OPINION

Is birth a critical period in the pathogenesis of autism spectrum disorders?

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Abstract | Birth is associated with a neuroprotective, oxytocin-mediated abrupt excitatory-to-inhibitory GABA shift that is abolished in autism, and its restoration attenuates the disorder in offspring. In this Opinion article, I discuss the links between birth-related stressful mechanisms, persistent excitatory GABA actions, perturbed network oscillations and autism. I propose that birth (parturition) is a critical period that confirms, attenuates or aggravates the deleterious effects of intrauterine genetic or environmental insults.

The developing brain is not a small adult brain. The immature brain undergoes progressive alterations in molecular composition and in synchronized currents that enable neurons to fire and wire together and to construct functional neuronal circuits. In the immature brain, large, synchronized patterns of neuronal activity engage many or possibly most neurons of developing brain networks, which is in contrast to the sparse firing and time-locked, behaviourally relevant oscillations that occur in the adult nervous system. As well as the gradual and progressive molecular and brain activity changes that occur during development, there is a large step-change during parturition (that is, birth) that involves the maturation of various systems, including microbiotic, endocrine, vascular and immunological systems[1–5]. Collectively, these observations raise the possibility that the deleterious effects of intrauterine genetic mutations and environmental insults are mediated by the deviation of these developmental sequences of changing brain activity. This also raises the possibility that if these immature signatures persist into maturity, they are likely to continue to disrupt brain function over a lifetime. However, in contrast to the extensive amount of clinical, epidemiological and experimental information available on the links between genetic mutations and the cellular and molecular pathology of brain disorders, little is known about the impact they have on the sequential transition of brain activity characteristics during development and birth. Here, I discuss the brain functions that rely on the excitatory-to-inhibitory GABA sequence that occurs during development and particularly at birth, and I propose that autism spectrum disorders (ASDs) are caused, in part, by incomplete or inadequate transition to mature electrical patterns of activity.

Developmental brain activity patterns

Virtually all ionic currents and brain patterns (including those driven by voltage-gated calcium channels[6], potassium channels[7,8] and other intrinsic currents[9–11]) follow specific sequences during development. Receptor channel subunits undergo developmental alterations, leading to modifications of synaptic currents such that they have shorter kinetics[12–14]. During development, GABAergic signals shift from depolarization and excitation to hyperpolarization and inhibition owing to a reduction inintracellular chloride concentration ($[Cl^-]_i$)[15–18]. Brain patterns shift from intrinsic non-synapse-driven voltage-gated calcium currents to large calcium plateaus in neurons connected by gap junctions. This is followed by a shift to primitive, synapse-driven patterns such as the giant depolarizing potentials (GDPs) that are then replaced by more elaborate patterns[16,17,19,20] (FIG. 1). GDPs synchronize virtually all hippocampal pyramidal neurons[16,17,20] — a situation that is never observed under physiological conditions in adults, except possibly during severe seizures. The importance of these shifts is illustrated in sensory and motor systems. In animal species and preterm babies, the immature retina generates long-lasting retinal waves[21–28]; these disappear in rodents shortly before eye opening[21]. In the rodent visual cortex, around the time of eye opening, spontaneous activity undergoes a transition from a synchronous activity state in which 75% of neurons are active during each slow wave cycle to a state in which 12% of neurons are active per cycle[29]. Developing hair cells of the cochlea display long-lasting bursts that disappear with time to enable hearing[6,30]. This 'sparsification' (that is, a shift to more sparse patterns of activity)[31,32] is a fundamental property of information coding and illustrates the major differences in the operation of immature versus adult networks, possibly owing to the lack of efficient feedforward GABAergic inhibition in immature networks. Therefore, the developing brain has the intrinsic capacity to synchronize large neuronal ensembles without generating seizures, despite poorly developed GABAergic inhibition. These immature signals must stop at the correct time to enable behaviourally relevant activity patterns to emerge. Thus, striatal medium spiny neurons that are initially very active with a GDP-like pattern abruptly shift to little or no discharge around postnatal day 10 (P10) to enable targeted movements[33]. As synchronized hyperactivity in the striatum is linked to Parkinson disease and akinesia[34,35], failure in the timing of this shift is thought to delay the emergence of targeted movement. Therefore, a genetic mutation that alters developmental sequences might lead to faulty circuit development and defective electrical properties of neurons. These in turn could lead to abnormalities in the sequential changes in brain activity that occur during development, with potentially deleterious consequences.

Abnormal neuronal development in ASD

ASDs are a heterogeneous family of developmental disorders that are associated with difficulties in social interactions and communication, and a restricted range of interests and stereotypies. The underlying pathology is poorly understood, and there are currently no drugs available that target the core symptoms of the disorder[36,37]. Initially considered quite rare, the incidence of ASDs is now estimated to be 1% of the population. Autism pathology begins early in life, often *in utero*[38,39], when neurons are engaged in essential developmental processes, including proliferation, neuronal growth and differentiation, migration, synapse formation and network construction. The recently shown patches of displaced neurons in post-mortem cortical structures of children with autism support the notion of faulty axon pathfinding and circuit development in ASDs[38,39]. Interestingly, complicated or preterm birth[40], and intrauterine environmental

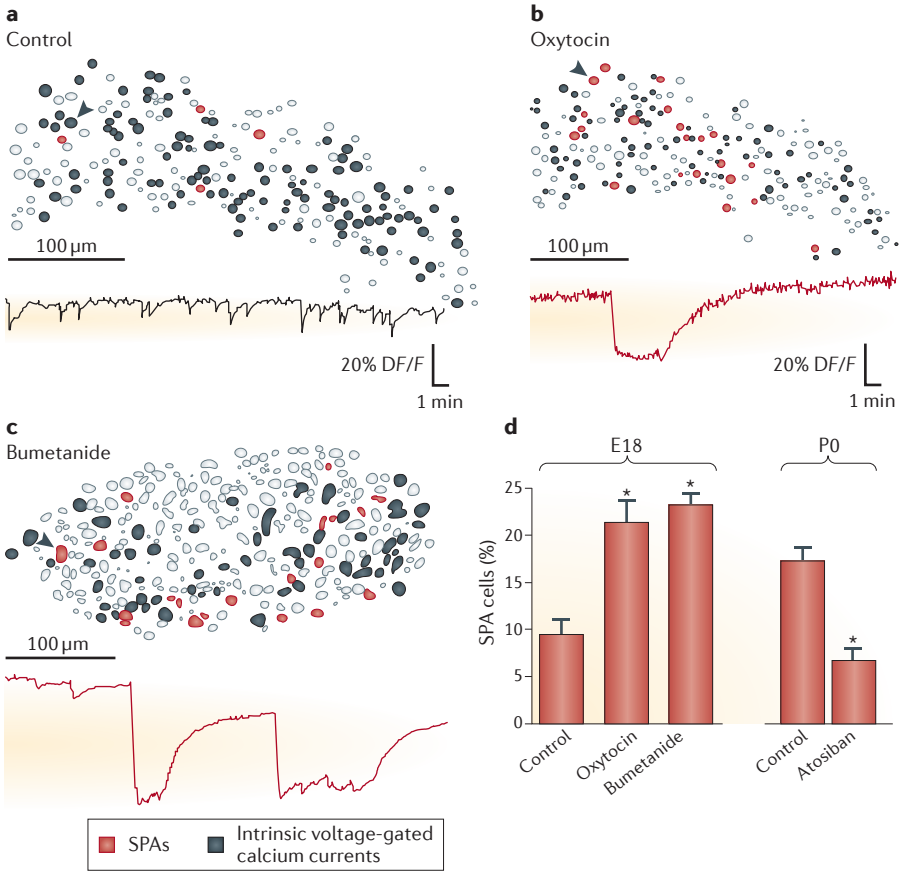

Figure 1 | **Synchronous calcium plateau assemblies are regulated by oxytocin.** Synchronous calcium plateau assemblies (SPAs) are intrinsic non-synapse-driven, long-lasting depolarizations that are present around the time of delivery (that is, birth) and are regulated by oxytocin. The figure shows dynamic, two-photon, quantified imaging of hippocampal slices obtained from embryos at embryonic day 18 (E18) or shortly after delivery (postnatal day 0 (P0) or P2–P3) in the presence of 10 µM NBQX and 40 µM D-APV to block AMPA receptor- and NMDA receptor-mediated currents, respectively. At the top of panels **a**–**c** are representative still images from movies of neuronal activity (contour maps) taken at E18. The traces below show activity changes in a single cell (indicated on the contour maps above with an arrowhead). **a** | Under control conditions, at E18, most neurons generate intrinsic voltage-gated calcium currents (shown as black dots on the two-photon image). The bottom trace shows the changes in calcium current in a single neuron over time (marked with an arrowhead on the contour map above): very few cells generate SPAs. **b** | By contrast, when 10 µM oxytocin is added to the saline, a substantial proportion of cells detected under control conditions as generating calcium spikes generate SPAs, as shown in the illustrated contour map for a representative still image from a movie of calcium fluxes taken at E18. The trace below shows the SPA in a single neuron over time (identified by an arrowhead on the contour map). **c** | Similar effects are produced by the diuretic bumetanide, which reduces intracellular chloride concentration. The contour map of a single representative image above shows the large number of neurons generating SPAs, and the trace below shows the SPA in a single neuron over time (identified by the arrowhead in the contour map). **d** | The histogram shows that the fraction of cells generating SPAs is increased by oxytocin (10 µM) and bumetanide (10 µM) but reduced by the selective oxytocin receptor antagonist atosiban (1–5 µM). Error bars indicate the s.e.m.; *$P < 0.001$. Note that SPAs are also generated when GABAergic signals are blocked, indicating that neither GABAergic nor glutamatergic ionic currents contribute to the generation of SPAs. Adapted with permission from REF. 19, Elsevier.

insults (such as pesticides)[41], can contribute to the pathogenesis of ASDs. Moreover, hundreds of autism-associated mutations or networks of mutations have been identified in genes affecting cell proliferation, synaptic function and plasticity, cytoskeletal proteins, voltage- and transmitter-gated ionic currents, chromatin structure, neuroimmunology, and so on[42–45]. All of these insults and mutations could conceivably alter circuit formation and neuronal function in immature neurons before and shortly after birth, and thus contribute to the pathogenesis of ASDs[46,47].

Checkpoint and neuroarcheology

The links between genetic programming and neuronal development have been conceptualized by Ben-Ari and Spitzer[48]. They suggested that developmentally active genes and neuronal activity operate in series, the latter validating the correct implementation of the developmental programme. In this 'checkpoint' concept, the properties of ionic currents indicate the developmental stage. It is suggested that major events in brain development — including proliferation, migration, axon guidance, neuritic extension and neuronal phenotype — are activity dependent and likely to require a control checkpoint[48]. A variety of ionic currents, notably voltage-gated calcium and NMDA receptor-mediated currents, have a central role in these functions[49–53]. Interestingly, syntaxin-binding protein 3 (*Stxbp3*; also known as *Munc18*)-knockout mice that have no vesicular transmitter release have apparently normal brain and synaptic structures[54]. However, using the same mice, a subsequent study showed that non-vesicular release that operates before vesicular release is functional, which potentially provides an alternative source for activity-dependent modulation of brain development[55]. Other studies have shown that genes which control the attraction or repulsion of axonal growth can be altered by electrical activity, illustrating the complex relationship between activity and genetic programmes[56].

What happens when these checkpoints fail? Elsewhere, it has been suggested that genetic mutations or environmental insults can lead to stalling of developmental sequences and long-term developmental and behavioural defects (known as the 'neuroarcheology concept')[57]. This concept has been confirmed in many genetic disorders associated with migration deficits — notably, the double cortex mutation and other mutations that lead to malformed cortices, which in turn exhibit immature currents in misplaced neurons[57–60]. In the cerebellum of waggler mice, mutation of the voltage-dependent calcium channel gamma subunit 2 (*Cacng2*) gene entrained developmental arrest, which was accompanied by long-lasting immature GABAergic and NMDA currents[61]. Interestingly, experimental attempts to correct these disorders by genetic interventions failed unless they were performed a few days after birth[62], illustrating the limitations of gene therapy in multifactorial, complex disorders in which developmental sequences have been altered. The important implication of the

neuroarcheology concept in developmental disorders such as ASDs is that failure to reach a particular checkpoint stalls certain aspects of development, preventing progression past that point and leading to the persistence of an immature signature in the mature nervous system. Alterations in the polarity of GABA actions (that is, the shift from excitatory to inhibitory actions of GABA) have been extensively investigated, as GABA is developmentally regulated and highly susceptible to insults that reinstate immature excitatory actions.

Excitatory actions of GABA

Brain maturation is associated with a developmental depolarizing-to-hyperpolarizing GABA shift and an excitatory-to-inhibitory GABA shift owing to a progressive reduction in $[Cl^-]_i$ (REFS 16,63). This is mediated by sequential maturation of the bumetanide-sensitive sodium-(potassium)-chloride co-transporter 1 (NKCC1; also known as SLC12A2), which imports chloride, and the electroneutral potassium-chloride co-transporter 2 (KCC2; also known as SLC12A5)[64,65]. This shift has been confirmed in a wide range of animal species and brain regions, suggesting that it has been conserved throughout evolution[18,66]. The depolarization produced by GABA removes the voltage-dependent magnesium block from NMDA receptor channels and activates voltage-gated calcium currents, leading to calcium influx, both of which underlie the trophic actions of GABA[67]. Interestingly, birth is associated with an oxytocin-mediated, dramatic, abrupt and short-lasting reduction in $[Cl^-]_i$ to levels that are never observed before or afterwards[68] (FIG. 2). Maternal administration of a selective oxytocin receptor antagonist shortly before birth prevents this shift in the neurons of the offspring[68], raising the possibility that oxytocin signalling has a direct effect on chloride co-transporters. This shift exerts neuroprotective actions on the newborn, as neurons are more susceptible to anoxic episodes when oxytocin receptors are blocked[68]. Interestingly, human babies delivered by elective, programmed caesarian section (C-section) are more susceptible to pain than those born by vaginal delivery after the mother has gone into labour[69], and oxytocin has an analgesic action on newborn rodent pups that is mediated by high $[Cl^-]_i$ in nociceptive pathways[70]. Therefore, endogenous oxytocin exerts a multitude of actions during birth, adapting $[Cl^-]_i$ and the polarity of GABA actions to reduce the deleterious actions of insults during this highly vulnerable period.

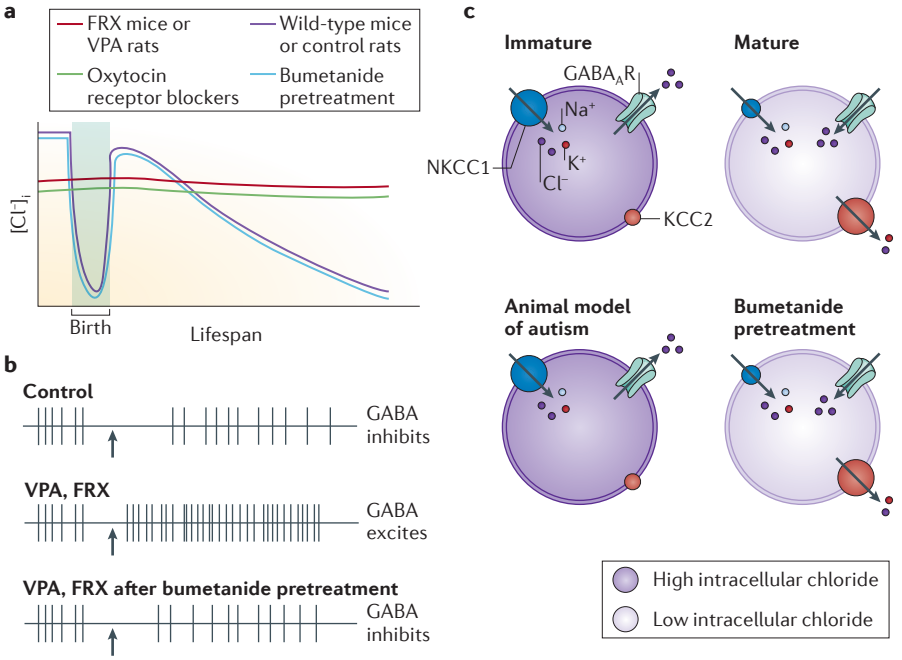

Figure 2 | **The excitatory-to-inhibitory GABA developmental switch is abolished in animal models of autism and fragile X syndrome.** **a** | The ratio of intracellular to extracellular chloride concentration is what determines whether GABA is excitatory or inhibitory. The graph shows intracellular chloride concentration ($[Cl^-]_i$) in hippocampal neurons from the embryonic to adult stage in naive rats or mice. Note the abrupt reduction during the birth period. This shift is abolished in fragile X syndrome (FRX) and in rodents treated with valproate (VPA) *in utero*. Maternal pretreatment with bumetanide restored chloride fluxes back to naive levels, including the reduction in $[Cl^-]_i$ during and after birth. Also, pretreatment of naive maternal rats with an oxytocin receptor antagonist before parturition abolished the shift, reflecting the importance of oxytocin signals during birth. **b** | Cell-attached recordings illustrating that GABA has inhibitory actions in naive neurons. In the VPA and FRX animal models of autism, application of GABA (represented by arrows) results in increased spiking, which indicates that GABA is excitatory compared with controls, but when the animals are pretreated with bumetanide GABA becomes inhibitory, similar to observations in naive rats. **c** | A schematic diagram to depict the alterations in $[Cl^-]_i$ in neurons recorded from immature, mature and animal models of autism without and with maternal pretreatment with bumetanide. The bumetanide-sensitive sodium-(potassium)-chloride co-transporter 1 (NKCC1) and the electroneutral potassium-chloride co-transporter 2 (KCC2) are illustrated. In immature rats, expression of NKCC1 is high and that of KCC2 is low, which results in high $[Cl^-]_i$. Activation of GABA receptors causes chloride efflux from the cell: that is, activation of GABA is excitatory. In the normal mature nervous system, the situation is reversed; expression of NKCC1 is low and that of KCC2 is high, resulting in low $[Cl^-]_i$ and GABA activation being inhibitory. In an animal model of autism, immature patterns of chloride transporters are recapitulated in the mature rat, resulting in high $[Cl^-]_i$, and type A GABA receptor ($GABA_AR$) activation being excitatory. Bumetanide pretreatment restores $[Cl^-]_i$ to near-normal levels, thus allowing GABA to function as an inhibitory neurotransmitter.

$[Cl^-]_i$ is dynamically regulated by neuronal activity, leading to a large degree of plasticity in the polarity of type A GABA receptor-mediated currents[71]. In immature neurons, as in adult neurons, even short episodes of enhanced activity produce an increase in $[Cl^-]_i$ and excitatory actions of GABA[72–74]. Indeed, excitatory actions of GABA have been reported in a wide range of pathological conditions, including enhancement of electroencephalography (EEG) discharges and seizures[73–77], stress[78–81], spinal cord lesions[82,83], brain traumas[84,85], cerebrovascular infarcts[86] and chronic pain[87,88], which suggests that this is a common response of neurons to insults[72]. In many pathological conditions, KCC2 is downregulated and internalized, and the co-transporter NKCC1 is upregulated, which raises the possibility that NKCC1 antagonists and/or KCC2 enhancers might constitute potential therapeutic agents[89,90]. Therefore, high $[Cl^-]_i$ and excitatory actions of GABA that are reminiscent of immature neurons are observed in various pathological conditions.

Reduced GABAergic tone in ASD

There are several direct and indirect lines of evidence indicating that chloride levels and GABAergic signalling are altered in animal models of ASD, and in people with ASDs and

other developmental disorders[91]. The incidence of epilepsies in children with autism is higher than that of the general population[92–95]; indeed, EEG measurements from people with autism show that 60% exhibit epileptiform activity[96], which is indicative of reduced GABAergic inhibition. In keeping with this, a reduction in GABAergic markers, and an increased excitatory glutamatergic drive, which leads to an excitation–inhibition imbalance, has been observed in various animal models of ASD[97–100]. Gamma oscillations, which are instrumental in higher cognitive functions[101,102] and are generated by GABAergic neurons[99,102,103], are altered in various pathological conditions[104] including ASD[105], which suggests that a deficiency in inhibitory GABAergic signalling might contribute to the pathology underlying these disorders. Furthermore, pharmacological agents that act at GABA receptors have paradoxical reactions in patients with autism compared with controls, which suggests that high $[Cl^-]_i$ and excitatory actions of GABA are implicated in ASDs[106]. For example, in some people with autism, GABA-acting benzodiazepines increase anxiety[106] and decrease catatonia when other treatments fail[107–109]. Taken together, these findings suggest that, in the autistic brain, GABAergic inhibition is reduced and excitatory actions of GABA persist — both of which are hallmarks of GABAergic signalling in the immature brain.

Importance of oxytocin during birth

Influence of oxytocin in ASD models. In addition to the progressive changes in GABAergic signalling in the developing nervous system, there is a substantial and important step-shift that occurs during birth, driven by the hormone oxytocin[68]. Recently, we directly tested the hypothesis that the GABAergic excitatory-to-inhibitory developmental sequence is altered in ASD, using the fragile X syndrome[110,111] and the *in utero* valproate animal models of ASD, in which high $[Cl^-]_i$ and excitatory effects of GABA persist in hippocampal neurons from birth to adulthood[112–114]. We found that the oxytocin-mediated neuroprotective shift that occurs during birth is abolished in both models[115] (FIG. 2). Consequently, GABA remains excitatory after birth, and the frequency of glutamatergic excitatory postsynaptic currents is augmented almost fivefold, leading to enhanced network activity and increased gamma oscillations. In these models, acute *in vitro* administration of oxytocin or the diuretic bumetanide restored control $[Cl^-]_i$ and GABAergic inhibition. In addition, it was reported that maternal administration of the diuretic and highly specific NKCC1 chloride importer bumetanide shortly before, during and after parturition (a 24-hour period) restored physiological $[Cl^-]_i$ and GABA inhibition in offspring, and also attenuated increased glutamatergic currents, brain oscillations and various behavioural manifestations; notably, these effects persisted into adulthood[115,116]. Therefore, in these rodent models of ASD, the polarity of GABA actions during this vulnerable period exerts a long-term priming effect on the expression of electrical manifestations of autism-like behaviours.

In naive rats, blocking oxytocin signals in the mother during birth produces increased $[Cl^-]_i$, excitatory GABA actions and enhanced ongoing activity in offspring, which suggests that oxytocin signals have an important role in the reduction of $[Cl^-]_i$ during birth[68]. Moreover, oxytocin enhances the coordinated activity patterns — known as synchronous calcium plateau assemblies (SPAs) — that are generated by gap junctions between hippocampal neurons during birth[19,68] (FIG. 1). Oxytocin and other hormones are known to open gap junctions in a variety of cell types — notably, in myometrial smooth muscle cells during labour[117–120]. Therefore, oxytocin signals are instrumental in generating a wide range of effects during labour. Interestingly, oxytocin modulates the generation of gamma oscillations by paravalbumin-expressing GABAergic interneurons, thereby synchronizing hundreds of pyramidal neurons via their abundant somatic inhibitory drive[121,122].

Influence of oxytocin in human ASD. If a similar oxytocin-dependent chloride shift occurs in humans, then this could provide insight into the developmental mechanisms underlying the abnormal electrical activity observed in patients with ASDs.

Clinical observations suggest that the administration of a diuretic to children with autism attenuates the severity of the syndrome. In a double-blind randomized placebo–treatment trial, 54 children with autism (3–11 years old) were treated with bumetanide for 3 months, which reduced the severity of the autistic symptoms and had few side effects (diuresis and hypokalaemia)[123]. This was recently extended to a combined functional MRI (fMRI) and eye tracking trial in which eight adolescents with Asperger syndrome were similarly treated with bumetanide for long-lasting periods[124]. Visual communication was improved, with better recognition of emotive figures and fear images, and increased activation of brain regions involved in facial, emotional and social processing, after treatment compared with pretreatment (FIG. 3). Despite the different developmental stages, these observations in rodents and humans suggest that restoring GABAergic inhibition to normal levels during parturition in rodents or in children attenuates the severity of the syndrome. Why is the presence of oxytocin during birth so important in the emergence of mature patterns and the shift of GABAergic functions?

Resetting neural processes during birth

The emergence of life from the sea to the terrestrial environment that took millions of years during evolution is accomplished within hours through labour and parturition. In the seminal paper — The 'Stress' of Being Born[125] (also see REF. 126) — Lagercrantz and Slotkin emphasized four important transitions that take place during birth: a shift from an aquatic to a dry environment, with oxygen acquired through the lungs instead of the placenta; a reduction in environmental temperature; a replacement of continuous nutrient supply with transient nutrient supply; and a shift from a sterile bacterial environment to a neonatal microbiota that has an important role in the developing immune system[3]. External and internal factors contribute to this sequence, including the squeezing of the fetus through the birth canal and the cold temperature outside. As during other stressful reactions, the stress at birth is associated with endocrine support and an enormous surge of catecholamine, with noradrenaline and adrenaline levels rising within minutes of term birth and cord clamping to levels that are seldom observed even after severe stress[127,128] (FIG. 4). High catecholamine levels are due to fetal adrenal release, as they are absent in adrenalectomized ovins[129,130] and lower in C-section of the unlaboured fetus[130,131]. Similarly, cortisol levels are increased dramatically and abruptly — from 5 to 10 $\mu g\,ml^{-1}$ until about 30 weeks of gestation to about 45 $\mu g\,ml^{-1}$ prior to labour at term and to 200 $\mu g\,ml^{-1}$ a few hours after term birth[128]. Cortisol plays an important part in helping neonates to adapt to extrauterine life by promoting lung maturation, increased cardiovascular performance and blood flow to the brain, functional maturation of the gut and thyroid axis, and control of energy metabolism. Therefore, stress molecules released during birth are essential for major biological functions, including clearance of fetal lung fluid, surfactant secretion and breathing, transition of fetal to neonatal circulation, and reducing pulmonary vascular resistance and pulmonary blood flow[132,133].

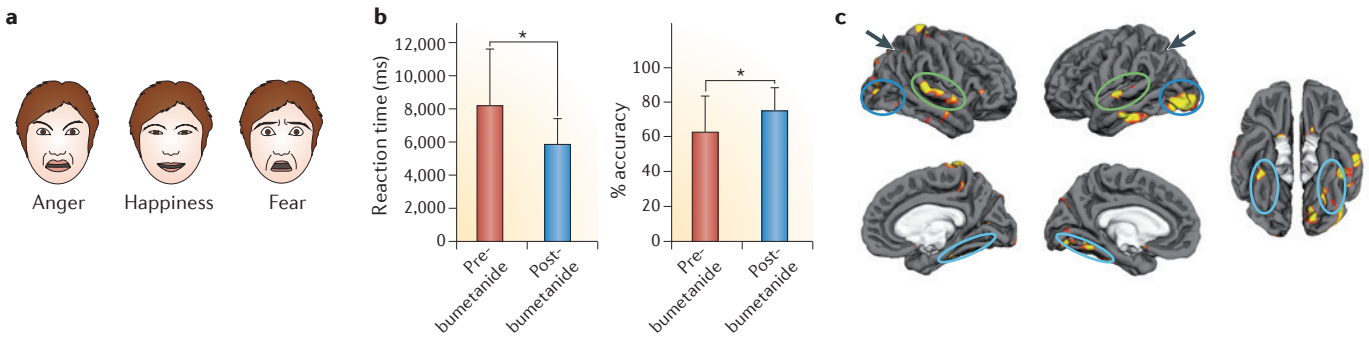

Figure 3 | **Bumetanide treatment improves recognition of facial expressions in adolescents with ASDs.** It has been shown that chronic treatment of adolescents with autism spectrum disorders (ASDs) using bumetanide ameliorates recognition of different facial expressions and activation of specific brain regions. **a** | Adolescents with ASDs were shown faces expressing either a neutral expression, or angry, fearful or happy expressions. **b** | These adolescents showed an improvement after bumetanide treatment in the reaction time and accuracy of recognition of different emotional facial expressions (compared with before bumetanide treatment; asterisk indicates $P = 0.04$). **c** | Functional MRI (fMRI) shows the difference between pre- and post-bumetanide treatment of individuals with ASD following exposure to different emotional facial expressions. Bumetanide treatment resulted in increased activation of brain areas involved in face processing (such as the inferior occipital cortex (dark blue ovals) and fusiform cortex (light blue ovals)), as well as in areas involved in emotional processing (such as the nucleus accumbens and amygdala), in social processing (the superior temporal cortex (green ovals)) and attention (the intraparietal sulcus (arrows)). Parts **b** and **c** are adapted from Hadjikhani, N., Zürcher, N. R., Rogier, O., Ruest, T., Hippolyte, L., Ben-Ari, Y. & Lemonnier, E., Autism (19,2) 149–157, copyright © 2015 by SAGE. Reprinted by Permission of SAGE.

Oxytocin is neuroprotective during birth

Such important stress mechanisms are bound to have an impact on central neuronal activity, and indeed have been shown to alter GABAergic mechanisms. For instance, it has been shown that, in rodents, exposure to a variety of stress protocols produces high catecholamine levels, downregulation of KCC2 and a depolarizing shift of GABA[78,79,81,134–137]. If the stress molecules that are released at birth exerted similar effects in human newborns, they would produce high $[Cl^-]_i$ and strong excitatory actions of GABA, possibly generating seizures (notably, during anoxic episodes). However, as discussed above, newborn rat pups have low $[Cl^-]_i$ and strong inhibitory actions of GABA, which appear to be dependent on oxytocin. Therefore, I suggest that oxytocin (among other hormones and molecules) has evolved to counter these deleterious actions of stress molecules on neurons. In keeping with this, blocking oxytocin receptors during birth produces hyperactivity and excessive synchronization[115]. Hyper-synchronized activity is observed in many pathological conditions — notably, severe stress[79,135,136] and Parkinson disease — and is alleviated by appropriate treatments, confirming its relevance to these disorders[34,138]. At present, the developmental stage at which the excitatory-to-inhibitory GABA shift occurs in humans is not known. Based on detailed studies in macaques, it seems likely that this shift occurs *in utero*[139] and is temporarily reversed during the stress of birth (which probably produces high $[Cl^-]_i$ and excitatory GABA actions). In summary, it is suggested that parturition is a critical period that confirms, attenuates or aggravates the effects of genetic or environmental intrauterine insults.

Is oxytocin involved in ASDs?

Other observations reflect the importance of oxytocin signals in relation to birth, communication and ASD[140]. Children with ASD have lower baseline oxytocin, and oxytocin levels are inversely correlated with levels of difficulty in parent–child communication[141,142]. Rodent knockout models of oxytocin signals are associated with autism-like behaviours[143–145]. Administration of oxytocin to trigger and accelerate labour disrupts early postnatal development and produces long-term adverse effects, illustrating the importance of fine-tuning oxytocin signals[146,147]. Indeed, a comparative study of 625,042 births in North Carolina, USA, revealed an increased risk of autism following the administration of oxytocin to trigger labour, which raises some concerns regarding its widespread use in these settings[148]. Furthermore, it has been shown that the incidence of autism is increased by complications during birth, hypertension, pre-eclampsia and anoxic episodes[149], which lead to increased $[Cl^-]_i$ and excitatory GABA actions and appear to be consistent with the experimental work in rodents. Epidemiological investigations into the links between autism and programmed C-sections have led to more controversial results, possibly because of the greater need to take into account the various types of C-sections (for example, those with or without labour, whether complications were present or absent, and so on).

Concluding remarks

We are standing at a crossroads in autism research. Genetic investigations have enabled the identification of potentially hundreds of mutations that are implicated in ASD, which have provided useful experimental tools but have so far failed to provide a unifying conceptual framework or promising therapeutic breakthrough. This, I suggest, is due to an underestimation of the dynamic aspect of brain development, in which developmental sequences are altered by *in utero* genetic (or environmental) insults, which in turn lead to aberrant cellular and network activities that perturb the maturation of essential, behaviourally relevant oscillations. However, this might not be the only factor, or even necessarily the initial trigger, of the pathogenic cascade that causes the clinical manifestations. A recent study provided interesting clues showing that the development of infants who are later diagnosed with autism differs from their peers even at 2–6 months of age[150,151]. The authors stressed that "given the interdependence of individual experience with brain structure and function … single individual outcome will be shaped not only by initial genotypic vulnerabilities but also by the atypical experience that arises as a consequence of these vulnerabilities" (REF. 150). These observations stress the importance of early treatments, which are now feasible and considered to be more efficient that interventions at later stages[152–154]. Early intervention is vital to prevent persistent alterations of synaptic network function and cumulative deleterious effects of environmental factors,

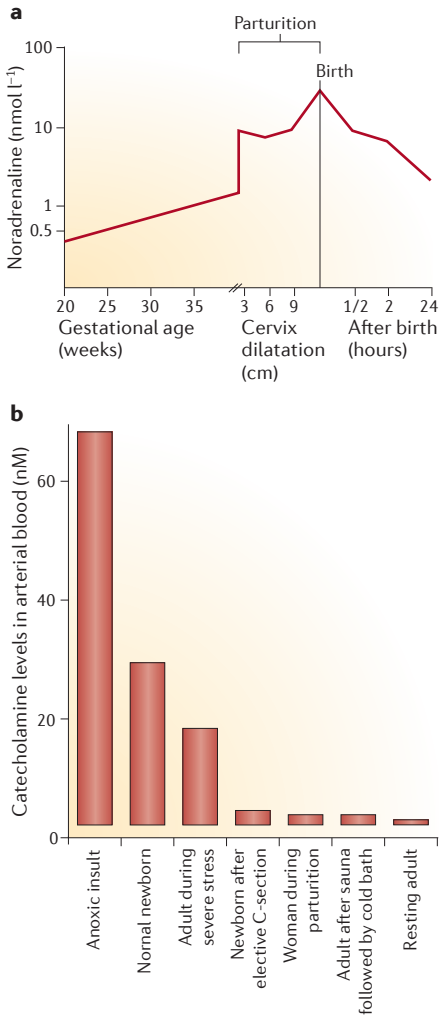

Figure 4 | **Effect of different birth conditions on catecholamine levels in newborns.** **a** | The graph shows a dramatic increase in catecholamine during parturition. Note the logarithmic ordinate (*y* axis); noradrenaline levels are increased for a few hours before, during and after birth. **b** | Comparison of catecholamine levels in normal newborns, newborns after anoxic insults, newborns after elective caesarian sections (C-sections), women during parturition and adults under various conditions. Note that other than asphyxiated newborns, babies born by vaginal birth have catecholamine levels that are several orders of magnitude higher than in any other conditions, including C-sections (see REFS 3,127,128,131 for more details). Adapted from REF. 125 with permission from Patricia Wynne.

including poor communication and social interactions[152,153,155]. I suggest that a modest approach aimed at reducing abberrant oscillations as early as possible, combined with social therapeutic interventions, might attenuate disease progression in children with autism. In the complex cascade of events leading from an *in utero* insult or altered early neuronal development to ASD lie important opportunities for more detailed investigations of the setting–resetting function of brain activity during birth and early postnatal periods, and its roles in the emergence of ASDs.

Note added in proof

In a recent paper, Du *et al.* report that treatment with bumetanide combined with applied behaviour analysis (ABA) training may result in a better outcome in children with autism than ABA training alone[156].

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Competing interests statement
The author declares competing interests: see Web version for details.