review evidence relating to the hypothesis from behavioural, brain, genetic, and intervention studies
- We present a neurocomputational model instantiating the over-pruning hypothesis, extending the work of Thomas, Knowland and Karmiloff-Smith (2011a)

to demonstrate: (1) that the three main sub-types of ASD (early onset, late onset, regressive) can be produced by a single pathological mechanism interacting with population-wide individual differences in neurocomputational properties; and (2) unaffected siblings of individuals with ASD may differ from controls either by inheriting a milder version of the pathological mechanism or by inheriting the risk factors without the pathological mechanism.

- The over-pruning hypothesis generates several novel predictions, including that the first few months of development in ASD will be indistinguishable from typical, and that the earliest atypicalities will be sensory and motor rather than social; both predictions gain cautious support from emerging longitudinal studies of infants at risk of ASD.

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Introduction

Current theories of the cause of autism tend to propose that the earliest atypicalities appearing in infancy are either in social orienting (e.g. Chevallier, Kohls, Troiani, Brodkin & Schultz, 2012; Dawson, Meltzoff, Osterling & Rinaldi, 1998; Johnson, Griffin, Csibra, Halit, Farroni *et al.*, 2005; Mundy & Neale, 2000; Schultz, 2005) or in some more general attentional process contributing to the development of social skills (e.g. Bryson, Landry, Czapinski, Mcconnell, Rombough *et al.*, 2004; Kawakubo, Kasai, Okazaki, Hosokawa-Kakurai, Watanabe *et al.*, 2007; Landry & Bryson, 2004; van der Geest, Kemner, Camfferman, Verbaten & van Engeland, 2001). Such theories appeal to a causal model in which secondary, downstream atypicalities in skills whose development relies on the atypical processes then produce the full autistic spectrum phenotype, comprising impairments in social-communication and a restricted repertoire of behaviours and interests. The theories therefore predict a particular order of the appearance of atypical behaviours, with those in social orienting or attention exhibiting the earliest occurrence. Emerging data from infants who are younger siblings of children with autism, who are at risk of developing autism through inheritance, have thus far not offered strong support to either theory (Gliga, Jones, Beford, Charman & Johnson, 2014; Jones, Gliga, Bedford, Charman & Johnson, 2014). The majority of studies suggest that neither social orienting nor attentional problems emerge as the first symptoms over the first 12 months of life.

In this article, we propose an alternative hypothesis for the cause of autism, the *over-pruning hypothesis*. This hypothesis predicts a different pattern of the emergence of atypicalities in infancy, and indeed that early atypical profiles in autism may differ markedly from the behavioural profile found in childhood and adulthood. The over-pruning hypothesis derives from a recent neurocomputational model of the regressive sub-type of autism (Thomas, Knowland & Karmiloff-Smith, 2011a, 2011b). In the first section below, we summarize the findings of the original computational model and then present new simulation results. We first show how the model can capture early-onset autism, late-onset autism, and the regressive sub-type via a single pathological mechanism in brain development, which then interacts with population-wide individual differences in other neurocomputational factors to generate diverse atypical trajectories. We go on to show how the model can account for the effects of 'risk', as observed in studies of unaffected younger siblings of individuals with ASD (see e.g. Gliga *et al.*, 2014). In particular, we demonstrate ways in which development in these 'at-risk' individuals may nevertheless differ from that found in low-risk controls.

In the subsequent sections of the paper, we lay out the more general over-pruning hypothesis based on the model, including a set of novel empirical predictions. We then consider existing empirical evidence both consistent and inconsistent with the over-pruning hypothesis. We finish by situating the hypothesis with respect to other extant theories of autism and of atypical pruning, and by highlighting aspects of the over-pruning hypothesis that are in need of further development in order to adequately test the theory.

The origin of the over-pruning hypothesis in a neurocomputational model of development

Thomas, Knowland and Karmiloff-Smith (2011a), henceforth TKK, used an artificial neural network model of development to simulate developmental regression in autistic spectrum disorder (ASD). Regression is the loss of previously established behaviours, usually occurring in the second year of life (Baird, Charman, Pickles, Chandler, Loucas *et al.*, 2008; Lord, Shulman & DiLavore, 2004; Pickles, Simonoff, Conti-Ramsden, Falcaro, Simkin *et al.*, 2009). Estimates of the proportion of children with ASD exhibiting this sub-type range from 15 to 40% (e.g. Charman, 2010; Nordahl, Lange, Li, Barnett, Lee *et al.*, 2011; Zwaigenbaum, Bryson & Garon, 2013). While the loss of language is the most overt marker, loss of social, cognitive, and motor skills is also noted, and regression is usually followed by recovery and improvement in skills (Pickles *et al.*, 2009).

Previous neurocomputational models of autism have hypothesized a variety of anomalies, including an imbalance in excitatory versus inhibitory connectivity, an impairment in long-range connectivity, an over-allocation of neural resources, and neural codes that are either too conjunctive or too noisy (Cohen, 1994, 1998; Grossberg & Seidman, 2006; Gustaffson, 1997; Lewis & Elman, 2008; McClelland, 2000; Simmons, McKay, McAleer, Toal, Robertson *et al.*, 2007). None of these proposals readily accounts for regression.

The TKK model employed a population modelling technique (Thomas, Baughman, Karaminis & Addyman, 2012), in which development was simulated in a large number of individuals (i.e. several thousand). Variation was included both in the richness of the structured learning environment to which the individual was exposed and in the learning properties of each artificial

neural network. The environment was manipulated by altering its information content, while variation in 14 neurocomputational parameters interacted to determine each individual's learning ability. These parameters related to how each network was built, activated, maintained, and adapted. Networks included a process of connectivity pruning, in which unused connections (those whose strengths fell below a certain threshold) were progressively pruned after a certain point in development. This captured the normal phase of brain development in which excess connectivity is progressively eliminated. Within the computational framework, a single parameter was able to produce developmental regression when set to atypical values. This was the *pruning threshold parameter*, determining how weak a connection had to be in order to be classified as unused and therefore available for pruning. If the size of this threshold was increased, so that stronger connections could be pruned, then with the onset of pruning, functionally important connections could be lost, thereby producing a decline in performance. The model therefore instantiated the following theoretical claim: developmental regression in autism could be caused by the exaggeration of a normal phase of brain development, the pruning of connectivity. If pruning is too aggressive and damages functional circuitry, it may cause a loss of established behaviours. Following the regression of behaviour, many of the networks exhibited a phase of recovery, as residual connectivity was exploited to complete development as well as could be achieved using these reduced resources. The model therefore accommodated recovery without the spontaneous cessation of the pathological process.

However, the computational model only explained one sub-type of ASD, the regressive sub-type. This raised the question of whether other sub-types would need to be explained by alternative atypical mechanisms. For example, Figure 1 reproduces a diagram from Elsabbagh and Johnson's (2010) article, 'Getting answers from babies about autism'. It depicts three hypothetical developmental trajectories of ASD drawn from the literature (see e.g. Landa, Gross, Stuart & Faherty, 2013; Ozonoff, Iosif, Young, Hepburn, Thompson *et al.*, 2011). The diagram includes both early-onset and late-onset sub-types, in addition to the regressive sub-type. How are these other trajectories to be explained according to the model? One possibility, suggested by case studies drawn from the simulated populations, was that the pathological pruning mechanism might interact with population-wide variations in other parameters, such as the timing of pruning onset, to produce variations in atypical trajectories. An earlier onset of atypical pruning might deflect trajectories without an initial phase of normal-looking
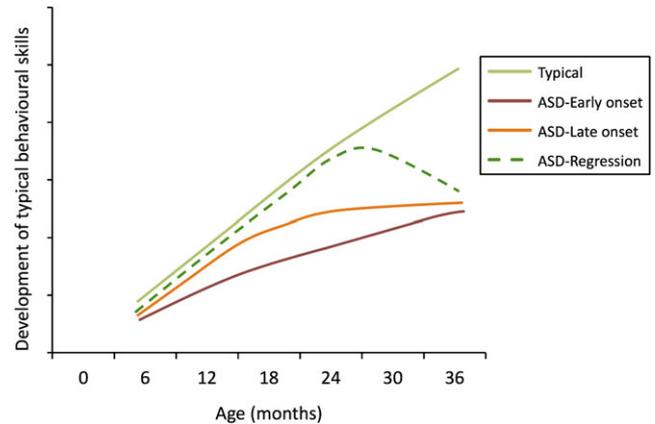
Figure 1 *Schematic of proposed developmental trajectories within ASD, reproduced with permission from Elsabbagh and Johnson (2010). These include typical development and three sub-types of ASD: early onset, late onset, and regression.*

development. However, this was not systematically demonstrated in the TKK model.

In addition, the model did not account for the broader autism phenotype, in terms of the observed similarities between individuals with ASD and their family members. Indeed, no computational model of ASD has yet been applied to this question. However, increasing numbers of prospective studies of infants at risk for developing autism because they have an older sibling with ASD have shown that behavioural and neural differences can be found by virtue of risk status itself, whether the infant goes on to receive a diagnosis of ASD or not (e.g. Elsabbagh, Gliga, Pickles, Hudry, Charman *et al.*, 2013). This finding supports the view that some common inheritance alters trajectories of development. The population-modelling framework is in a position to investigate this issue, since multi-scale versions of the TKK model have encoded the variation in neurocomputational parameters in an artificial genome (Thomas, Forrester & Ronald, in press). This allows networks to be generated that are 'siblings' of each other, that is, which share 50% of their artificial genes on average. We can then evaluate simulated siblings at risk for ASD who do or do not go on to exhibit the disorder.

Computer simulations

Method

Architecture

The simulations employed connectionist pattern associator networks trained using the supervised backpropagation

learning algorithm, a derivative of Hebbian learning. This type of architecture has been employed in a number of cognitive-level models of development, for example, infant categorization, child vocabulary acquisition, semantic memory, morphosyntax acquisition, and reading development (Mareschal & Thomas, 2007; Thomas & McClelland, 2008).

Training set

The training set was considered only as an abstract mapping problem (see Thomas, Ronald & Forrester, 2011c, for its psychological origin in the domain of language development). The mapping problem was quasi-regular, in that it included a predominant regularity, which could be generalized to novel input patterns, along with a set of exception patterns. The learning environment was designed to assess the role of similarity, type frequency, and token frequency in development, together creating a dimension of task difficulty. On this dimension, regular mappings were easier and exception mappings were harder. Through these properties, the domain was taken to be representative of some of the mapping problems that the cognitive system faces, including category formation and language development. The mapping problem was defined over 90 input units and 100 output units, using binary coded representations. The training set comprised 508 patterns. This was complemented by a generalization set of 410 patterns. Further details can be found in TKK. In the following simulations, we focus on regular and exception mapping performance, referring to the former as *Easy* and the latter as *Harder* mappings.

The population modelling technique

Development was simulated in a large number of networks, which varied according to their learning properties and the quality of the learning environment to which they were exposed. These variations produced individual differences in the shape of the developmental trajectories exhibited by different networks.

Differences in learning properties were created by varying 14 neurocomputational parameters. The parameters were as follows: *Network construction*: Architecture (two-layer network, three-layer network incorporating a layer of hidden units, or a fully connected network incorporating a layer of hidden units and also direct input–output connections); number of hidden units (10 to 500); range for initial connection weight randomization (±0.01 to ±3.00); sparseness of initial connectivity between layers (50% to 100% connectivity). *Network activation*: unit threshold function (sigmoid temperatures

between 0.0625 and 4); processing noise (0 to 6); response accuracy threshold (.0025 to .5). *Network adaptation*: backpropagation error metric (Euclidean distance or cross-entropy); learning rate (.005 to .5); momentum (0 to .75). *Network maintenance*: weight decay (0 to 2×10^{-5} per pattern presentation); pruning onset (0 to 1000 epochs); pruning probability (0 to 1); pruning threshold (0.1 to 1.5). For each individual, the 14 parameters were independently sampled from distributions for each parameter in which intermediate values were more probable than extreme values (see Thomas *et al.*, 2011c, for detailed specification of distributions).

The quality of the learning environment was manipulated by altering the amount of information available, by applying a filter to the full training set. For each individual, a subset of this training set was stochastically selected, to represent the family conditions in which each simulated child was being raised. Each family was assigned a quotient, which was a number between 0 and 1. The value was used as a probability to sample from the full training set. Thus, for an individual with a family quotient value of .75, each of the 508 training patterns had a 75% chance of being included in that individual's training set. Family quotients were sampled randomly depending on the range selected for the population, in this case between 0.6 and 1.0. Siblings raised in the same family were given the same family training set (see below).

Simulating typical and atypical pruning

Connection pruning was implemented via three parameters: the *pruning onset*, the *pruning rate*, and the *pruning threshold*. The pruning onset indicated the epoch of training at which pruning would begin, where an epoch corresponded to presentation of all the mappings in each individual's training set. Once pruning had begun, each epoch thereafter, every connection weight was evaluated with respect to whether it fell below a certain strength threshold, whether excitatory or inhibitory. Weak connections were then available for pruning, and were removed with a probability specified by the pruning rate. (Early developmental growth in the number of connections was not implemented; rather the outcome of this growth was captured by the sparseness parameter.) Typical pruning, using the parameter ranges indicated in the previous section, generally produced no observable effect on behavioural developmental trajectories. Atypical pruning was implemented by increasing the size of the pruning threshold, which allowed stronger and therefore potentially functional connections also to be pruned. The typical range of variation for the pruning threshold was 0.1 to 1.5. The atypical range of variation

for the pruning threshold was 0.1 to 4.0. Two populations of 1000 networks were simulated. Individuals with pruning threshold values drawn from the typical range are referred to as the low-risk population; those with pruning thresholds drawn from the atypical range are referred to as the high-risk population, where pruning constitutes a pathological mechanism (see Thomas et al., 2011a, Table 1).

Encoding genetic similarity in an artificial genome

In order to simulate siblings, parameter values were encoded in an artificial genome (Thomas et al., in press). Siblings were defined by their genetic similarity. Each parameter was encoded in a set of binary genes, with the number of 1-valued alleles from the set determining the parameter value via a look-up table. For example, hidden unit number was coded over 10 binary genes. If an individual had a genotype of 0110101100, a total of five 1s corresponded to a hidden layer with 60 units. A look-up table was created for each parameter.[1] Sibling pairs then constituted genomes that shared 50% of their genes, constraining the neurocomputational parameters to be similar. Five hundred siblings were simulated in the high-risk condition, constituting 250 sibling pairs.

Results

Simulating heterogeneous atypical trajectories via the interaction of a pathological mechanism with population-wide individual differences

Population modelling identified possible interactions between the pathological mechanism (specified by the pruning threshold) and other neurocomputational parameters varying across the whole population. These interactions can be clarified by focusing only on key parameters and eliminating variability in all other parameters. In particular, we focused on possible interactions between the different pruning parameters. Networks were simulated with pruning rate set to only two values within the typical range (0 and 25); pruning onset set to only two values within the typical range (.025 and .05); and pruning threshold set either to a value in the typical range (.5) or to an atypical, pathological level (3.0). All other parameters were held at a single value (respectively: architecture = 3-layer, hidden units = 60, initial weight variance = ±0.5, sparseness = 95% connec-

tions present, activation function temperature = 1, processing noise = .2, response accuracy threshold = .1, backpropagation error metric = cross-entropy, learning rate = .125, momentum = .2, weight decay = 1×10^{-7}, environment = 1.0).
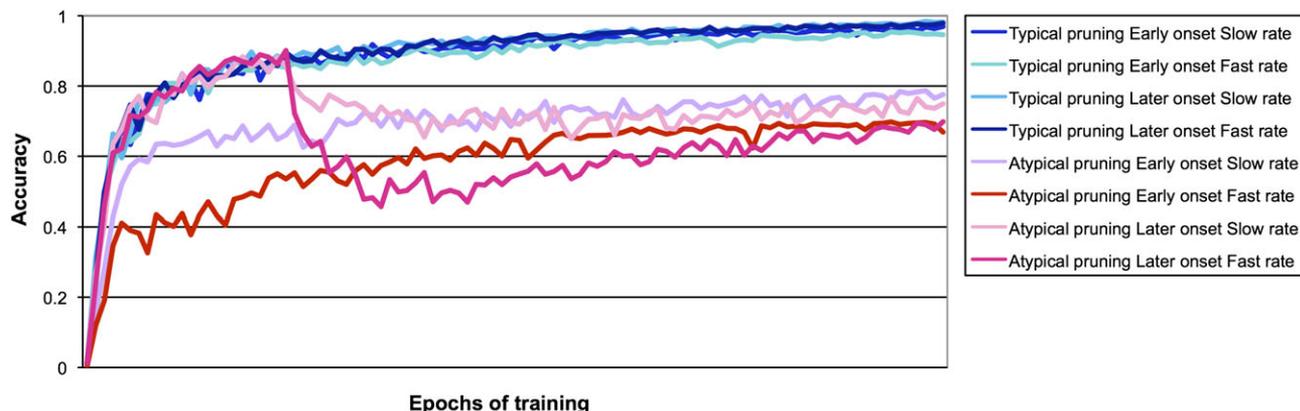
Figure 2 shows developmental trajectories for *Easy* mapping patterns, averaged over 12 replications with different random seeds. The trajectories in shades of blue represent typical development, with connectivity pruning at typical levels. Under these conditions, variations in pruning onset and pruning rate had little impact on development. The trajectories in shades of red represent cases where pruning was pathological, allowing stronger connections to be pruned. The same (otherwise typical) variations in onset and rate now produced different divergences from typical development equivalent to early-onset atypicality, late-onset atypicality, and regression.

The model demonstrated that a single pathological mechanism that affected pruning could interact with population-wide variation to produce heterogeneous hypothetical ASD trajectories. The model is therefore consistent with views that reject the notion of separate, causally homogeneous sub-types within ASD, and instead argues that ASD trajectories lie on a mechanistic continuum (see e.g. Zwaigenbaum et al., 2013, for a similar proposal). As Figure 2 demonstrates, the simulations predicted that, inasmuch as one can identify different subgroups within non-regressive ASD (early versus late onset), one should be able to identify different rates at which regression occurs in regressive ASD (fast versus slow decline).

Simulating at-risk sibling studies of development in ASD

Two hundred and fifty pairs of siblings were simulated within the high-risk population. Trajectories of development in learning the mapping task were hand-rated for presence or absence of our marker of ASD atypicality, developmental regression (see TKK for details of coding and inter-rater reliability). One hundred and fourteen sibling pairs both showed regression, 60 pairs both showed absence of regression, while in 76 pairs, one sibling showed regression while the other did not. (Note, in this model no attempt was made to manipulate the relative frequencies of pathological factors and risk factors in the population in order to simulate the observed incidence of ASD in at-risk siblings.) We focused on these discordant pairs, in particular evaluating the extent to which the unaffected siblings were similar to individuals from the low-risk population. Figure 3(a) compares performance on *Easy* and *Harder* mapping problems for the affected siblings, unaffected siblings, and a large

[1] These tables are available at http://www.psyc.bbk.ac.uk/research/DNL/techreport/Thomas_paramtables_TR2011-2.pdf
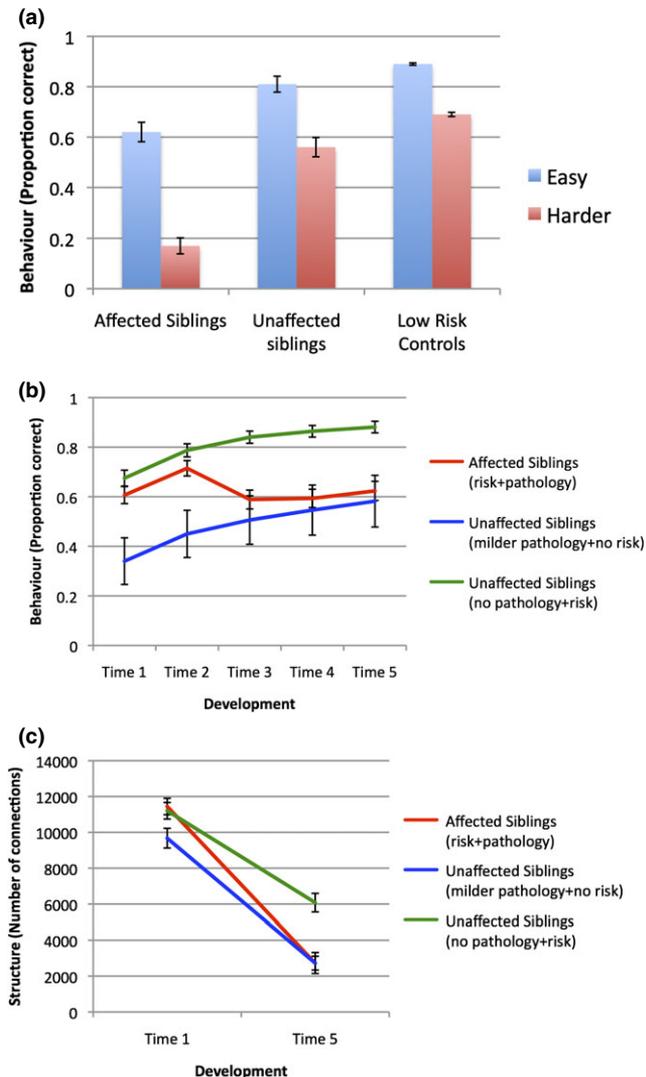
Figure 2   *Simulated developmental trajectories in a notional cognitive domain, from the Thomas, Knowland and Karmiloff-Smith (2011a) model of regression. The trajectories in shades of blue represent typical development, with connectivity pruning at normal levels. From the onset of pruning, at each epoch of training, connections below size ±0.5 may be pruned at a certain probabilistic rate (Typical pruning). Two onsets are shown (early = 0 and later = 25 epochs) and two probabilistic rates (fast = 5% and slow = 2.5%). These have little impact on typical development. The trajectories in shades of red/purple represent cases where pruning is atypically severe, such that connections below size ±3 may be pruned (Atypical pruning). The same variations in onset and rate now produce different divergences from typical development equivalent to early onset, late onset, and regression. (Data shown for first 100 epochs of training, averaged over 12 replications with different random seeds. To focus on these three parameters, and in contrast to the original TKK model, all other parameters were fixed at 'typical' values).*

sample of low-risk controls for a point late in development when the effects of connectivity pruning had stabilized (750 epochs). While unaffected siblings (USib) performed better than affected siblings (ASib), both groups differed from the low-risk controls (LRC); moreover, both showed different effects of task difficulty (main effect of group – ASib vs. USib: $F(1, 150) = 43.46$, $p < .001$, $\eta_p^2 = .225$, ASib vs. LRC: $F(1, 1028) = 290.75$, $p < .001$, $\eta_p^2 = .220$, USib vs. LRC: $F(1, 1028) = 19.39$, $p < .001$, $\eta_p^2 = .019$; interactions of group with task difficulty – ASib vs. USib: $F(1, 150) = 19.98$, $p < .001$, $\eta_p^2 = .118$, ASib vs. LRC: $F(1, 1028) = 114.74$, $p < .001$, $\eta_p^2 = .100$, USib vs. LRC: $F(1, 1028) = 5.9$, $p = .015$, $\eta_p^2 = .006$). The mean pruning thresholds differed between the groups: for ASib it was 2.51 (standard deviation .97), compared to .99 (.81) for USib, and .52 (.15) for LRC (all $p < .001$). Therefore, on average, unaffected siblings had higher but not pathological pruning. Nevertheless, in these simulations, risk status per se was associated with divergence from typical development.

Previous results had indicated that population-wide (i.e. typical) variation in neurocomputational parameters could serve as protective or risk factors that modulated the probability that a pathological pruning threshold would lead to regression, in the main by altering the size of the connection weights present at the onset of pruning. For example, Table 2 in Thomas *et al.* (2011a) contains results from a stepwise logistic statistical regression analysis, which indicates that a higher temperature in the sigmoid activation function was a risk factor for

showing developmental regression, as were, to a lesser extent, parameters leading to networks with initially more connections (architecture, number of hidden units, initial sparseness of connectivity). Having a higher sigmoid temperature meant that the network suffered entrenchment and was less able to adapt the remaining connection weights to deal with the ongoing process of connection loss. Having a larger initial network was a risk factor for connection loss, since larger networks tended to develop less strong connection weights, which were then more vulnerable to pruning. In the current simulations, since variation in the neurocomputational parameters was encoded in the artificial genome and genes were inherited from parents independently of each other, in principle either these risk factors (temperature, connections) or the pathological pruning threshold could be inherited independently. This raises the possibility that 'at-risk' unaffected siblings might differ from typical development for two reasons: they might have inherited a milder version of the pathology without the risk factors; or they might have inherited the risk factors but not the pathology. Either could be sufficient to avoid a positive diagnosis.

We split the unaffected siblings according to whether their pruning threshold was above or below 1. We refer to these sub-groups as high pruning [$_{hp}$USib] and low pruning [$_{lp}$USib] unaffected siblings. The $_{hp}$USib sub-group by definition had a reliably higher pruning threshold ($_{hp}$USib = 2.2, $_{lp}$USib = .65; $p < .001$). Notably, the $_{lp}$USib sub-group showed greater evidence of risk factors, including a higher mean temperature ($_{hp}$USib =

Figure 3 *(a) Performance on Easy and Harder mapping patterns late in development, for Affected Siblings, Unaffected Siblings, and Low Risk Controls. (b) Developmental trajectories for Easy mapping patterns, for Affected Siblings, and Unaffected Siblings split by whether they had co-inherited higher pruning values without risk factors (pathology+ no risk) or risk factors without high pruning (no pathology+ risk). (c) Changes in network structure, measured by number of connections, for early and late in development, for these three groups. Error bars show standard errors.*

.75, $_{lp}$USib = .95; p = .028) and a trend for a larger initial network size ($_{hp}$USib = 9.7k connections, $_{lp}$USib = 11.2k connections; p = .109).

Figure 3(b) depicts developmental trajectories of ASib, $_{hp}$USib, and $_{lp}$USib. These trajectories make clear that the milder pathology caused delayed development without overt regression (i.e. a different sort of

atypicality), while the risk factors alone caused faster development. Note that in the model one of the unaffected groups is lower at Time 1 than the affected group. Empirical studies of infants at risk of ASD have not demonstrated an early disadvantage for subsequently unaffected siblings. However, in the model, it is known by design whether unaffected siblings have inherited a milder version of the pathology or solely risk factors, and so the unaffected siblings can be split into these two groups. It is the milder pathology group that has the early disadvantage, because there are no risk factors that accelerate early growth. In the empirical literature, no such split can yet be made for unaffected siblings. When the $_{hp}$USib, and $_{lp}$USib groups are combined, their Time 1 performance is almost identical to the ASib group (t (150) = .045, p = .964), in line with empirical observations.

Figure 3(c) plots the number of connections in the three groups across development. Both groups with the risk factors (ASib and $_{lp}$USib) had larger initial networks, although this difference was still only a trend (p = .089). By the late stage of development, the two groups with the pathology, of different strengths (ASib and $_{hp}$USib), converged (significant group by time interaction, $F(2, 149) = 38.16$, $p < .001$, $\eta_p^2 = .339$).

In sum, these simulations demonstrated mechanistically how 'risk status' in the absence of the marker of atypicality (here, developmental regression) could nevertheless lead unaffected siblings to show differences compared to low-risk controls; and that unaffected siblings could express these differences either through inheriting a milder version of the pathology without risk factors, or risk factors without the pathology.

Discussion

We have seen how modelling atypical developmental mechanisms against a background of population-wide variation in neurocomputational mechanisms can lead to the simulation of heterogeneous profiles of atypical development. The variation observed in disorders, as in early-onset, late-onset, and regressive sub-type ASD can therefore be parsimoniously explained with respect to *a single pathological mechanism* (in this case, over-pruning) *interacting with pre-existing individual differences in the population*. The possibility of separate contributions of pathology and risk factors to the behavioural profile then allowed us to distinguish two ways in which unaffected siblings of individuals with ASD might differ from low-risk controls: either by inheritance of a milder version of the pathology, or inheritance of the risk factors (such as possessing a large initial network) without the pathology.

Two final implications of incorporating risk and protective factors deserve highlighting from the original TKK model, in this case with respect to the low-risk population. First, the 'low-risk' population also exhibited infrequent cases of regression. These occurred where the pruning threshold was typical (albeit at the higher end of the range) but a chance combination of risk factors had combined to generate regression even with this modest level of pruning threshold. This contrasts with regression caused by very high pruning thresholds in the high-risk population. Overall, therefore, regression could either result from an unlucky combination of typical variation (low-risk population) or due to a very high pruning threshold causing regression, largely irrespective of other parameters (high-risk population). This can be seen as analogous to the idea that both common genetic variation and rare genetic variation could contribute to ASD. The second important finding in TKK was that when the low-risk population was placed in an extremely impoverished environment, the numbers of individuals showing regression increased. Less stimulation from the environment failed to lead to strong connection weights, increasing vulnerability to pruning. This demonstrated that environmental factors could exacerbate underlying vulnerability within the normal range.

Of course, in common with any model that places the cause of disorder at the neurocomputational level (or lower), it is necessary to develop arguments concerning how the proposed anomaly should lead to the particular behavioural profile observed in ASD, including in high-level behaviours such as executive functioning and social cognition (e.g. Charman, Jones, Pickles, Simonoff, Baird *et al.*, 2011; Happé & Ronald, 2008). It is an assumption of the model, and not yet implemented, that over-pruning differentially impairs long-range connectivity over short-range connectivity. This in turn has greater impact on integrative functions and shifts processing to rely on locally available information within domains (Lewis & Elman, 2008; Keown, Shih, Nair, Peterson, Mulvey *et al.*, 2013). Under this type of account, aspects such as echolalia and repetitive and stereotype behaviours are explained either in terms of the functional isolation of components (such as the phonological loop) or adaptive responses to a subjectively incoherent environment (see Johnson, 2012). And task domains where individuals with ASD appear to show an advantage, such as visual search or recognizing inverted faces (e.g. Blaser, Eglington, Carter & Kaldy, 2014; Dimitriou, Leonard, Karmiloff-Smith, Johnson & Thomas, 2014) are explained in terms of an over-allocation of computational resources to the processing of locally available information, creating ele-

vated feature-based performance (see Annaz, Karmiloff-Smith, Johnson & Thomas, 2009, for discussion). Overall, it is the assumption of a differential effect on different types of connectivity that leads to the distinctive ASD behavioural profile, rather than, say, the more global depression of cognitive skills observed in general developmental delay.

The over-pruning hypothesis and its predictions

From the implemented neurocomputational model, a more general hypothesis can be developed. ASD is caused by the exaggeration of a normal system-wide phase of brain development, elimination of excess connectivity. Normal individual differences in the onset or rate of this phase interact with the pathological pruning process to create different trajectories of atypical development. Individual differences in other neurocomputational parameters and in environmental stimulation operate as risk or protective factors. The atypical pruning is assumed to impact more on long-range connectivity, impairing integrative functions, which leads to the unique behavioural profile of ASD. A number of novel predictions can be derived from the general over-pruning hypothesis.

First, it is known that the onset of pruning occurs at different times in different regions of the human brain (Gogtay, Giedd, Lusk, Hayashi, Greenstein *et al.*, 2004; Huttenlocher & Dabholkar, 1997; Huttenlocher, 2002). Broadly, pruning occurs first in low-level sensory and motor areas, then in higher association areas, and last in prefrontal cortex. For example, in the data of Huttenlocher and Dabholkar (1997), synaptic density peaked in visual cortex around the age of 6 months, in auditory cortex around the age of 3 years, and in prefrontal cortex around the age of 5 years. If pruning is atypical, then *the first symptoms emerging in infancy should be sensory and motor rather than social*. That is, the earliest onset of the disorder may look quite different from the characteristics of the disorder observed in later childhood and adulthood. In early infancy, social skills may initially be developing typically while sensory and motor skills already begin to show impairments. The extended course of pruning, indeed, predicts that changes in the profile of the disorder might extend through mid-childhood into adolescence (e.g. Petanjek, Judaš, Šimic, Rasin, Uylings *et al.*, 2011). This prediction of a temporally sensitive phenotype contrasts with existing theories, which posit that the first atypicalities will be in domains central to the subsequent phenotype of the disorder.

Second, if the pathology is only in the pruning process, then *there should be a phase of typical development prior*

to the emergence of atypicality. This phase of 'typical' development will, however, be influenced by any risk factors that render the individual more likely to suffer a behavioural impact through aggressive pruning. For example, if slower development were a risk factor for suffering an impact from aggressive pruning (because pre-pruning connectivity is less robust), then the 'typical' pre-pruning phase of development would nevertheless be slower than the population mean. For at-risk siblings who subsequently do not go on to gain an ASD diagnosis, the separation of pathological and risk factors nevertheless suggests two ways that unaffected siblings may differ from low-risk controls: either in inheriting a milder version of the pathological process leading to a sub-clinical phenotype, or in inheriting the risk factors leading to a different trajectory of development. The notion of the 'broader autism phenotype', whereby unaffected family members of individuals with autism are seen to exhibit personality traits that are milder but autistic-like in nature (Piven, Palmer, Jacobi, Childress & Arndt, 1997), should therefore be expanded to accommodate the impact of co-inherited risk factors.

Third, *atypicalities in structural brain connectivity will be emergent across development*. Some of these might be expected to be compensatory (for instance, frontal modulation attempting to optimize performance given emerging problems in lower-level representations; Johnson, 2012). But many emerging connectivity differences will reflect ongoing pathology. Emergent disruptions to connectivity may alter the regulation of recurrent neural activity and so increase the risk of seizures.

Fourth, all other things being equal, *the later the onset of atypical pruning and subsequent behavioural divergence from typical development, the more severe the underlying pathological process must have been*. TKK demonstrated this effect in their original model, with a later onset associated with poorer outcome. The prediction arises because the connectivity at that later point in development will be more robust, due to more experience-dependent change. Therefore, later behavioural onset suggests a more severe underlying pathological process. This prediction stands in contrast to that of Landa *et al.* (2013), who hypothesized that individuals with ASD who exhibit early-manifesting behavioural symptoms should ultimately be worse affected by the disorder, on the basis that early symptom expression may reflect more substantial abnormalities in developmental synaptic plasticity. Note, however, that in Landa *et al.*'s (2013) prospective study, the authors found no difference in short-term prognosis for their early-onset and late-onset ASD groups, supporting neither prediction. It will be possible to better evaluate whether early- and late-onset ASD groups in such prospective studies differ in outcome when these cohorts have been studied into the school-age years.

Fifth, the over-pruning hypothesis stipulates that protective and risk factors can interact with the pathological process. While the pathological process is argued to be system wide, there is no reason why some risk and protective factors might not be system specific (in the way that some aspects of intelligence are held to be domain specific). For example, some individuals might have more robust sensory systems, or motor systems, or prefrontal systems. A domain-specific protective factor would lessen the impairment of that skill, but not those skills driven primarily by other systems. This would predict *modulation of the cognitive profile in ASD; not all individuals should have identical strengths and weaknesses.* Once more, this prediction is rendered testable because, if one assumes that risk and protective factors are heritable, modulation of the profile of ASD should be accounted for by (typical) patterns of cognitive strengths and weakness in unaffected family members.

The next prediction concerns intervention. Of course, it is necessary to be cautious here in making strong claims about intervention based on a computational model. However, as Gliga *et al.* (2014) argue, intervening in development is ultimately the only way in which causal developmental theories of autism can be validated. The sixth prediction, then, is that *intervention will not restore connectivity already lost through pruning* and therefore will not be able to normalize the system. Late interventions can only maximize abilities using the remaining atypical connectivity. If intervention is behavioural, *early intense behavioural stimulation is likely to be most effective* to strengthen connectivity against the effects of pruning. Moreover, behavioural and psychosocial interventions will only work on the system that is targeted. Since the atypicality is wide, *intervention must be wide*, targeting the key, integrative skills most at risk by pruning of long-range connectivity. This would entail focusing on promoting, supporting and engendering processes that activate such connections. One clear focus for intervention would be social interaction and social communication, which is likely to rely on such integrated and connected networks. This prediction contrasts with theories positing early deficits in attention or social orienting, which imply that an early intervention can be narrow to target the primary atypicality, and that this will automatically serve to alleviate all secondary effects on, for example, general social skills, without the need for further support of, say, real-world social interaction (see discussion in Karmiloff-Smith, D'Souza, Dekker, Van Herwegen, Xu *et al.*, 2012).

Inter-disciplinary data evaluating the over-pruning hypothesis

Emergence of symptoms

Several reviews have summarized data emerging from longitudinal studies of infants at-risk of ASD on the basis of an older sibling with the disorder (Elsabbagh & Johnson, 2010; Jones *et al.*, 2014; Gliga *et al.*, 2014; Rogers, 2009; Yirmiya & Charman, 2010; Zwaigenbaum *et al.*, 2013). The common theme among these reviews is that few behavioural markers of ASD have been identified in the first year of life. This is consistent with our prediction that ASD should be characterized by an early, essentially typical phase of development. Notably, this early phase of indistinguishable-from-typical development prior to 12 months includes social behaviours, such as frequency of gaze to faces, shared smiles, and vocalization to others (Ozonoff, Iosif, Baguio, Cook, Hill *et al.*, 2010).

Two recent studies of infants who went on to be diagnosed with ASD offer possible exceptions: Chawarksa, Macari and Shic (2013) and Jones and Klin (2013) both reported an early reduced gaze fixation to actors in social scenes compared to typically developing controls. In the Chawarksa *et al.* study, the authors noted the difference at 6 months of age, while Jones and Klin reported a fall in fixation, particularly to the eye region, in a longitudinal design between 2 and 6 months. However, it is not clear how robust these effects were. Focusing on the 6-month data alone, the studies showed conflicting results. In contrast to Chawarksa *et al.*, Jones and Klin found no difference in social orienting compared to controls at 6 months of age; longitudinal trajectories aside, there was no reliable ASD–TD group difference in the Jones and Klin data until around 12 months of age; and at 2 months, the ASD group showed initially *elevated* levels of fixation to the eye region compared to controls. Neither study included a non-social scene comparison, or a social scene where the actor was not centrally presented, to establish the specificity of the effect to social orienting per se and rule out more general perceptual accounts. Overall, taking a wider view of the existing studies, Zwaigenbaum *et al.* (2013) concluded that there is very limited evidence of ASD-specific differences in social attention from eye-tracking studies involving infants younger than 12 months of age.

While social behaviours are central to the later characterization of ASD, the over-pruning hypothesis predicts that the earliest symptoms will be sensory and motor. Given the behavioural repertoire of young infants, it is a challenge to investigate what may be subtle atypicalities in low-level perception. There are, therefore, few existing data to evaluate this prediction. Parental report data of infants at-risk of ASD who go on to meet criteria for the disorder have indicated elevated perceptual sensitivity (Clifford, Hudry, Elsabbagh, Charman, Johnson *et al.*, 2013). A study by McCleery, Allman, Carver and Dobkins (2007) used sinusoidal gratings to test chromatic and luminance contrast sensitivities in 6-month-old infants at risk for ASD. The at-risk group demonstrated difficulties in detecting chromatic contrasts, leading the authors to propose that ASD may be associated with atypicality in the magnocellular visual processing pathway. Elison, Paterson, Wolff, Reznick, Sasson *et al.* (2013) measured oculomotor functioning and visual orienting in 7-month-olds who later met criteria for ASD. Visual orienting latencies were longer in these infants, compared both to at-risk infants who did not go on to meet criteria for ASD and to low-risk controls. Orienting latencies also showed an atypical relation to brain connectivity in the ASD group. The authors measured white matter in fibre tracts including cortico-spinal pathways and the corpus callosum. Visual orienting latencies were associated with these connectivity measures in the low-risk group, but not in infants later diagnosed with ASD.

More data are available with respect to the possible early emergence of motor atypicalities. Later in development, motor problems are a persisting characteristic of ASD, over and above cognitive atypicalities (Staples & Reid, 2010). Both retrospective (Teitelbaum, Teitelbaum, Nye, Fryman & Maurer, 1998; Esposito, Venuti, Maestro & Muratori, 2009) and prospective data (Flanagan, Landa, Bhat & Bauman, 2012) suggest that motor differences in infants who go on to have ASD are observable at or before 6 months of age, for instance in measures of static and dynamic symmetry, postural control, and head lag (see Zwaigenbaum *et al.*, 2013, for a review). Using standardized tests, Leonard, Elsabbagh, Hill and the BASIS team (2014) reported lower motor skill scores in infants at risk of ASD from the age of 7 months compared to a low-risk group, and that infants who were later diagnosed with ASD showed significantly poorer fine motor skills at 36 months than at-risk infants without developmental difficulties. However, standardized tests of fine and gross motor control have also revealed null effects comparing ASD and TD groups below 12 months of age (Brian, Bryson, Garon, Roberts, Smith *et al.*, 2008; Landa & Garrett-Mayer, 2006; Landa, Gross, Stuart & Bauman, 2012; Ozonoff *et al.*, 2010; Zwaigenbaum, Bryson, Rogers, Roberts, Brian *et al.*, 2005).

It may be that sensitive, qualitative measures of early motor behaviour are required to detect differences, rather than standardized measures. Bolton, Golding, Emond and Steer (2012) noted that parental reports of fine motor behaviours at 6 months were informative of risk of ASD. In addition, there is a debate about whether early motor atypicalities in ASD are distinguishable from those observed in infants with developmental delay and therefore a specific feature of ASD (Ozonoff, Macari, Young, Goldring, Thompson *et al.*, 2008a; Ozonoff, Young, Goldring, Greiss-Hess, Herrera *et al.*, 2008b). However, specificity of the difference is a diagnostic issue, not a test of a causal model. That is, because the over-pruning hypothesis predicts the emergence of early motor atypicalities, it does not simultaneously argue there should be no other causes of such differences.

The literature on the order of emergence of symptoms in ASD infants is still developing. Divergence from typical development is noted in multiple domains from 12 months of age, and results report a mixture of differences that are specific to ASD outcome or shared by infants at-risk (Jones *et al.*, 2014). If the divergence were uniform across domains, this would not fit with the over-pruning hypothesis. In addition, the over-pruning hypothesis predicts that risk is carried by population-wide individual differences interacting with a pathological process specific to ASD outcome. Unaffected siblings may be exhibiting milder versions of the pathology, or showing similarities to affected siblings for risk factors, even though these were typical dimensions of variation in the whole population. One would therefore predict heterogeneity in unaffected siblings, and behavioural profiles that alter over time compared to both affected children and low-risk controls (per the simulation data in Figure 3).

The stability of the ASD phenotype beyond infancy through childhood and adolescence has recently been questioned. Studies have demonstrated that in some children (perhaps 10%), there is a 'very positive' or 'optimal' outcome, with individuals largely overcoming developmental difficulties (Anderson, Liang & Lord, 2014; Fein, Barton, Eigsti, Kelley, Naigles *et al.*, 2013). Picci and Scherf (2014) argued for a 'second hit' in around 30% of individuals with autism, with a marked decline in adaptive functioning during adolescence. Typical pruning of brain connectivity continues into the adolescent years. Caution is required, however, since long-term outcomes are sensitive to diagnostic criteria and also incorporate complex interactions with the social environment, as well as adaptive processes. Nevertheless, these findings are consistent with the temporally extended pathological mechanism proposed by the over-pruning hypothesis and its interaction with risk and protective factors.

Genetic data

Findings from the genetic level cannot yet constrain the neurocomputational effects of the pathological molecular process(es) involved in ASD. Genes associated with ASD have so far tended to be associated with the development and function of synapses, implying that atypicalities may not be specific to particular cognitive domains but rather are system-wide, and at best domain-relevant to certain sorts of computational functions (Karmiloff-Smith, 1998). One window into possible genetic mechanisms has been via syndromes that exhibit autistic symptoms. For example, Rett's syndrome exhibits developmental regression similar to that sometimes found in ASD. Glaze (2004) argued that abnormalities in synapse maintenance and modulation contribute to regression in both disorders. However, Kelleher and Bear (2008) argued that the hypoconnectivity observed in Rett's syndrome is opposite to the hyperconnectivity and possible hyperplasticity found in several other genetic disorders associated with a diagnosis of ASD, including Fragile X syndrome, Tuberous sclerosis, PTen harmatoma syndrome, MECP2 duplication syndrome, neurofibromatosis, and Angelman's syndrome. In their view, the performance of neuronal networks mediating cognition depends on the level of synaptic protein synthesis, whereby deviations in either direction from the optimal level adversely affect synaptic capture and consolidation, and the resulting perturbations in synaptic connectivity underlie the development of autistic traits (Kelleher & Bear, 2008; Zoghbi & Bear, 2012). Focusing on ASD itself, several transmitted or de novo mutations have been found to be mutated in some individuals with an ASD. These genes include Synapsin 1 (Fassio, Patry, Congia, Onofri, Piton *et al.*, 2011), SynGAP1 (Hamdan, Daoud, Piton, Gauthier, Dobrzeniecka *et al.*, 2011), SHANK3 (Bozdagi, Sakurai, Papaetrou, Wang, Dickstein *et al.*, 2010; Durand, Betancur, Boekers, Bockmann, Chaste *et al.*, 2007) and NLGN4 (Laumonnier, Bonnet-Brilhault, Gomot, Blanc, David *et al.*, 2004), all of which are involved in synaptogenesis, neurotransmitter release or pruning, and some of which are X-linked (Fassio *et al.*, 2011; Piton, Gauthier, Hamdan, Lafrenière, Yang *et al.*, 2010).

Current views are possibly in favour of insufficient synapse elimination rather than over-pruning (e.g. Tang, Gudsnuk, Kuo, Cotrina, Rosoklija *et al.*, 2014; Tsai, Wilkerson, Guo, Maksimova, DeMartino *et al.*, 2012; Zoghbi & Bear, 2012). Indeed, in a small cross-sectional study of post-mortem dendritic spine density in the

temporal lobe, Tang *et al.* (2014) found no reduction across age in 10 children with ASD but a reduction in controls. However, these data are currently inconsistent with macro-level measures indicating increased cortical thinning in temporal areas in ASD (Wallace, Dankner, Kenworthy, Giedd & Martin, 2010; see below). Moreover, in line with Kelleher and Bear's (2008) proposal, both over- and under-pruning may represent disruptions to synaptic function associated with ASD. That multiple genes have been implicated, through both syndromic and non-syndrome cases of autism, fits with the complexity of processes of synapse formation, maintenance, and elimination, and the possible causal heterogeneity of ASD.

Brain data

At a detailed level, examination of post-mortem tissue has indicated an excess of neurons in the prefrontal cortex in children with ASD (Courchesne, Mouton, Calhoun, Semendeferi, Ahrens-Barbeau *et al.*, 2011); and more widely in prefrontal, temporal and occipital cortical tissue, focal patches of abnormal laminar cytoarchitecture and cortical disorganization of neurons (Stoner, Chow, Boyle, Sunkin, Mouton *et al.*, 2014). This points towards anomalies in neural proliferation and migration at prenatal developmental ages. Focal differences in neural organization have been linked to other developmental disorders, such as dyslexia (Galaburda, LoTurco, Ramus, Fitch & Rosen, 2006) and were not entirely specific to ASD cases in Stoner *et al.*'s study (observed in 10/11 cases, 1/11 controls).

A more established picture began to emerge with respect to macro-level measures of brain size, as indexed by measures such as head circumference, brain weight, and magnetic resonance imaging measures of grey and white matter volume. Here data have been presented to suggest larger brain size early in development in ASD compared to controls, characterized as brain 'overgrowth', but a pattern that changes across development, such that by adolescence and adulthood, brain sizes may be smaller than controls (Nordahl *et al.*, 2011; Redcay & Courchesne, 2005; Schumann, Bloss, Carter Barnes, Wideman, Carper *et al.*, 2010; though see Raznahan, Wallace, Antezana, Greenstein, Lenroot *et al.*, 2013, for methodological cautions with respect to population head size norms; Davis, Keeney, Sikela & Hepburn, 2013, that the relationship between head size and disorder is only found in families with a single child with ASD; Nordahl *et al.*, 2011, that larger head size is associated with regressive sub-type of ASD). However, the robustness of early head size differences has recently been questioned. In a large prospective study of 442 infants at risk of ASD compared to 253 low-risk controls, no overall difference in head circumference growth over the first 3 years of life was observed between high-risk and low-risk infants (Zwaigenbaum, Young, Stone, Dobkins, Ozonoff *et al.*, 2014). Although Zwaigenbaum *et al.* (2014) did report a possible increased total head circumference growth in high-risk infants in their secondary analyses, there was no difference observed between those high-risk children who received an ASD diagnosis at 3 years of age and those who did not.

Were early overgrowth to be real and viewed as the direct cause of dysfunction in ASD (see e.g. Lewis & Elman, 2008), then later emerging effects would need a separate explanation. For instance, when Wallace *et al.* (2010) observed greater cortical thinning in temporal cortex in ASD compared to controls in a cross-sectional study across adolescence and young adulthood, they were required to postulate 'a second period of abnormal cortical growth (i.e. greater thinning)' (p. 3745).

The over-pruning hypothesis instead views elevated brain size as a risk factor rather than a pathology. The ASD group would therefore oversample individuals with larger brains, hence a larger group average compared to controls. Over-pruning then readily explains why the pattern should alter across development, with faster cortical thinning in ASD, and smaller brain sizes observed in ASD by adolescence. If the over-pruning account is correct, two patterns should be observed. First, since we have argued that risk factors are likely independently heritable from pathology, we should find that unaffected siblings of children with ASD should nevertheless have larger-than-average brain sizes (as a group). Froehlich, Cleveland, Torres, Phillips, Cohen *et al.* (2013) recently reported that brain size (as measured by head circumference) showed the predicted tendency to be larger than expected in twins with ASD compared to twins without; but it was no different between affected and unaffected members of a twin pair. Zwaigenbaum *et al.*'s (2014) data show a similar pattern: those head circumference differences that were observed were associated with familial risk, not with ASD outcome. Second, the pathology should not show the same familiality: it should only be observed in affected siblings. If regression is indeed a marker for the pathological process, then Parr, Le Couteur, Baird, Rutter, Pickles *et al.* (2011) report just this pattern of data: regression did not show familiality.

Turning to brain connectivity, it has recently been argued that studies investigating structural and functional connectivity also only make sense if a developmental perspective is adopted (Karmiloff-Smith, 2010). Structural and functional studies have reported both over- and under-connectivity in ASD, with patterns

sometimes being regionally specific (Kana, Uddin, Kenet, Chugani & Müller, 2014). Uddin, Supekar and Menon (2013) proposed that the data can be reconciled if over-connectivity is seen as a feature of early development, while under-connectivity is seen as a feature of later development. This fits with the idea that disruptions to connectivity are an emergent, time-sensitive, developmental phenomenon. Consistent with the over-pruning hypothesis, a recent study by Keehn, Wagner, Tager-Flusberg and Nelson (2013) using near-infrared spectroscopy in infants at risk for ASD reported increased overall functional connectivity in the high-risk group compared to low-risk controls at 3 months, no difference at 6 and 9 months, and decreased functional connectivity compared to controls at 12 months. Similarly Wolff, Gu, Gerig, Elison, Styner *et al.* (2012) reported on a prospective study that examined white matter fibre tract organization from 6 to 24 months in high-risk infants who developed ASD by 24 months. They observed that the majority of measured fibre tracts differed significantly between the infants who developed ASD and those who did not. However, the relative pattern altered across development, with fibre tracts in the infants with ASD showing higher fractional anisotropy values at 6 months but lower by 24 months of age. Although the relation of fractional anisotropy measures to actual connectivity is not transparent, the authors noted that aberrant development of white matter pathways appeared to precede the manifestation of autistic symptoms in the first year of life. They argued that the organization of neural networks underlying ASD involves atypical patterns of connectivity differing across systems and time, specific neither to a single brain region nor behavioural domain, and proposed atypical axonal pruning and/or myelination as possible causes. Nevertheless, it may be too early to draw strong conclusions based on studies of brain connectivity in ASD, given the methodological issues involved (Kana *et al.*, 2014).

Lastly, the over-pruning hypothesis suggested that emergent disruptions to connectivity might risk destabilizing recurrent circuitry in vulnerable areas, and thereby increase the risk of seizures. In line with this prediction, Bolton, Carcani-Rathwell, Hutton, Goode, Howlin *et al.* (2011) recently reported that epilepsy developed in 22% of children with ASD who were followed up into adulthood. Giovanardi Rossi, Posar and Parmeggiani (2000) found that 38% of adolescents with autism had epilepsy and in 67% of cases epilepsy onset was after age 12. Even children with ASD who do not exhibit overt seizures can nevertheless show atypical epileptiform activity: one study by Hughes and Melyn (2005) found abnormal EEG in 75% of children with autism. Notably, in the Bolton *et al.* (2011) study, no increased risk of epilepsy was observed in family members. Once more, this is consistent with it being a marker of pathology (the putative damage from pruning) rather than the operation of risk factors that might be separately heritable in family members.

Protective and risk factors of environments on outcome

Recent reviews indicate that the most effective behavioural and psychosocial interventions are those that involved early intense behavioural intervention (EIBI; Howlin, Maglati & Charman, 2009; Warren, VeenstraVanderWeele, Stone, Bruzek, Nahmias *et al.*, 2011), and those that combine behavioural approaches with developmental social-communication approaches (e.g. Early Start Denver Model (ESDM): Dawson, Rogers, Munson, Smith, Winter *et al.*, 2010; Joint Attention Symbolic Play Engagement and Regulation (JASPER): Kasari, Paparella, Freeman & Jahromi, 2008; Kasari, Gulsrud, Freeman, Paparella & Hellemann, 2012). These involve intervention commencing between 2 and 4 years of age. In some cases these interventions are delivered intensively over a one- to two-year period (>15 hours per week (ESDM); >25 hours per week (EIBI)), although in others that focus more on early social communication skills, they are less intensive and more short term (JASPER). These interventions target a wide range of social, communicative and cognitive skills. However, studies demonstrate considerable variability in outcome (Charman, 2011, 2014; Howlin *et al.*, 2009). The importance of wide-ranging early intervention is consistent with the over-pruning hypothesis, in that stimulation must be applied early to resist ongoing pruning, must be system wide rather than narrow, and must engage complex integrative systems such as those involved in social interaction and social communication.

A recent mouse model of autistic-like traits reported a similar protective effect of enriched environments (albeit in this case enrichment through increased opportunities to explore and interact with the environment rather than the structured interactions created by a therapist). Lacaria, Spencer, Gu, Paylor and Lupski (2012) created a mouse model of the human Potocki-Lupski syndrome, which is characterized by neurobehavioural abnormalities, intellectual disability, and congenital abnormalities, and in which 70–90% of individuals are diagnosed with ASD. The authors reported that in their mouse model, alterations were identified in both core and associated ASD-like traits, but rearing these animals in an enriched environment mitigated some, and in selected animals all, neurobehavioural abnormalities. In this case, enrichment corresponded to weaning at 3 weeks into a larger cage that contained a changing menu of enrichment items to

enhance running, climbing, nesting, chewing, and social behaviour (e.g. a social environment with 7–8 mice versus the normal 4–5). To the extent that this mouse model replicates the proposed pathology through over-pruning, the mouse model is consistent with environmental enrichment providing protection against connectivity loss.

The over-pruning hypothesis also predicts that severely impoverished environments that lead to weaker connectivity prior to the onset of pruning will exacerbate the effects of aggressive pruning. In line with this prediction is the finding of Rutter and colleagues (Rutter, Anderson-Wood, Beckett, Bredenkamp, Castle *et al.*, 1999) that around 10% of children raised in Romanian orphanages in the late 1980s and early 1990s who experienced severe physical and social privation also exhibited a form of 'quasi' autism, similar to ASD on standardized instruments. Although by early adolescence in some of these children ASD symptoms had ameliorated, many continued to present with autistic-like behaviours (Rutter, Kreppner, Croft, Murin, Colvert *et al.*, 2007). The converse finding that 90% of these children did *not* develop quasi-autism under conditions of severe privation suggests that the negative environmental effect only served to exaggerate underlying risk in some individuals. Per the hypothesis, the 10% of individuals who suffered impairments to their connectivity and thus autism-like traits would be those who had higher-but-typical pruning thresholds, which would be damaging to function only if early-developed connectivity were weak, while in the other 90%, the lower-but-typical pruning thresholds would not damage function even with weaker connectivity.

Taken together, the data suggest that the environmental dosage needs to be large to overcome genetic influences on the relevant neural mechanisms contributing to the ASD phenotype, either positive in the case of intervention or negative in the case of the privation experienced in Romanian orphanages. And the variable response to the environmental dose suggests the necessity of considering such environmental effects within a framework that specifies the mechanistic operation of protective and risk factors.

Relation to other theories: under-pruning, excitation–inhibition imbalance

In this article, we are considering a hypothesis of over-pruning of connectivity within the brains of individuals with ASD. However, a more familiar proposal argues for the opposite: that ASD involves *under-pruning* (C. Frith, 2003, 2004). How can the two accounts be reconciled?

The primary evidence motivating C. Frith's under-pruning proposal was data showing increased head size/brain size in young children with autism (see previous section). For example, when C. Frith (2004) discussed functional magnetic resonance imaging data that demonstrated lower functional connectivity in ASD than controls (Just, Cherkassky, Keller & Minshew, 2004), he argued: 'reduced interactions between brain regions need not imply that there are fewer anatomical connections. Indeed, the little evidence about abnormalities of brain structure in ASD suggests that there are too many anatomical connections. Children with ASD show a greater increase in brain size, particularly of white matter, during infancy than healthy children. This could reflect a lack of pruning during the normal growth spurt, leading to excessive preservation of unneeded connections. Such an effect would certainly lead to abnormal functional connectivity between brain regions' (p. 577).

By contrast, within the over-pruning account, evidence of early larger brain size in ASD is explained in terms of a risk factor. The over-pruning hypothesis has two additional advantages. First, it resolves the paradox of why larger brain size should be *beneficial* in typical development (i.e. positively correlated to intelligence; McDaniel, 2005) yet a risk factor for ASD: large networks have greater learning power, but they develop smaller connection weights, rendering them more vulnerable to pathologies of pruning. Second, it explains why larger brain size in ASD should be a feature only of early development (Redcay & Courchesne, 2005). However, one should note recent post-mortem evidence for increased dendritic spine density in children with ASD, which support C. Frith's hypothesis (Tang *et al.*, 2014). These direct data of synaptic density are certainly suggestive. However, they are cross-sectional. The key finding, of an absence of a relationship between spine density and chronological age in the disorder group but the presence of such a relationship in the control group, is reminiscent of a familiar artefact established in comparisons of typical and atypical behavioural cross-sectional trajectories (Thomas, Annaz, Ansari, Serif, Jarrold *et al.*, 2009). Because the disorder group combines individuals with variations in disorder severity that are not correlated with age, the relationship between age and behaviour can be destroyed in the cross-section, even if the relationship could be found in any disordered individual followed longitudinally.

Another leading account of autism at the neural level proposes that the disorder is caused by deficits in establishing or maintaining the balance between excitatory and inhibitory neural activity (Persico & Bourgeron, 2006; Rubenstein & Merzenich, 2003; see LeBlanc & Fagiolini, 2011, for review). This account is not

self-evidently consistent with the current over-pruning hypothesis. Such excitatory–inhibitory disruption could conceivably be a consequence of atypical pruning, thereby reconciling two accounts, but this would need to be demonstrated.

The over-pruning hypothesis has some similarity to other recent proposals. For example, LeBlanc and Fagiolini (2011) suggested that ASD may involve the alteration of the expression and/or timing of critical period circuit refinement in primary sensory brain areas, leading to secondary high-level atypicalities. And Saugstad (2011) argued for over-pruning of the supplementary motor area in ASD, albeit in that case implicating an environmental (dietary) influence as a risk factor.

It has been argued that synaptic perturbations may contribute to several neuropsychiatric disorders, including schizophrenia and Alzheimer's disease, as well as ASD (Penzes, Cahill, Jones, VanLeeuwen & Woolfrey, 2011). Indeed, there exists an over-pruning hypothesis of schizophrenia (Feinberg, 1982). In that account, over-pruning occurs in prefrontal cortex in late adolescence and early adulthood, and results in psychosis. Recent reappraisals of the over-pruning hypothesis of schizophrenia commented that it had survived 40 years of accumulated data (see Boksa, 2012; Faludi & Mirnics, 2011; Keshavan, Anderson & Pettegrew, 1994). It has also been supported by computational simulations similar to those presented here (Hoffman & Dobscha, 1989).

The over-pruning hypotheses of autism and schizophrenia could be linked if they were to pertain to different time-dependent phases of pruning, one early and more general, the other more directly linked to reorganization of prefrontal cortex during adolescence (e.g. Petanjek et al., 2011). A range of studies has considered the relationship between ASD and schizophrenia. Genome-wide genotype data indicate very limited shared genetic aetiology between the two disorders, albeit a greater overlap than that between ASD and major depressive disorder, bipolar disorder, or attention deficit hyperactivity disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Recent studies have argued that both ASD and schizophrenia may represent disorders of chromatin remodelling, affecting the properties of cells from very early in development (Casanova & Casanova, 2014; McCarthy, Gillis, Kramer, Lihm, Yoon et al., 2014). Family studies have also indicated limited shared risk for ASD and schizophrenia (Bolton, Pickles, Murphy & Rutter, 1998; Sullivan, Magnusson, Reichenberg, Boman, Dalman et al., 2012). Of note is that in both the over-pruning accounts of ASD and schizophrenia, the proposal of a pathology involving the exaggeration of a normal, late phase of brain development serves to explain *why the respective disorders should have late onset despite predominantly genetic causes.* It is less obvious why late onset should occur if these disorders primarily affect prenatal brain development, although there have been immuno-related accounts which argue that environmental events, such as treatment with antibiotics, can in some cases interact with genetic vulnerability to produce late onset effects (e.g. Mezzelani, Landini, Facchiano, Raggi, Villa et al., 2014).

Current limitations and future directions

There are a number of areas where the over-pruning hypothesis is in need of clarification or lacks supporting evidence, and some areas where data are inconsistent. First, the most direct evidence to evaluate the hypothesis is longitudinal data on synaptic density in humans with and without autism. These data do not currently exist. Existing longitudinal macro-level data of grey matter and white matter development are only indirect indices (see e.g. Schumann et al., 2010), while cross-sectional data, such as those of Tang et al. (2014), have inherent limitations for testing theories of developmental change (see above). As Kana et al. (2014) argue, knowledge of brain anomalies at the cellular level in ASD is hampered by a lack of *in vivo* imaging techniques that can detect cytoarchitectural changes over time.

Two assumptions of the hypothesis need supporting evidence and further computational models: the assumption that long-range connectivity (necessary to explain the behavioural phenotype in ASD) is any more vulnerable to pruning than short-range connectivity; and the assumption that there are individual differences in the onset and rate of pruning that explain variations in ASD trajectories but do not manifest in marked differences in typical development. Further work is required, for instance, to consider possible variations in timing of developmental regression, and whether the proposed sources of variation could account for the late-occurring regression observed in childhood disintegrative disorder (Rosman & Bergia, 2013).

The over-pruning hypothesis stems from a high-level artificial neural network model, but further clarification is needed in translating to a more general hypothesis that can be tested through neuroscientific or behavioural data. (Indeed, a similar translation upwards is necessary to link current synaptic-level accounts with neurocomputational and behavioural outcomes.) In the model, pruning severs connections. But pruning at the neural level has multiple possible manifestations, in changes to

synapses, axons, and dendrites (see Low & Cheng, 2006). Where is the pathological pruning process operating? Further clarification is needed to identify the best brain-level data to test the hypothesis. In the model, pruning is triggered by a threshold operating on 'connection strength'. But in reality, synaptic pruning is a change in the balance of a dynamic process of synapse formation and elimination (Hua & Smith, 2004). How can the simplified pruning threshold be translated into more realistic biological mechanisms? For example, might a more realistic threshold operate on how (in)frequently a synapse has been activated? Might deficits in consolidating synapses (also) be the cause of greater synapse loss during pruning? Greater precision is also required in identifying differences in the timing of onset of pruning in different brain regions if there is to be a tighter link to predicted emergence of symptoms, thereby rendering the hypothesis more testable.

Environmental influences also need greater clarification (Karmiloff-Smith *et al.*, 2012). For example, if environmental enrichment is proposed as a behavioural intervention to strengthen pre-pruning connectivity, what form should this intervention take? Should there be sensory stimulation, when indeed some children with ASD appear over-sensitive to sensory input (Rogers & Ozonoff, 2005)? Moreover, extensive evidence points to pre- and peri-natal risk factors for ASD, such as foetal distress, birth trauma, multiple birth, maternal haemorrhage, summer birth, and low birth weight (e.g. Gardener, Spiegelman & Buka, 2011; Newschaffer, Croen, Fallin, Hertz-Picciotto, Nguyen *et al.*, 2012). It is necessary to develop a mechanistic account of how these factors would *interact* with the putative atypical pruning processes directly, or serve as risk factors reducing the robustness of pre-pruning connectivity.

We need a better account of how individual differences in cognitive ability (or 'intelligence') might interact with atypical pruning, to explain differences in the level of functioning in ASD. We don't yet understand the full set of neurocomputational parameters that contribute to higher intelligence. The most parsimonious account would show how some of these parameters interacted with atypical pruning to permit high functioning despite severe loss of connectivity, perhaps with differential use of more locally recruited computational resources.

Finally, there may be multiple causes of ASD at the neurocomputational and genetic levels. Multiple hypotheses may be correct, some of them representing opposing variations from typical development (Kelleher & Bear, 2008). The onus from a computational perspective is to reconcile the common causal pathway that leads to a shared ASD diagnosis.

General discussion

The origin of the over-pruning hypothesis was in a neurocomputational model of development (Thomas *et al.*, 2011a, 2011b). Models have a number of advantages, including forcing clarification of theories via implementation, establishing the viability of theoretical proposals to explain observed behaviour, unifying disparate empirical data sets, and generating novel predictions. Their main drawback is obviously the requirement for simplification. The TKK model is advantageous in that it provides a parsimonious explanation of the variety of observed atypical developmental trajectories within ASD, including early onset, late onset, and regression, as arising from a single pathological process, over-pruning of brain connectivity. The wider hypothesis is parsimonious in that it explains why putative high-level cognitive atypicalities (e.g. deficits in theory-of-mind reasoning, or in executive functions, or a cognitive 'style' marked by weak central coherence; Happé & Ronald, 2008) should also be associated with low-level sensory and motor atypicalities in the later ASD phenotype.

Since pruning has differential onset across brain areas, our hypothesis generated the novel prediction that ASD should first emerge as sensory and motor atypicalities, followed by higher-level cognitive differences. Though caution is necessary given the preliminary nature of data coming from longitudinal studies of infants at-risk of autism, initial findings appear to fit with the over-pruning hypothesis and do not support social orienting and attentional deficit accounts of predicted early atypicalities.

The computational implementation, with its use of population modelling, for the first time also provided a mechanistic framework to consider risk and protective factors that might operate alongside pathological mechanisms, in line with current theoretical proposals (Newschaffer *et al.*, 2012). Specification of mechanism is required to move from correlations (such as predictors of outcome) to causal models. The model offered a clear definition to distinguish *pathology* from *risk*: pathology is uniquely associated with disorder outcome, while risk and protective factors represent individual differences found in the whole population, including unaffected family members of individuals with ASD. This distinction can be readily drawn within a model because, by design, the cause of the disorder is known and is distinguishable from population-wide individual differences. In reality, empirical data comprise only correlations between measures (of behaviour, brain, genes, etc.) and disorder outcome. There is no independent measure

of pathology. Nevertheless, we saw here how the application of the mechanistic framework could make sense of the conflicting evidence on the role of brain size in ASD, and explain why unaffected siblings could differ from low-risk controls. This type of explanatory framework will become increasingly important to interpret findings from at-risk sibling studies, which exhibit a mixture of differences between high-risk and low-risk groups that are either associated with disorder outcome or with risk itself.

Stipulation of risk and protective factors demonstrated that the concept of the broader autism phenotype, i.e. family members of individuals with ASD, needs further elaboration. It incorporates at least three causal models. First, there is the threshold liability model, where ASD represents the extreme of one or more traits that vary continuously across the whole population (Robinson, Koenen, McCormick, Munir, Hallett *et al.*, 2011). Disorder is defined by a cut-off position somewhere on that continuum. Unaffected family members may be on the same continuum but not sufficient to cross the cut-off. Our simulations captured this possibility in individual networks that inherited a milder version of the pathological pruning process. Second, there is a pathological process that interacts with population-wide individual differences serving as risk factors. Unaffected family members may differ from controls because they have co-inherited the risk factors. Our simulations captured this possibility in individual networks that inherited risk-factor processing properties such as unit activation dynamics and network size. Third, and not considered here, is the possibility that unaffected family members have co-inherited the pathology but received a different inheritance of protective factors ameliorating the pathology; those protective factors may then manifest in an altered developmental trajectory compared to low-risk controls (see Johnson, 2012, for discussion).

The causal account of ASD that we propose is not simple. Our account is intrinsically developmental, arguing that the earliest phases of development in ASD may entail a cognitive profile different from the profile subsequently observed in childhood and adulthood (Karmiloff-Smith, 1998). It involves a time-varying, multi-system pathological process. There is every reason to expect attendant secondary atypicalities from each impaired system, along with compensatory processes, and interactions with a co-specified atypical environment. This picture of widespread deficits contrasts with approaches proposing narrow deficits, even to modular processes (such as theory of mind; e.g. Baron-Cohen, 1991, 1998; Leslie & Thaiss, 1992). Some researchers have proposed that in complex disorders, core deficits to single neurocognitive systems or brain mechanisms

might represent simpler clues to genetic causes than the disease syndrome itself (e.g. Gottesman and Gould's idea of an endophenotype; Gottesman & Gould, 2003). The multi-system deficit proposed here would undermine such an approach to understanding ASD. There is no single core deficit with secondary deficits. A common cause impairs multiple systems in a time-dependent way across development.

The increasing availability of longitudinal data following infants at-risk of ASD should accelerate the determination of which hypothesis best fits the data, (though this progress is reliant on the multiplex families [those with multiple children with ASD] turning out to be representative of the ASD that occurs in simplex families [those with only one child with ASD]). The over-pruning hypothesis suggests that future longitudinal studies of children at-risk of ASD should focus on sensitive measures of early sensory and motor skills, and brain measures seeking to tap processes of generating and eliminating brain connectivity.

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