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Circuits for social learning: A unified model and application to Autism Spectrum Disorder

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Abstract

Early life social experiences shape neural pathways in infants to develop lifelong social skills. This review presents the first unified circuit-based model of social learning that can be applied to early life social development, drawing together unique human developmental milestones, sensitive learning periods, and behavioral and neural scaffolds. Circuit domains for social learning are identified governing Activation, Integration, Discrimination, Response and Reward (AIDRR) to sculpt and drive human social learning. This unified model can be used to identify social delays earlier in development. We propose social impairments observed in Autism Spectrum Disorder are underpinned by early mistimed sensitive periods in brain development and alterations in amygdala development to disrupt the AIDRR circuits. This model directs how interventions can target neural circuits for social development and be applied early in life. To illustrate, the role of oxytocin and its use as an intervention is explored. The AIDRR model shifts focus away from delivering broad treatments based only on diagnostic classifications, to specifying and targeting the relevant circuits, at the right time of development, to optimize social learning.

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Declaration of Competing Interest

Professor Ian Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012–18). He is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and an equity shareholder in, Innowell. Innowell has been formed by the University of Sydney and PwC to deliver the $30 m Australian Government-funded 'Project Synergy'. Project Synergy is a three year program for the transformation of mental health services through the use of innovative technologies. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017–20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies.

Keywords

Social development; Social cognition; Oxytocin; Social skills training; Neurodevelopment; Amygdala; Research domain criteria; Infant; Biomarkers; Parent-child interaction; Bonding

1. Introduction

From the first moments of life, infants attune to their parents to share nurturing experiences for developing lifelong social skills. These learning experiences increase in complexity over time to shape and consolidate neural networks for social development. Sensitive learning periods in development are key to the consolidation of this social learning, with genetic factors influencing this potential for neural shaping (Takesian and Hensch, 2013). Early atypicalities in neural sculpting are believed to characterize the development of Autism Spectrum Disorder (ASD; Conti et al., 2015), a diagnosis currently based on the observation of a persistent reduction in social responsivity and a proclivity toward restricted and stereotyped behaviors (American Psychiatric Association, 2013). This neural divergence is proposed to begin prenatally or in the early post-natal period, explaining the alterations in eye gaze patterns (Jones and Klin, 2013) and reduction of cortical responsivity (Lloyd-Fox et al., 2018) to social cues in the first 6 months of life. This divergence often develops into a recognized observable behavioral phenotype by 18 months of age (Landa and Garrett-Mayer, 2006; Ozonoff et al., 2008; Zwaigenbaum et al., 2005); see recent discussion about regression patterns (Boterberg et al., 2019; Ozonoff and Iosif, 2019). Unfortunately, it appears that by the time diagnosis is made, commonly years after the emergence of symptoms (Bent et al., 2015), there has been a prolonged period of divergent neurodevelopment (Courchesne et al., 2011a; Emerson et al., 2017; Hazlett et al., 2017) and a missed opportunity for optimal timing of intervention.

2. Typical social development

Experience sculpts and refines neural connections throughout early life, a process that begins *in utero*. By 35 weeks gestation, fetuses show preference for native language (Graven and Browne, 2008; Kisilevsky et al., 2009), and by 38 weeks fetuses can distinguish their mother’s voice (Kisilevsky et al., 2003). At birth the affinity for parental voice (Ockleford et al., 1988) and innate preferences for visual social stimuli are evident, as greater attention is given to faces (Johnson et al., 1991) and biological motion (Simion et al., 2008) than equivalent nonsocial stimuli. Behaviorally, social developmental milestones are well-established (Frankenburg et al., 1992; Schaffer, 1996). Imitation is present throughout early development, beginning with facial mimicry in newborns (Meltzoff and Decety, 2003). At about 2–3 months of age, most infants will return smiles and by about 4 months begin to smile spontaneously (Gerber et al., 2010; Schaffer, 1996; Shultz et al., 2018). By 6 months, infants begin to make reciprocal sounds in response to language directed toward them (Frankenburg et al., 1992; Gerber et al., 2010; Shultz et al., 2018). By the end of the first year of life, most infants can gesture (waving, shaking head), respond to pointing and will follow parental gaze direction (Brooks and Meltzoff, 2005; Frankenburg et al., 1992; Gerber et al., 2010). Pretend play is generally evident by 18 months (Gerber et al., 2010; Schaffer,

1996). By 2 years of age, most children have basic phrase speech and can follow simple instructions (Gerber et al., 2010; Schaffer, 1996).

3. A circuitry approach to social development

There is a need for an integrated model that explains the process of early human social development. There have been many high caliber studies identifying basic mechanisms and broad clinical factors that facilitate social learning (Fitch et al., 2016; Gabard-Durnam et al., 2018; Graham et al., 2016; Grayson and Fair, 2017; Grossmann, 2015; Pitcher et al., 2017; Vasung et al., 2010). As yet there has been no model to bridge this research and stimulate translational human applications. In this paper, we propose a unified integrated model of the processes that underlie social learning. The model identifies neural and behavioral markers for typical social development. These markers could be applied to enable earlier identification of delay, identify novel treatment targets to improve outcomes, and provide direction for real-world applications.

It is well established that the amygdala and its connections are critical for early life social development (Saygin et al., 2015). The amygdala is the most densely connected structure in the primate brain (Putnam et al., 2018); linking cortical and subcortical regions, it coordinates social and affective behavior (Putnam et al., 2018). The amygdala develops early in gestation: it is identifiable at 8 weeks (Muller and O'Rahilly, 2006), is structurally connected at 13 weeks (Vasung et al., 2010) and is structurally mature by 8 months (Ulfig et al., 2006), the same period during which fetuses learn the emotional tone of voice (Kisilevsky et al., 2009). Structural connections *in utero* (Vasung et al., 2010) and functional connections at birth (Graham et al., 2016) lay the framework for the amygdala as the core structure facilitating social development. Early resting state functional connectivity studies of the amygdala in neonates (measured within the first month of life) have evidenced lasting behavioral associations at 6 months (Graham et al., 2016) and 2 years (Rogers et al., 2017) of age.

The amygdala has an important but discrete role in social development, likely as a gatekeeper that coordinates and integrates processing between other critical circuits for attention (Hennessey et al., 2018), sensory integration (Pitcher et al., 2017), motor coordination (Grezes et al., 2014), and reward (Stuber et al., 2011). We propose it plays a crucial role for facilitating the ability to engage and learn from social experiences (e.g. nursing, play) within the caregiver-infant dyad. This is a multi-stage process that we propose can be defined by Activation, Integration, Discrimination, Response and Reward (AIDRR) circuits, illustrated in Fig. 1. This novel model is based on a synthesis of current evidence of early social development in animals and humans.

To begin to learn from social experiences an infant must have the capacity to be alert and to orient attention. Alertness can be both tonic, state-based (e.g. wakefulness), and phasic, cue-based (e.g. responding to gaze; Keehn et al., 2013). In newborns, tonic alertness initially develops rapidly, as newborns spend more time awake (Keehn et al., 2013), followed by increases in phasic alertness as infants learn to follow cues (such as pointing; Keehn et al., 2013). Orienting is the process of selecting and attending to information from sensory input,

for example, initiating and maintaining eye gaze (Keehn et al., 2013). It interacts with alertness and can be either automatic or conscious (Keehn et al., 2013). This activation gathers information from multiple sensory stimuli which are synthesized into a coherent signal, a process we term integration. Integration requires cognitive flexibility and control to appropriately weigh attention to multiple sources of information in order to form an integrated whole (Iarocci and McDonald, 2006). Early in development, temporal synchrony is vital for learning new objects, however, as the infant develops more automatic integration skills, synchrony becomes less key and the infant is able to extra-polate (Gogate et al., 2000). Discrimination, of the salience (strength) and valence (positive or negative value) of the integrated signal informs response (Janak and Tye, 2015). The development of this discrimination is evident by 7 months as infants attend more to a combination of affectively coherent auditory and facial information, compared to when this combined information is incoherent (Grossmann, 2010). This process informs an adaptive response, which is rewarded when positively received. Reward has two known and complementary effects (Delgado, 2007). Firstly, the circuit pathway for the adaptive behavior is consolidated (Delgado, 2007). Secondly, anticipation of future predicted opportunities to engage and receive reward is reinforced to enhance conditioned preferences (Delgado, 2007). It is proposed that the repeated engagement of the AIDRR pathways results in gradual consolidation of what is learned over time, making the AIDRR process rapid and automated.

4. The neural pathways of AIDRR

There have been outstanding reviews of discrete brain regions and separately, specific social behaviors that are important for social learning (Adolphs, 2009; Fitch et al., 2016; Grayson and Fair, 2017; Grossmann, 2015; Hennessey et al., 2018; Janak and Tye, 2015; Johnson et al., 2009). These models are drawn upon to describe, and are integrated into, the neural pathways that facilitate the AIDRR processes and how they develop during early childhood. There is evidence to suggest the pathways that regulate AIDRR are primarily coordinated by the amygdala, particularly the basolateral amygdala (BLA). This is based on functional and structural connectivity findings linking it to the superior temporal sulcus (STS; Abivardi and Bach, 2017; Iidaka et al., 2012), orbitofrontal cortex (OFC; Abivardi and Bach, 2017; Grezes et al., 2014), motor regions (Grezes et al., 2014) and the striatum (Cohen et al., 2009). The amygdala facilitates cortical responsivity, theorized to result in increased sensitivity to social stimuli (Adolphs and Spezio, 2006). This information is then synthesized into a coherent signal, utilizing the bidirectional links between the amygdala and STS (Iidaka et al., 2012), a key node for integration (Beauchamp et al., 2004). This coherent signal is projected back to the BLA, which has distinct neuronal circuits dedicated to positive and negative affective stimuli (Janak and Tye, 2015). This affective association is relayed to the OFC, which stores representations of stimuli and valence associations (Saddoris et al., 2005). The response is adapted by projections from the amygdala to the motor cortex (Grezes et al., 2014). The BLA also connects to the nucleus accumbens and this link facilitates reward for engagement with stimuli, developing and reinforcing social approach behaviors (Delgado, 2007; Janak and Tye, 2015).

We propose that the development of cortical specialization to facilitate the AIDRR steps is driven by the amygdala and its projections. The connections of the amygdala sculpt the

rapidly developing cortex, a process enhanced by interactive experience (Johnson, 2000), as the cortically diffuse connections of the amygdala become gradually refined throughout childhood (Saygin et al., 2015). For example, the subcortical face processing system dominates at birth but gradually develops a specialized cortical network (Johnson, 2005). In the first few years of life, functional connectivity of the BLA to the sensory and motor regions increases (indicating strengthening), theorized to be reflective of growing amygdala-cortical connections (Gabard-Durnam et al., 2018) and a mechanism whereby adaptive motor responses are directed. The OFC-amygdala connection does not show this effect (Gabard-Durnam et al., 2018), likely reflective of the early establishment of the OFC functioning. The BLA is positively connected to the striatum, facilitating the reward component of AIDRR (Delgado, 2007). The dorsal striatal pathway reinforces the adaptive response while the ventral pathway (with the nucleus accumbens) activates to predict future reward (Delgado, 2007). These projections from the amygdala therefore lay the foundations for habitual and automatic responses to be seemingly integrated within more complex, goal-directed behaviors (Johnson et al., 2009), creating functional cortical specialization that continues into adulthood (Johnson, 2005).

The AIDRR model can be used to study how known developmental risks influence the function of specific circuits. The impact on AIDRR, and hence the ability to learn from social experiences, will be dependent on developmental timing and severity of the risk experience. For example, rhesus macaques separated at 1 week of age show decreased social behavior in later life, while those separated at 1 month show increased social affiliative attempts (Sabatini et al., 2007). These behavioral differences in response to early life risk are accompanied by alterations in the expression of a gene (GUCY1A3) in the amygdala (Sabatini et al., 2007). These observed alterations were dependent on the timing of the maternal separation. Analogous effects of early life adversity have been also shown in humans, investigating cohorts that have experienced institutional care. These cohorts show decreased connectivity between the medial pre-frontal cortex and the amygdala, regions involved in AIDRR, compared to their non-institutionalised peers (Gee et al., 2013). In humans, such risks to AIDRR pathways may begin prenatally, with ongoing developmental impact. For example, maternal immune activation during pregnancy has recently been proposed as potentially important to the development of social difficulties in some ASD cases (Patel et al., 2018) and early life circuits (Careaga et al., 2017). The AIDRR model provides targets for assessment of human social development (Fig. 2) to investigate the specific effect of developmental risk factors on circuit development.

5. Alterations in neurodevelopment in ASD

Many of the genes and pathways found to be involved in ASD are related to neural wiring and synaptic function (Bozdagi et al., 2010; De Rubeis et al., 2014; Gilman et al., 2011) and these may alter the normal progression and timing of amygdala development and connectivity. We propose two critical brain development processes characterize the initial development of social impairments observed in ASD and AIDRR disruption. These are *in utero* or perinatal alteration to amygdala development (both in function and connectivity), and mistiming of known sensitive periods for cortical development. These alterations result in a reduction of shaping potential. The severity of disruption may further negatively

influence child engagement with learning opportunities. Early social withdrawal by the child can result in multiple compensatory and adaptive mechanisms in the caregiver relationship to further reduce social learning opportunities (Wan et al., 2018). There is an important distinction to be made between the point of onset, the genesis of social difficulties in ASD, and the point of differentiation, when research is currently able to identify the developmental differences at a statistically significant level. At present, research is unable to identify the point of onset, but we propose it is prenatal, with alterations in cortical-subcortical interaction caused by divergent amygdala development and functioning.

It is known that by 2 years of age there is statistically significant overgrowth of the amygdala in children with ASD (Mosconi et al., 2009), which continues up until 4 years (Mosconi et al., 2009; Munson et al., 2006; Nordahl et al., 2012; Schumann et al., 2009). The greater amygdala size (theorized developmental disruption) the larger the decrease in social responsivity (Munson et al., 2006; Schumann et al., 2009). This is significant as lower initial responsivity is a key predictive factor of longer-term intervention outcomes (Ben-Itzchak and Zachor, 2007). Although significant differences are only found in amygdala volume at 2 years of age, the early divergence of the amygdala function and consequent disruption of the AIDRR circuitry is theorized to result in reduced cortical responsivity to social cues between 4 and 6 months (Lloyd-Fox et al., 2018).

Sensitive periods of brain development appear mistimed in ASD, resulting in early growth, e.g. increases in cortical surface area by 6 months (Hazlett et al., 2017). This is occurring without adequate sculpting from experience, the suggested mechanism through which AIDRR develops. A sensitive period is defined as a time when parvalbumin (PV) cell maturation creates an optimal ratio of excitatory/inhibitory circuit activity for cortical plasticity (Gogolla et al., 2014; Hensch, 2005; Takesian and Hensch, 2013; Toyoizumi et al., 2013). This maturation induces a sequence of molecular events that facilitate cortical plasticity and experience-dependent shaping of neural circuits by inducing neural changes, such as spine pruning, regrowth and axonal rewiring (Gogolla et al., 2014; Hensch, 2005; Takesian and Hensch, 2013; Toyoizumi et al., 2013). In children with ASD, the early experience of these sensitive periods is likely due to the genetic alterations in the mTOR/PI3K and NRXN-NLGN-SHANK pathways (Bourgeron, 2009; Chen et al., 2014; Tang et al., 2014). The mTOR/PI3K pathway is associated with abnormal synaptic growth (Bourgeron, 2009; Tang et al., 2014) and the NRXN-NLGN-SHANK is involved in synaptogenesis and balancing excitation/inhibition (Bourgeron, 2009; Chen et al., 2014).

It is proposed here that alterations to PV cells and sensitive periods (Gogolla et al., 2014; Hensch, 2005; Takesian and Hensch, 2013; Toyoizumi et al., 2013) within the BLA are a key signaling mechanism for divergent development in ASD. The PV cells fluctuate in density in the BLA throughout development (Davila et al., 2008) and influence circuit signaling in response to positive and negative stimuli (Janak and Tye, 2015). It is proposed that when this signaling is disrupted, the amygdala does not act effectively as a functional gatekeeper. This is theorized to result in divergence in the sculpting of cortical development (Takesian and Hensch, 2013) and may explain accelerated growth of frontolimbic regions in ASD (Courchesne et al., 2011a, 2003; Courchesne et al., 2001, 2011b; Courchesne and Pierce, 2005; Redcay and Courchesne, 2005; Schumann et al., 2009). For instance, the

amygdala's connections in adults (Abivardi and Bach, 2017) are critical for social and emotional regulation (Kim et al., 2011). In children with ASD, larger amygdala volume is associated with greater impairments in social attention (Mosconi et al., 2009) and social reciprocity (Nordahl et al., 2012; Schumann et al., 2009), reflecting its functional importance as the gatekeeper of socioemotional learning and regulation. Divergence in early life amygdala development is believed to result in initial reductions in social attention (e.g. by 6 months of age; Jones and Klin, 2013). This may also have a compounding influence on broader social communication skills later in life (Charman, 2003). A likely contributor to these early neurodevelopmental alterations is the increasingly recognized impact of epigenetic factors, such as DNA methylation across multiple brain regions within the frontal and temporal lobes that overlap with the localization of AIDRR (Ladd-Acosta et al., 2014; Nardone et al., 2014; Wong et al., 2019). The application of the AIDRR framework creates new opportunities for early identification of divergence by focusing on markers of circuit processes that support social learning across development. It also emphasizes the critical importance of coordination and interaction between these circuits. Disruption in one circuit is likely to negatively impact other circuits. Further, no single circuit on its own will explain all social developmental divergence.

Specific social and behavioral impairments proposed to result from disruption of the AIDRR pathways in ASD are now provided as examples. These are drawn from across the lifespan as relatively little research has been conducted identifying risk markers for ASD in the first months of life. In terms of activation, tonic alerting is facilitated by arousal levels, with evidence of both hyper- and hypo- arousal in children with ASD (Keehn et al., 2013). Hyper-arousal is proposed to result in sensory overload and difficulty integrating multi-sensory information, while hypo-arousal may result in poor attention and reduced aptitude for learning from the environment (Keehn et al., 2013). For example, the pupil light reflex, a measure of stimulus-based arousal, appears overly responsive in the first year of life for some infants later diagnosed with ASD (Nystrom et al., 2018). In terms of phasic (cue-based) alerting, children with ASD show a reduction in the automatic processing of stimuli (Keehn et al., 2013), as indexed by decreased amplitude in the event-related potential (ERP) markers of N1c and Nc to novel stimuli (Keehn et al., 2013; Marco et al., 2011). In regards to the orienting component of activation, by 6 months of age infants later diagnosed with ASD evidence reduced automatic gaze shifts to the eyes (Jones and Klin, 2013). Challenges in activation are compounded during multisensory integration, as evidenced by reduced amplitude of and delay in ERPs following multisensory stimuli (Marco et al., 2011). Divergence in discrimination is also apparent, with the P400 response to eye movements reduced in infants later diagnosed with ASD (Elsabbagh et al., 2012). Response impairments are evident by 1 year for those later diagnosed with ASD; those who later receive a diagnosis show less turning in response to a researcher calling their name (Nadig et al., 2007). Finally, reduced sensitivity to social reward (compared to monetary reward) is evidenced in children with ASD (Demurie et al., 2011). This is accompanied by functional divergence in circuitry associated with both reward anticipation and reception (Supekar et al., 2018).

We note the emergence of cohort studies identifying early life risk markers in infancy (Emerson et al., 2017; Gammer et al., 2015; Hazlett et al., 2017; Jones and Klin, 2013;

Landa and Garrett-Mayer, 2006; Lloyd-Fox et al., 2018; Rozga et al., 2011; Wan et al., 2013; Wolff et al., 2014; Zwaigenbaum et al., 2005). These studies are expensive, time-consuming and challenging to conduct. Equivocal results on different markers have been noted in these early studies (Gammer et al., 2015; Landa and Garrett-Mayer, 2006; Rozga et al., 2011; Wan et al., 2013; Wolff et al., 2014; Zwaigenbaum et al., 2005). Research addressing possible developmental sub-types (Ozonoff and Iosif, 2019) and the use of more precise theoretical models of child development to guide measurement is required. This AIDRR framework provides new targeted opportunities to sensitively measure circuits and their interactions in a coordinated and comprehensive manner to support such studies

6. Current treatments for ASD

Traditional interventions for ASD focus on creating social learning experiences. Social-learning therapies that have been developed for ASD include the Early Start Denver Model (Rogers, 2016), Parent Child Interaction Therapy (Hembree-Kigin and McNeil, 2013), Applied Behavior Analysis (Foxx, 2008), Pivotal Response Therapy (Koegel et al., 1999) and parent-mediated communication-focused treatment (Green et al., 2015). Recent reviews provide excellent summaries of the current evidence-base regarding the state of early intervention trials (French and Kennedy, 2018; Green and Garg, 2018). In practice, social learning interventions are currently recommended at the point of diagnosis but are often not implemented until much later (Liptak et al., 2008). Efficacy of these therapies has been primarily demonstrated through caregiver questionnaires and observations of play between the child and researcher, clinician or parent (Wong et al., 2015). There is some evidence, however, that these social learning interventions are less effective when provided after the age of 4 (Harris and Handleman, 2000). Further, they vary widely with respect to skill focus, intensity and length of program (Dawson, 2008) and to the degree that they are adapted to the needs of the child (Jaswal and Akhtar, 2018). Therapies often begin with developmentally appropriate, simple, clear stimuli with highly directive instructions. These can begin with focusing on directed attention (e.g., Starting with focusing attention on a smile: “look at the smile, see what makes a smile”), which are interpreted (“they’re smiling, that means they are happy”) and followed by an adaptive directed response (“smile back”). When an adaptive response is provided, it is reinforced. Reinforcement may be provided by the therapist or caregiver with high levels of joy and encouragement expressed and by the giving of explicit reward. Gradually, a social repertoire may build from relatively simple social tasks, into more complex tasks. Successful learning of these tasks requires integration of multiple sensory inputs and more complex responses (introducing yourself and responding to conversation), although there is great heterogeneity in progression across social skills between children (Dawson, 2008). Innate responsivity of the child to this process has been proposed to strongly influence the outcomes of such interventions, along with factors such as the resources of the families to invest time into the learning process (Liptak et al., 2008). Children without verbal skills, those with attentional deficits, or those with lower assessed intelligence quotient seem to show poorer responses to therapy (Eapen et al., 2013).

Examination of the effects of social skill treatment on the shaping of neural circuits is limited. An open label group study of 19 children with ASD (mean age 5.8) who received

Pivotal Response Therapy showed increased coupling of the posterior cingulate and the occipital-temporal cortex with decreased coupling of the posterior cingulate and the OFC (Venkataraman et al., 2016). The lack of evidence supporting neural changes following behavioral therapies may reflect the fact that treatments are being implemented too late to make more significant neural changes, and it follows that waiting until the point of diagnosis unnecessarily reduces the possibility of early interventions to improve outcomes.

More recently, a new wave of early intervention studies have targeted infants at risk of social impairment in ASD between the ages of 7 and 12 months (Green et al., 2015, 2017; Jones et al., 2017; Rogers et al., 2014). At risk is defined as those with older siblings diagnosed with ASD (Green et al., 2015, 2017; Jones et al., 2017) or with early signs of ASD (Rogers et al., 2014). These interventions focus on care-giver attention to infant social engagement and encouragement of positive and sensitive responding. One open-label study with 9-month old at-risk children provided 12 h (1 h a week for 12 weeks) of intensive social intervention and found reduced ASD symptomology and lower rates of ASD diagnosis at 3 years of age (Rogers et al., 2014). Other similar studies have reported improved social attention (Green et al., 2017; Jones et al., 2017) up to 3 years of age (2 years post intervention; Green et al., 2017). Excitingly, one study reported that the P400 in response to faces, improved to typically-developing levels by 12 months of age (Jones et al., 2017). This suggests a first potential biomarker of improvement in AIDRR behavior (discrimination). This marker is particularly relevant to ASD cohorts as the P400 has been implicated in early social impairments in ASD (Elsabbagh et al., 2012). We propose that these interventions work within the AIDRR framework, encouraging development of the relevant circuits, similarly to the impact of more established interventions outlined above. It is proposed that the early life timing of these interventions enhances the learning outcomes, facilitated by increased neural plasticity. AIDRR may be best applied as a framework for broad dimensional social developmental risks that transcend single diagnostic categories (e.g., ASD). A deeper understanding of the AIDRR pathways can inform future treatment approaches.

7. Novel interventions for ASD based on the AIDRR model

The AIDRR model describes pathways that can be targeted and sculpted during developmentally sensitive periods. Currently, best practice interventions require structured therapy and support to engage children in the AIDRR process. A neural enhancement approach focuses on optimizing learning and brain development to improve lifelong outcomes, rather than the mechanisms by which children might have developed a diagnosis of ASD. By utilizing a more developmentally proximal approach to intervention, and understanding the circuits that guide learning, new markers of change based on AIDRR circuits and interventions that target this change can be developed. The BLA, key in the AIDRR circuitry, should be a primary target of intervention. Moreover, a focus on circuits will also result in identification of developmental windows of opportunity where these circuits might be most malleable, although much work remains to understand how such neural malleability might be targeted to accelerate human developmental learning for children with ASD. Research is, however, emerging to suggest the potential of new therapies, such as oxytocin (DeMayo et al., 2017), vasopressin modulators (Bolognani et al., 2019; Parker et al., 2019), dopamine agonists (Kim et al., 2018) and stimulants (Hara et al.,

2016) in augmenting windows for social learning. We argue that such benefits might emerge through their influence on AIDRR circuits. Understanding the potential of using environmental situations and therapies that stimulate endogenous release of natural modulators will be critical. The safety and utility of exogenous therapies will need careful evaluation. The influence of these new therapies may be further potentiated via their interaction. This was evidenced in a recent study that showed long-term effects on oxytocin induced by 3,4-methylendioxymethamphetamine (MDMA) in mice (Nardou et al., 2019). MDMA adminstration re-opened the sensitive period for social learning, illustrating influence on AIDRR.

8. Oxytocin applied as an example of next generation intervention

At present, oxytocin appears to be the most promising endogenously stimulated or exogenously adminstered treatment to target the AIDRR components. Oxytocin, a naturally occurring neuromodulator and hormone, is synthesized within the hypothalamus and stored in and released by the pituitary (Meyer-Lindenberg et al., 2011). Endogenous oxytocin release is highly sensitive to environmental stimuli (Uvnas-Moberg and Petersson, 2005). Socially rich experiences such as touch, eye gaze, massage, intimacy and playful interactions have all been linked to the release of oxytocin (Uvnas-Moberg and Petersson, 2005). The role of oxytocin in enhancing social behavior is well-established (MacDonald and MacDonald, 2010) but there is little research providing guidance around how to apply this knowledge to improve outcomes in early life. Investigation of oxytocin at present is predominantly focused on a time when AIDRR pathways are relatively entrenched (above 6 years of age; DeMayo et al., 2017). Further, trials have not measured AIDRR pathways specifically and the opportunity to capitalize on enhanced learning (for example, by delivering simultaneous behavioral interventions) has not been embraced. To encourage this translation, we illustrate how oxytocin might offer a potential agent to alter neural excitability and manipulate the disrupted pathways in ASD, utilizing research from both animals and humans.

We propose that one function of oxytocin release is to facilitate AIDRR pathways. Oxytocin’s effects on the amygdala are well documented (Bethlehem et al., 2013), aligning with the central role of the amygdala in the AIDRR model and its role as the functional gatekeeper. Oxytocin has also been linked to neural plasticity (Rajamani et al., 2018), so it may simultaneously work on AIDRR while creating optimal opportunities to sculpt these pathways.

Current research suggests that oxytocin improves activation. In mice, oxytocin administration enhances function of the subcortical olfactory bulb which drives the function of the olfactory cortex (Oettl et al., 2016), creating scent sensitivity. Oxytocin administration increases the signal to noise ratio (Owen et al., 2013) and sensitivity to sensory stimuli (Marlin and Froemke, 2017; Marlin et al., 2015; Oettl et al., 2016) through alterations in the excitatory/inhibitory balance that modulate cortical responsivity (Marlin and Froemke, 2017; Marlin et al., 2015; Oettl et al., 2016; Owen et al., 2013). This effect may be partly due to oxytocin receptors located on PV cells, believed to modulate cortical inhibition (Marlin et al., 2015). Analogously, for activation in humans, alterations in functional connectivity

following administration (Grace et al., 2018) may increase the signal to noise ratio and enhance stimulus propagation. Oxytocin increases pupil dilation (Leknes et al., 2013) and flexibility in respiratory sinus arrhythmia (Weisman et al., 2012), markers indicative of enhanced capacity for adaptability and responsivity to sensory signals. In terms of orienting, the localization of oxytocin receptors within the visual system supports a role for oxytocin in reflexive gaze shifts to visual stimuli (Freeman et al., 2014a, b; Freeman and Young, 2016).

During integration, oxytocin is involved in strengthening the pathways that create a coherent signal from multiple senses. In rodents, it is linked to the development of cross-modal sensory association cortices (Zheng et al., 2014). The removal of whiskers (somatosensory deprivation) or dark rearing (visual deprivation) decrease the cortical firing of the non-deprived cortices, oxytocin secretion and cortical oxytocin (Zheng et al., 2014). In humans, intranasal administration studies of oxytocin in children and adolescents with ASD have found increased activation of the STS (Gordon et al., 2016; Grace et al., 2018), insula (Riem et al., 2011) and precuneus (Gordon et al., 2016), regions known to be key for integration. Further, oxytocin administration has been linked to increased coupling of the STS and the amygdala (Riem et al., 2012), which may facilitate greater capacity for sensory attention and integration (Pitcher et al., 2017; Redcay, 2008). Behaviorally, oxytocin has been shown to sharpen feelings associated with the combination of sensory information (Ellingsen et al., 2014). To illustrate, when a smiling face is viewed with a gentle human touch, intranasal oxytocin enhances the associated positive feelings (Ellingsen et al., 2014). The converse occurs for frowning faces, where oxytocin and touch results in a more negative appraisal of face stimuli (Ellingsen et al., 2014).

In terms of discrimination, oxytocin in the medial amygdala is critical for social recognition in mice (Ferguson et al., 2001). While in humans, oxytocin induced alterations in functional activity of the amygdala have been linked to performance on a broad range of social-cognitive tasks (Bethlehem et al., 2013; Gamer et al., 2010). Nasal oxytocin administration enhances attention to the eyes (Guastella et al., 2008a) and improves emotion recognition (Guastella et al., 2010). This is proposed to be coordinated by the OFC and amygdala, which work in concert to develop associations between cue-based stimuli with feelings of reward and fear to create emotional learning (Kringelbach, 2005). These regions are anatomically linked (Janak and Tye, 2015) with oxytocin fibers found within the OFC (Rogers et al., 2018). The action of oxytocin on these two regions is theorized to strengthen the ability to develop these links and discriminate social salience. The OFC is complemented by the actions of the anatomically proximal anterior cingulate (AC), which also has oxytocin fibers (Rogers et al., 2018), and has shown enhanced functional activation following intranasal oxytocin administration (Riem et al., 2012). Oxytocin within the AC is necessary for prairie voles to comfort a distressed cagemate (Burkett et al., 2016), illustrating oxytocin's importance in discriminating cue-based associations. In humans the function of the AC is debated, though it has recently been proposed to optimize control efforts (Shenhav et al., 2016). The action of the AC is theorized to complement the OFC (Shenhav et al., 2016), focusing control on experiential learning, a function potentially enhanced by oxytocin.

Oxytocin improves the development and consolidation of a response. Virgin mice can learn to respond to pup distress calls and oxytocin administration accelerates the acquisition of

this learnt response (Marlin et al., 2015). In humans, oxytocin appears to facilitate social imitation, as following oxytocin administration individuals are more influenced by video of another completing a distinct motor task (De Coster et al., 2014).

There are converging lines of evidence that support the important links oxytocin has with the striatum and, therefore, reward processing. Across rodents, there is a positive correlation of oxytocin receptor density in the striatum and parental responsiveness to non-related pups (Olazabal and Young, 2006). Relatedly, there is a positive correlation between parental responsivity to offspring and oxytocin receptor density within the striatum in prairie voles (Olazabal and Young, 2006). This attachment is proposed to be facilitated by oxytocin-induced enhanced coordinated activity within the ventral striatum (Johnson et al., 2016, 2017). In humans, oxytocin receptors are dense within the striatum, offering a mechanism through which genetic oxytocin receptor pathways influence striatal connectivity (King et al., 2016; Loth et al., 2014). These genetic links appear particularly pertinent in ASD, as genetic variation within the oxytocin receptor pathway appears to contribute to alterations in reward circuitry and symptoms (Hernandez et al., 2017). For children and adolescents with ASD, intranasal oxytocin has been found to increase activation within the striatum (Gordon et al., 2013), an effect theorized to increase the reward associated with social processing. Further, in adult women, oxytocin induced increased activation within the striatum and regions important for integration and social processing (such as STS, precuneus, insula and frontal lobe; Bethlehem et al., 2017) illustrating how striatal reward could link back to other parts of AIDRR to reinforce pathways.

The effects of oxytocin on reward circuits are facilitated by its interactions with dopamine (Young and Wang, 2004). Throughout animal literature, both oxytocin and dopamine are critical for social learning. It is postulated that oxytocin develops the social salience and valence connections which are reinforced by the experience of the dopaminergic reward (Shamay-Tsoory and Abu-Akel, 2016). For example in prairie voles, pair bonding, the formation of monogamous partnership, relies on both oxytocin and dopamine (Walum and Young, 2018; Young and Wang, 2004). Administration of these agents can induce the pair bond in the absence of mating and antagonizing dopamine-2 (D2) receptors can block the formation of a pair bond (Young and Wang, 2004).

Further, the administration of MDMA has been shown to re-open sensitive periods via long-term depression of oxytocin receptors in the NAcc, a key reward region (Nardou et al., 2019). This long-term depression in the NAcc appears specifically to facilitate social-reward learning, highlighting both the interactive effects of oxytocin with other systems and providing a mechanism through which oxytocin may increase the reward component of AIDRR.

9. Oxytocin and moderating factors

Despite the promising evidence of pathway manipulation (summarized in Fig. 2), results of the efficacy of exogenous oxytocin for ASD on social outcomes are mixed (DeMayo et al., 2017). We argue this is to be expected as most trials do not specifically measure AIDRR related outcomes, target treatment at the optimal stage of development, or include a social

learning intervention that is adapted to the individuals needs. Nor do most trials account for individual differences in responsivity to oxytocin manipulations that can target AIDRR circuits. Genetic linkage studies show links between oxytocin receptor genes and ASD (LoParo and Waldman, 2015; Quintana et al., 2019), with particular relevance for social impairment symptoms (Lerer et al., 2008). One important study has shown that lower levels of endogenous oxytocin prior to intranasal oxytocin administration predicted greatest response in children with ASD aged 6–12 (Parker et al., 2017).

To best capitalize on the optimized pathways, oxytocin should be manipulated, potentially either endogenously or exogenously, early in development during sensitive periods and paired with behavioral intervention. To intervene early, the onset of social impairment needs to be identified at a much younger age than it is presently and needs to focus on the specific social impairment rather than a diagnosis. This would allow the intervention to be better matched to the needs of the child. The need for this early oxytocin manipulation is evidenced in animal models. Both MAGEL2 and Cntnap2 mutant mice (models for ASD) exhibit genetically determined alterations in oxytocin synthesis and receptor sites that are associated with social deficits (Meziane et al., 2015; Penagarikano et al., 2015). Early in life administration of oxytocin to these mice either within the first week of life (Meziane et al., 2015) or during weeks 2 and 3 postnatal (Penagarikano et al., 2015), restores social behaviors long-term and alters the oxytocin system, trending towards normalization. Such early intervention in humans, however, has not yet been evaluated. A recent review reported that intranasal oxytocin was safe and well-tolerated across 261 children in 10 pediatric studies (DeMayo et al., 2017). The study with the youngest participants with ASD was 3–8 year-olds and it reported oxytocin increased social responsiveness (Yatawara et al., 2016). A recent open-label study, however, targeted infants with Prader-Willi Syndrome, finding oxytocin administration was tolerated by children less than 6 months of age (Tauber et al., 2017). Further, there was enhanced activation of the OFC in resting state fMRI activity induced by intranasal oxytocin in this age group (Tauber et al., 2017), one neural pathway of AIDRR.

For exogenous oxytocin to be administered for effective manipulation of the AIDRR pathways, intranasal delivery needs to be well understood and controlled within pediatric populations (DeMayo et al., 2017). Relatively little is known about nose-to-brain intranasal delivery, though progress has been made in developing an oxytocin tracer to rectify this (Beard et al., 2018). AIDRR emphasizes a need to efficiently and reliably target these brain circuits. It is theorized oxytocin reaches the brain through uptake via one of, or a combination of, the olfactory, trigeminal, and peripheral routes (Quintana et al., 2016). The developmental trajectory of these routes, however, is not understood (DeMayo et al., 2017). Children have a differently shaped nasal cavity, with the smallest cross-section being more anterior than in adults (Riechelmann et al., 1993). This alters spray deposition which may complicate access to olfactory and trigeminal routes, the routes most likely to offer direct access to the brain. Children also show cycles of congestion and decongestion of both nostrils, resulting in large variations of nasal flow over time that further alters deposition and absorption (Van Cauwenberge and Deleye, 1984). These are critical factors for effective nasal delivery, which have largely been unexplored but require urgent investigation (DeMayo et al., 2017).

10. Promise and future directions

The National Institute of Mental Health has highlighted the importance of circuitry approaches for understanding, treating, and evaluating change in mental health and developmental disorders, under the Research Domain Criteria (RDoC; Insel, 2014). There is clear benefit to such circuitry-based approaches for creating a coherent multidimensional and transdiagnostic approach to understanding human behavior and to facilitate interdisciplinary research on understanding complex neurodevelopmental processes (Casey et al., 2014). AIDRR presents a circuit-based framework that has potential to transcend diagnostic boundaries for social development, identify potential markers of learning and social skill acquisition, and to develop synergistic learning and circuit based interventions, under the 'Systems for Social Processing' RDoC objective (Cuthbert and Insel, 2013).

This framework enables better understanding of the dynamic processes underpinning social learning without being constrained to the prediction of specific diagnostic categories. This is key as divergent social development is common across many neurodevelopmental disorders (Casey et al., 2014). This framework enables better understanding of the dynamic processes underpinning social learning to move focus away from identifying heritable causes, behavioral correlates, and observable phenotypes for diagnostic conditions. Instead, this approach is likely to result in a nuanced understanding of circuit development and social learning for each child and a deeper understanding of how these interact. We have used the example of ASD to illustrate how the application of AIDRR can delineate divergent social development. Such multi-dimensional assessments of social learning may afford the opportunity to map markers of impairment and risk, as well as protective or resilience factors, using continuous data points (e.g. genetic, multi-omic, environmental, cognitive, neural, symptomatic and behavioral impairment) to model risk, course, intervention response, function and disability for each child. To capitalize on this approach, assessment and intervention needs to capture and augment sensitive learning periods by instigating, altering the timing of, or targeting known sensitive periods in development. Utilizing the AIDRR framework will enable more sensitive and specific markers for identifying early life divergence and facilitate a more personalized approach to intervention creating greater potential to improve lifelong health and well-being.

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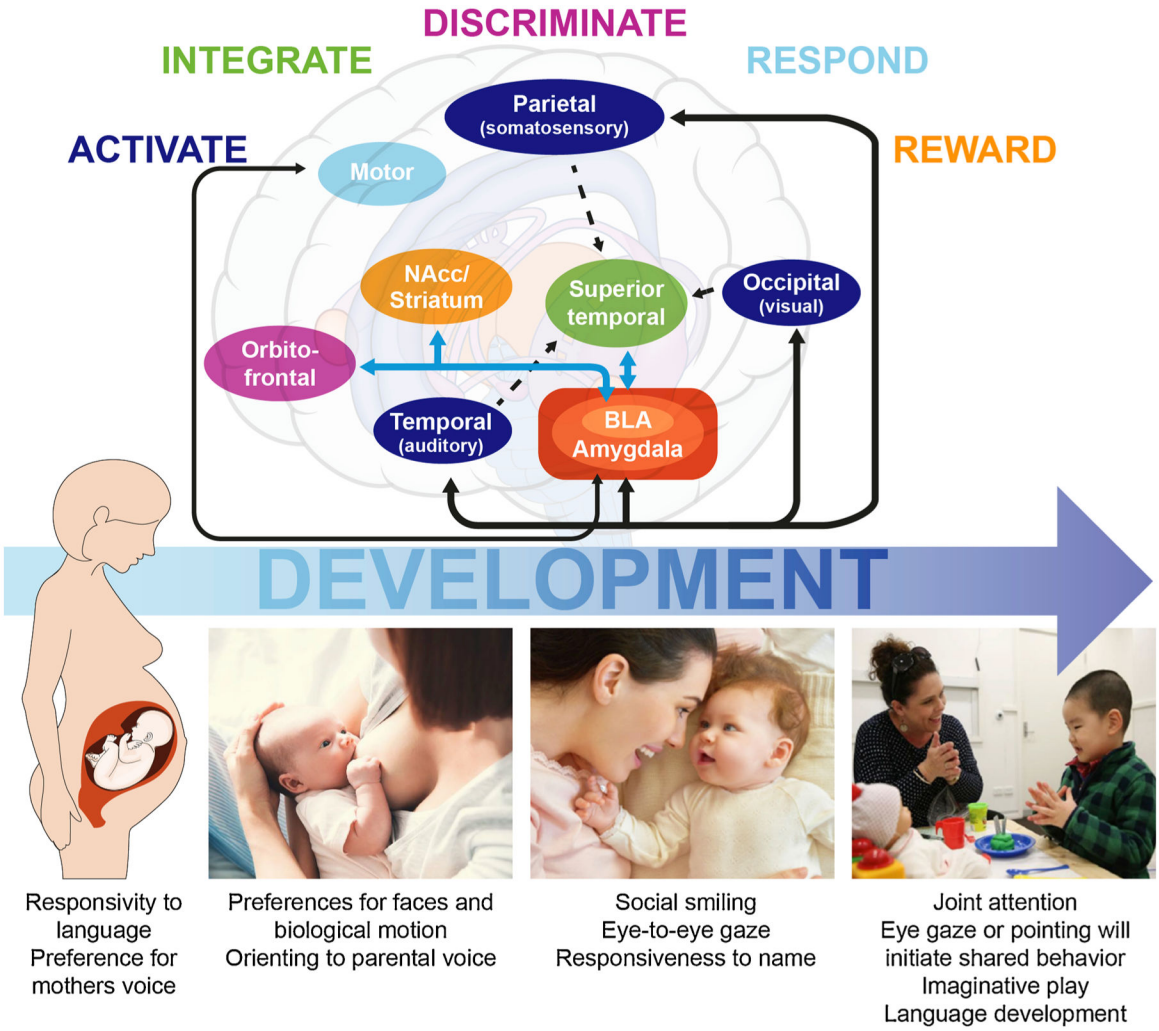

Fig. 1.

The neural pathways facilitating Activate, Integrate, Discriminate, Respond, Reward. Black bidirectional arrows from BLA to temporal, occipital and parietal lobes illustrate the link from the amygdala to the respective cortical regions that modulate responsivity, facilitating direct perception of social stimuli by the amygdala. The blue arrows show known tracts from diffusion studies, linking the amygdala directly to the orbitofrontal cortex (OFC), superior temporal sulcus (STS) and nucleus accumbens (NAcc). The amygdala-motor link directionality is theorized to be bi-directional but with the amygdala to motor path the more common direction. The colors of the AIDRR map to the predominant region: Activate (primary perceptual cortices), Integrate (STS), Discriminate (OFC), Respond (motor), Reward (NAcc/striatum).

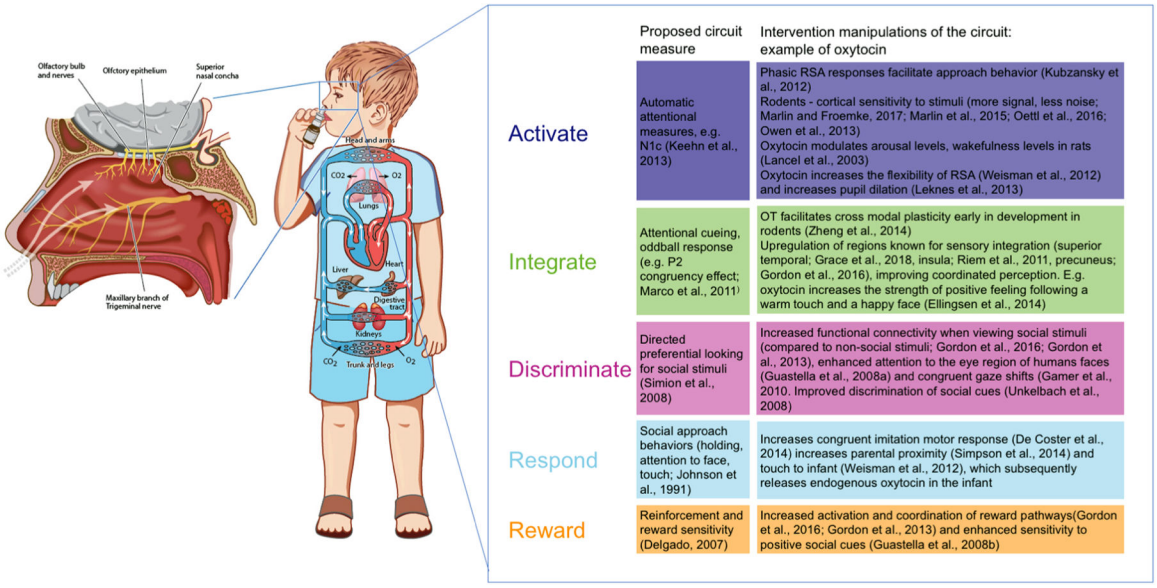

Fig. 2.

Left: the potential routes through which intranasal oxytocin exerts its neural effects, the olfactory, trigeminal and peripheral routes. Right: the proposed circuitry measures and the proposed effect of oxytocin manipulation on these circuits (Guastella et al., 2008b; Kubzansky et al., 2012; Lancel et al., 2003; Simpson et al., 2014; Unkelbach et al., 2008).