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RDoC-based categorization of amygdala functions and its implications in autism

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Abstract

Confusion endures as to the exact role of the amygdala in relation to autism. To help resolve this we turned to the NIMH's Research Domain Criteria (RDoC) which provides a classification schema that identifies different categories of behaviors that can turn pathologic in mental health disorders, e.g. autism. While RDoC incorporates all the known neurobiological substrates for each domain, this review will focus primarily on the amygdala. We first consider the amygdala from an anatomical, historical, and developmental perspective. Next, we examine the different domains and constructs of RDoC that the amygdala is involved in: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, and Arousal and Regulatory Systems. Then the evidence for a dysfunctional amygdala in autism is presented with a focus on alterations in development, prenatal valproic acid exposure as a model for ASD, and changes in the oxytocin system therein. Finally, a synthesis of RDoC, the amygdala, and autism is offered, emphasizing the task of disambiguation and suggestions for future research.

Keywords

Review; Amygdala; Autism; Research Domain Criteria; Oxytocin; Valproic Acid

1. Introduction

The principal focus of the field of social neuroscience in recent decades has been the elucidation of social brain networks capable of detecting cues, empathizing, interacting with

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others, and responding adaptively in ambiguous contexts (Dunbar, 2009; Frith, 2007; Stanley and Adolphs, 2013). An imperative of this work has been uncovering how psychiatric diseases impact these networks, particularly in autism spectrum disorder (ASD). One region consistently highlighted by this research as important in social functioning is the amygdala (Bickart et al., 2014).

The amygdala is a prime example of how neuroscience has shifted from a phrenological perspective mapping one function—fear—to one brain region and towards a network paradigm where actions arise from a dynamic affiliation of neural assemblages communicating with one another (Pessoa, 2014; Weiskrantz, 1956). The amygdala is now seen as a hub in several other, distinct networks: establishing valence or salience, cognition, reward, and social learning (Rutishauser et al., 2015). Despite its small size, the amygdala's anatomy and functioning is complex, including disparate nuclei with dense connectivity to cortical and subcortical brain regions.

Increasing knowledge of the amygdala is paralleled by new investigations of the social brain and autism. Since the original descriptions of Kanner (1943) and Asperger (1944), substantial research has been done to expand the understanding of autism leading, along with better awareness, to greatly increased rates of diagnosis (Fombonne, 2009; U.S. Department of Health and Human Services, 2014; Volkmar and Pauls, 2003; Wing, 2005, 1993, 1981; Wing and Potter, 2002). ASD's etiology remains obscure and has been posited to arise from the breakdown of particular genes, networks, or brain regions (Anney et al., 2012; Baron-Cohen et al., 2000; Markram et al., 2007; Poelmans et al., 2013; Voineagu et al., 2011). Presently, it is thought to be the product of altered expression in hundreds of genes, highly heritable, influenced by epigenetic factors, and deficits in connectivity between many different brain regions, including the amygdala (Eapen et al., 2013; Hallmayer et al., 2011; Kosmicki et al., 2017; Mintz, 2017).

Based on the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association, 2013), ASD is characterized by: “a) persistent deficits in social interaction and communication as well as b) restricted, repetitive patterns of behaviors, interests, or activities with an early onset of deficits.’ The detection of ASD is predicated on clinical measures that rely on parental reports, and on observations of the child's social aptitude during interactive tasks. These measures are crucial for diagnosing autism and categorizing the severity of symptoms. However, the DSM does not account for the vast heterogeneity of ASD and consequently it may not be the best predictor for treatment outcomes; it is thought that only 50% of individuals with ASD who receive treatment achieve significant gains as a result (Stahmer et al., 2010). In addition to improved clinical diagnosis, we need objective tools that acknowledge biological markers to demarcate variation in ASD. Towards this end the NIMH is adopting a new methodology, Research Domain Criteria (RDoC), to better characterize variation from typical behavior and enable precision medicine to improve psychiatric outcomes as it has in oncology and cardiology (Insel et al., 2010; Insel and Cuthbert, 2009). RDoC looks at psychological constructs dimensionally: from healthy to abnormal, examining the underlying genetics, neuropeptides, circuits, and physiology that ultimately gives rise to behavior (Cuthbert and Insel, 2013).

Along with renewed interest in nosology, there are questions regarding the amygdala and its contribution to neuropsychiatric disorders, including autism. Here we propose that by using RDoC to classify amygdala functions into constructs and dimensions, we can better characterize its role in normal functioning and explicate how it is altered in autism. Of the five currently defined RDoC domains—**Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, and Arousal and Regulatory Systems**—the amygdala is represented in each, within one or more constructs. The amygdala is not a unitary structure and we will decorticate its role in these domains and constructs by drawing on studies of lesions, animal behavior, in vivo and ex vivo electrophysiology, genetics, functional imaging, and optogenetics.

In this review, we will highlight: how conceptualizations of the amygdala's anatomy, development, and function within the social brain have changed overtime; amygdala functions in RDoC; dysfunction of the amygdala in autism throughout development; linkages to comorbid psychiatric disorders; amygdala alterations seen in the valproic acid (VPA) model of autism; and the effects of oxytocin (OT) on the amygdala and behavior. By understanding the diversity of amygdala functions, and the myriad ways it can be altered in autism, the route to improved therapies and outcomes for people with autism can be illuminated.

2. The Amygdala: anatomy, history, development

2.1 Anatomy

The human amygdala (Fig. 1) comprises 13 nuclei, distinguished by cytoarchitectonics, histochemistry, and connectivity with other brain regions. To greatly simplify the anatomical layout of the amygdala (see Duvarci & Pare, 2014; or Sah, et. al, 2003 for review), there are two main divisions 1) the **basolateral complex (BLA)** encompassing the **lateral (LA)**, **basal (BA)** and **accessory basal (AB)** nuclei with extensive connections to sensory and cortical brain regions and 2) the **central amygdala (CeA)** and its two sub-nuclei, the **central lateral (CeL)**, connected with the BLA, and **central medial (CeM)**, connected with brainstem areas related to the expression of innate behaviors (e.g. fear), along with the **medial amygdala (MeA)** linked to the olfactory system (Janak and Tye, 2015; LeDoux, 2008). The BLA is heavily innervated by sensory systems and the thalamus. The LA and the BA also receives information from higher-order sensory and associative cortices (Adolphs, 2009; Amaral et al., 2008). The BLA has strong efferent projections to reward regions like the nucleus accumbens (NAc), the ventral pallidum in the basal forebrain, and reciprocal connections with memory processing areas, associative and executive cortical sections, and with the CeA (Fig. 2).

2.2 Historical context

The classic studies of Klüver and Bucy in the 1930s first described the involvement of the amygdala in emotional processing by elucidating the behavioral consequences of large, non-selective temporal lesions in monkeys (Klüver and Bucy, 1939, 1937). Lesioned monkeys had 'psychic blindness' stemming from a lack of access to the value of social cues. Subsequent studies with more precise lesions of the amygdala caused more selective

behavioral disruptions: less caution and distrust in approaching novel objects (such as snakes) or human strangers, in line with the known role of the amygdala in resolving unpredictability or ambiguity (Adolphs, 2010; Bauman et al., 2006; Machado et al., 2009).

The most selective lesions of the human amygdala result from vascular damage or from Urbach-Wiethe disease (UWD), a rare autosomal disorder that causes the progressive calcification of the amygdala (Adolphs et al., 1994; Cinaz et al., 1993; Urbach and Wiethe, 1929). SM, the best described case of UWD, and other such patients showed impairments in fear recognition and autonomic conditioned responses in Pavlovian fear conditioning (Adolphs et al., 1994; Bechara et al., 1995; Cristinzio et al., 2010; Siebert et al., 2003). They also have deficits in social judgments from faces, more fixations on the mouth than the eyes during conversations, and general deficits in affective perspective taking (Adolphs et al., 1998; Hillis, 2014; Spezio et al., 2007). Individuals with UWD report experiencing no negative emotions in real life, exhibit no sensitivity to personal space, and fail to tag emotionally charged words as important to remember (Hampton et al., 2007; Hurlemann et al., 2007; Kennedy et al., 2010; Tranel et al., 2006). Research into UWD confirms the role of the amygdala not only in fear processing but also processing salient or unpredictable stimuli, and in social settings.

Historically the amygdala and the rest of the limbic system was thought of as ‘evolutionarily primitive’, and resistant to change (MacLean, 1955, 1952). However, components of the limbic system, principally the BLA, are in fact quite plastic, with evolutionary dynamism that has been attributed to the influence of social factors (Barger et al., 2007). The volume of the monkey’s BLA is about 30-40 times that of the rat, while the CeA and MeA are only four and eight times larger respectively (Chareyron et al., 2011).

Humans in turn have a BLA and, primarily, a lateral division, several times the size of any other ape or monkey (Barger et al., 2007). The LA’s neuronal density is substantially higher in the rat (99,000 neurons/mm³), compared to the monkey (42,000 neurons/mm³), and lowest in the human (9,000 neurons/mm³). This lower density reflects expanded dendritic arbors and glial populations, and greater opportunity for connections with many networks, particularly the social (Pessoa, 2014). Volume, density, and other structural elements of the amygdala are all established during development from fertilization to adulthood.

2.3 Development

In humans the BLA shows synaptogenesis from the first trimester until the seventh month, the CeA is identifiable in the fifth month, and overall neuronal migration is complete by the end of the eighth month of gestation (Schumann et al., 2011; Setzer and Ulfing, 1999; Ulfing et al., 2003). The cellular structure of the amygdala and its neurotransmitter systems are well established at birth, with similar distribution to that seen in adults (Bauman and Amaral, 2005). While the number of neurons in the amygdala does not increase, the volume grows throughout childhood and into adolescence (Payne et al., 2010; Schumann et al., 2004). This is due to significant increases in both the dendritic arbor (Fig. 3) and number of oligodendrocytes that myelinate input to the amygdala, a recapitulation of the evolutionary forces that increased its size and functionality in primates (Chareyron et al., 2012; Ryan et al., 2016).

Simultaneously, more connections are made within the amygdala between the projecting principal and local inhibitory neurons that tune the network, filtering out extraneous information and binding together the input of different sensory modalities (Ryan et al., 2012). The functional role of the amygdala shifts dramatically at these stages, especially in terms of its receptivity to external input and internal modulation. Not until the second week of rat development, (corresponding to a newborn human, Quinn, 2005), are they able to learn associations between painful shocks and odors, and to avoid them (King et al., 2014). During this same period Arruda-Carvalho et al. (2017) demonstrated with viral tracers and optogenetics that connections from the medial prefrontal cortex (mPFC) to the BLA in the mouse go from undetectable in early development (P10) to prominent by early adolescence (P15) and become increasingly functional from then on. This is just one facet of the development of the amygdala, a process that links its different nuclei to the rest of the brain and to each other.

Understanding the underlying neurobiology of the amygdala is essential to seeing how it is involved in both normal and pathological behaviors, and a cornerstone of RDoC (Cuthbert and Insel, 2013). With RDoC as a framework, we will identify the domains and circuitry that include the amygdala and are altered in autism.

3. Amygdala functions and RDoC

Using RDoC, we have here classified amygdala functions in the domains of negative valence, positive valence, cognition, social functions, and arousal. We are interested in both the behaviors and neural circuitry of these different constructs and the relative importance of the amygdala within them.

3.1 Negative Valence Systems (NVS)

Defined as “primarily responsible for responses to aversive situations or contexts such as fear, anxiety and loss,” NVS have a very strong link to the amygdala.

3.1.1 Acute Threat—The role of the amygdala in Acute Threat, i.e. fear learning, may be one of the most studied relationships in all of neuroscience. Weiskrantz (1956) first demonstrated that a lesion of the amygdala prevented monkeys from pairing an aversive unconditioned stimulus, such as a shock, with a neutral cue like a tone, the conditioned stimulus. More detailed studies in rodent models, including seminal papers by LeDoux and others, explicated which sub-regions of the amygdala (Fig. 2) are required: the UA for input, BA for associative learning, and CeM for expression (Clugnet and LeDoux, 1990; Kalin et al., 2004; Keifer et al., 2015; LeDoux et al., 1990, 1988; LeDoux, 1992; Madarasz et al., 2016; Romanski and LeDoux, 1992). The connection from the BLA to the mPFC is particularly important for acute threat; optogenetic depression of this connection both inhibited acquisition, and enhanced extinction, of fear learning (Klavriv et al., 2017). Structural and functional imaging studies in humans support a strong amygdala response to fearful faces. Recordings from implanted electrodes in epileptic individuals viewing faces reveal an extremely rapid response to fear, preceding a general response to any expression (Fullana et al., 2015; Méndez-Bértolo et al., 2016). Within the BLA, inhibition and

disinhibition of principal neurons by specific populations of interneurons is required for conditioned and unconditioned stimulus association learning to occur (Wolff et al., 2014).

In terms of neuromodulatory factors (Fig. 2), there are substantial serotonin (5-HT) inputs to the BLA from the dorsal raphe which are sensitive to the presence of stressors (Vertes, 1991). During non-stressful conditions, 5-HT release in the BLA decreases the excitability of neurons, presumably by increasing inhibition and depolarizing GABAergic interneurons (Rainnie, 1999). Conversely, the selective depletion of 5-HT in the LA results in significantly enhanced fear potentiated startle and increased expression of excitatory glutamate receptors (Tran et al., 2013). The role of 5-HT in the amygdala, in the expression of fear and anxiety, as well as the clinical implications of SSRIs are still not fully understood (for review see Burghardt & Bauer, 2013).

Dopamine is also released in the BLA during stressful situations and D1 receptors in the BLA seem to be necessary for the acquisition and expression of Pavlovian fear conditioning (Fadok et al., 2009; Muller et al., 2009). D1 receptors can have effects on long-term potentiation (LTP) induction through the modulation of NMDA receptors and facilitate the transition of salient sensory inputs and fear learning (Li et al., 2011). Dopamine also suppresses certain GABAergic interneurons of the BLA via D2 receptor activation to further boost relevant signals and promote learning (Chu et al., 2012).

3.1.2 Potential Threat and Sustained Threat—Potential Threat (or anxiety) and Sustained Threat (chronic stress) are closely related to each other, and to Acute Threat, differing in the physical or mental proximity to the perceived danger and in the time course (Avery et al., 2015; Davis et al., 2010).

Anxiety can be considered a generalization of fear learning and is an adaptive process from a survival perspective. However, overgeneralization of fear to harmless stimuli can become pathological and result in posttraumatic stress disorder (PTSD), phobias, obsessive compulsive disorder, panic disorder, and generalized anxiety disorder (Lissek et al., 2014). A delicate neuronal balance within the CeA (Fig. 2) regulates fear expression: the CeM is tonically inhibited by the GABAergic output of the CeL, which in turn is innervated by the BLA. If this balance is disrupted, and the CeM disinhibited, fear expression can generalize from conditioned, to non-conditioned stimuli as well (Ciocchi et al., 2010; Keifer et al., 2015). The MeA is also important in the response to stress, and impressive advances in single cell RNA sequencing technology recently identified a subpopulation of cholecystokinin expressing neurons activated by acute restraint stress (Crane et al., 2005; Wu et al., 2017).

The Stoop lab (2008) has shown that two neuropeptides, oxytocin (OT) and vasopressin (VP), have opposite effects on fear expression at the neuronal level in the amygdala. The CeM is excited by VP but fear responses are inhibited in the CeL, which is in turn excited by OT (Huber et al., 2005; Knobloch et al., 2012). Hence, an absence, reduction, or desensitization of oxytocin receptors (OTRs) in the CeL can lead to an imbalance at the neuronal level within the CeA and to generalized fear responses and anxiety. In rodents, chronic treatment with OT has been found to be anxiogenic at high doses (10ng/hr) but at

low doses (1 ng/hr) prevents psychosocial stress induced anxious behaviors (Peters et al., 2014).

There is increasing evidence for OT reducing fear, anxiety, and stress, in part by lowering amygdala activity (Bethlehem et al., 2013; Domes et al., 2007; Labuschagne et al., 2010; Meyer-Lindenberg et al., 2011; Petrovic et al., 2008). Researchers have found that intranasal OT facilitates the extinction of learned fear and reduces anxiety in patients with anxiety disorders (Acheson et al., 2013; Dodhia et al., 2014; Eckstein et al., 2015; Gorka et al., 2015; Labuschagne et al., 2010). It has also been shown that men with PTSD show diminished functional connectivity between the CeM and the ventromedial PFC, while in women with PTSD there is enhanced functional connectivity between the BLA and dorsal anterior cingulate cortex (ACC). OT administration normalized the functional connectivity between the amygdala and frontal areas during resting state in both sexes (Koch et al., 2016). In healthy controls though, Grillon (2013) found that intranasal OT enhanced startle response after unpredictable shock stress, which suggests that care should be taken in translating OT, it may be most efficacious specifically for anxiety related to social behaviors (Neumann and Slattery, 2016).

Considering neuromodulatory factors within the amygdala involved in stress and anxiety, norepinephrine is released into the BLA immediately following a stressful experience and enhances memory of emotionally salient events while 5-HT is released during prolonged, uncontrollable stress (Roozendaal et al., 2009). During stressful conditions there is reduced expression of serotonergic receptors (5-HT_{2A}) leading to a down-regulation in activation of GABAergic BLA interneurons, and increased excitability of BLA neurons (Jiang et al., 2009). Other 5-HT receptors can increase BLA excitability and lead to anxiety related behaviors, but infusion of the 5-HT_{2C} receptor antagonist SB242,084 into the BLA prevents the display of anxiety related behaviors in response to prolonged stressors (Christianson et al., 2010; Pockros-Burgess et al., 2014; Zangrossi and Graeff, 2014).

3.1.3 Frustrative Nonreward—The last construct in NVS linked to the amygdala is Frustrative Nonreward, reactions elicited in response to the withdrawal or prevention of reward (Amsel, 1958; Gallup, 1965; Machado et al., 2009). Frustrative nonreward is distinct from both offensive aggression which, as an expression of dominance or competition for resources is included in the social domain, and defensive aggression, one potential response to acute threat (NVS Working Group, 2011). Tye (2010) and Badrinarayan (2012) demonstrated that there was a distinct population of cells in the amygdala recruited after ‘frustrative events’ which predicted the intensity of response, and that they were unlike those neurons activated in response to freezing inducing shocks (Purgert et al., 2012).

Frustration, harm avoidance, and fear are all powerful motivators of behavior and the amygdala is involved in each construct, processing early autonomic and nonconscious stimuli that signal danger for instance, but it is also vital for the opposite mode of influence in **Positive Valence Systems**.

3.2 Positive Valence Systems (PVS)

In a world of ambiguous rewards and outcomes, the amygdala is vital for updating the value of stimuli based on the current state of the organism. The PVS domain “primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning’ is linked to the amygdala by two related constructs.

3.2.1 Approach Motivation—Approach motivation is the instigation and direction of behavior and generally entails approach when the valence is positive (Elliot and Covington, 2001; Harmon-Jones et al., 2013). Making decisions with incomplete information is a common experience, especially so in ambiguous social encounters. Key for these circumstances is awareness of what the internal state of the individual in that moment is and thus the relative value of incentives; information supplied by the amygdala and areas, like the OFC, that it is connected with (Gottfried et al., 2003; Janak and Tye, 2015). In terms of motivated behavior, the mPFC seems to play an important role in balancing the relative contributions of the NAcc and the amygdala (Ernst et al., 2006). Recent optogenetic studies by Kim et al. (2017, 2016) have also revealed a strong role for a subpopulation of BLA projections to genetically distinct CeL and CeM neurons in driving appetitive behaviors.

3.2.2 Reward Learning—The differential response of the BLA as a result of positive or negative learning (or valence encoding) can be seen in human fMRI studies as well as electrophysiology studies of non-human primates discriminating between cues; when those cues are reversed, some ‘positive’ or ‘negative’ neurons stopped responding, or were inhibited, demonstrating that it was not the sensory features of the cue that were triggering them, but the values they represented (Gottfried et al., 2003; Paton et al., 2006; Shabel and Janak, 2009). In rodents BLA neurons can be distinguished not only based on where they connect to, e.g. the NAc, part of the reward network, but also by what genes they express, as well as their firing patterns, allowing more fine grained dissections of how positive and negative signals are encoded in the brain (Beyeler et al., 2016; Jennings et al., 2013; Namburi et al., 2015).

OTR expression is an important modulator of the reward network. During reward anticipation, healthy individuals carrying the OTR rs2268493 autism risk allele showed decreased activation of the right amygdala and other parts of the reward network compared to non-carriers and heterozygotes (Damiano et al., 2014). Importantly, lesioning the amygdala does not impair all reward based behaviors, only those specifically related to changing reward value (Machado and Bachevalier, 2007). There is evidence of increased BOLD activity in the amygdala during monetary reward-learning and decision-making tasks. For example, the framing effect from economics where a participant’s decisions about which option to select is manipulated by presenting the choice in terms of either potential loss or gain; this effect is correlated with activation of the amygdala (De Martino et al., 2006).

The amygdala’s function in reward processing is part of a network of brain regions (Fig. 2) including the orbital frontal cortex (OFC) and NAc (Montague and Berns, 2002). Lesions that disconnect the amygdala from the OFC results in deficits on reward learning tasks

(Baxter et al., 2000). It appears that the amygdala acquires information about the value of stimuli and the OFC uses this to guide choices (Happé and Frith, 2014). Disrupting the connection between the amygdala and NAc can lead to deficits in instrumental behavior toward rewards (Ambroggi et al., 2008). Following the acquisition of information, the amygdala communicates the sensory aspects of stimuli to the NAc to guide approach behavior and reward learning by modulating dopaminergic neurons (Jackson and Moghaddam, 2001; Stuber et al., 2011).

The PVS domain, and within it the amygdala, has a fundamental role in initiating, and shaping activities, but command of thoughts and actions requires input from **Cognitive Systems**.

3.3 Cognitive Systems

In addition to the primary role of the amygdala in modulating emotional states, it has a crucial function at the perceptual level in integrating sensory information about stimuli. This domain, “responsible for various cognitive processes” covers a very large range of behaviors, one of which is the construct of attention, or salience.

3.3.1 Attention—The process by which the brain assigns attention to various stimuli depends on careful coordination of the top-down, value assigning areas, such as the dorsolateral PFC and inferior parietal cortex, associated respectively with appraisal and reappraisal (Ochsner et al., 2012); and the bottom-up middle frontal gyrus and superior parietal cortex, responsible for directing the visual gaze (Ferri et al., 2016). This coordination takes place within the amygdala in conjunction with the anterior insula and ACC (Fig. 2) as part of the larger saliency network (Jacobs et al., 2012; Rai et al., 2012). Interestingly, there is increased functional connectivity between the amygdala and the precuneus and dorsal ACC when resisting distraction particularly from arousing, negative images (Ferri et al., 2016; Kanske et al., 2011). This balancing of top-down control and bottom-up input requires the precise functioning of the inhibitory circuits within the amygdala that regulate its activity (Rainnie et al., 1991a, 1991b; Truitt et al., 2007).

Perception of fearful stimuli could be considered one highly specialized and conserved task of the amygdala within the larger context of salience assigning (Jacobs et al., 2012). To that end, some inputs from sensory thalami, and nociceptive signals from the pontine parabrachial nucleus (PBN), bypass the LA and project directly to the CeA (Fig. 2), allowing for very rapid and adaptable responses to danger signals (Keifer et al., 2015). The amygdala also has a role in gating connections between the cortex to the hippocampus and striatum tagging experiences with emotional marks, of any valence, which increases their salience and improves recall and learning (Hurlemann et al., 2007; Paz and Pare, 2013; Vuilleumier and Driver, 2007).

Attention control is vitally important for navigating any number of situations, but especially those involving **Social Processes**.

3.4 The Social Processes

These constructs “mediate responses to interpersonal settings of various types, including perception and interpretation of others’ actions.”

3.4.1 Affiliation and Attachment—The first construct in the social domain, Affiliation and Attachment, concerns both the initial engagement in positive interactions as well as the development of bonds that reinforce and motivate the communication constructs. In both non-human primates and humans, amygdala volume is positively correlated with the size of an individual’s social network (Bickart et al., 2011; Zhang et al., 2012). The enlargement of the BLA (Section 2.2) is correlated with, and may be the result of, a concomitant expansion in the cortical regions related to social behavior that it is connected with (Janak and Tye, 2015; Stephan and Andy, 1977). Direct evidence for the role of the amygdala in social motivation can be seen by lesioning the BLA which causes rats to stop preferring prosocial rewards (Hernandez-Lallement et al., 2016). In addition, optogenetic stimulation of BLA projections to the mPFC reduces social interaction and increases anxiety-like behavior, while inhibition of that same pathway increases social interaction in mice (Felix-Ortiz et al., 2016).

Particularly important in the discussion of attachment and the amygdala is the function of OT. This neuropeptide is released in key socio-emotional brain regions, including the amygdala, which is rich in OTRs. OT is known to modulate a wide range of social behaviors, such as maternal attachment, pair bonding, social recognition and empathy-based behaviors (Burkett et al., 2016; Ferguson et al., 2001; Johnson et al., 2016; Rilling and Young, 2014). OT acting on the amygdala also enhances social attachment, possibly by reducing fear and anxiety (section 3.1).

In accordance with the animal literature, there is substantial evidence in humans showing that OT plays a crucial role in maternal care and maternal motivation. Though the circuitry of human parental care is more elaborate than in rodent species, the reward and sub-cortical components involved in the motivational and emotional aspects of parenting are common to both. This circuitry includes (Fig. 2) the hypothalamus, ventral striatum, and amygdala (Feldman, 2015).

3.4.2 Social Communication—The next construct in Social Processes, Social Communication, and the sub-construct Reception of Facial Communication (including either implicit or explicit communication such as affect recognition, facial recognition and characterization) clearly involves the amygdala, particularly in the perception of emotions that signal danger, e.g. fear or anger (Adolphs et al., 1999, 1998; Gamer and Buchel, 2009). The amygdala’s role was formerly thought to be only in automatic and non-conscious rapid processing of such stimuli (LeDoux, 1996; Morris et al., 1999; Öhman et al., 2007). Today, we know that the purview of the amygdala is broad, neuroimaging studies show that the amygdala is activated in response to all faces, and not only to fearful expressions (Fitzgerald et al., 2006). These studies also show that the involvement of the amygdala in processing information from faces is complex, can show inter-individual variability, and is dependent on context (Adams et al., 2003; Kim et al., 2004).

The involvement of the amygdala in controlling attention and ambiguity resolution extends to this construct: SM's fear recognition impairment (Section 2.2) appears to arise from a failure to make spontaneous use of the eye region of faces, a potent source of disambiguating social information (Adolphs et al., 2005). In addition, it has been shown that when interpreting equivocal expressions positive interpretations are associated with decreased amygdala activation, and negative with increased (Kim et al., 2003; M. J. Kim et al., 2011). The amygdala's response to faces is also dependent on the motivational state of the perceiving individual; Radke (2015) discovered that testosterone administration biased individuals towards threat approach and increased amygdala activation, but decreased activity during threat avoidance. Anatomical differences affect facial reception as well; Zhang (2012) found a strong correlation in monkeys between larger amygdala and longer periods of gazing into the eye region of other monkeys. There is also evidence that the function of the amygdala in interpreting gaze changes throughout development, with amygdala size in children positively correlated to *cognitive* mental state inferences and in adults to *emotional* ones (Rice et al., 2014).

Clearly the amygdala has a significant role in social bonding and communication, how important is it for the last domain in RDoC, **Arousal and Regulatory Systems**?

3.5 Arousal and Regulatory Systems

These constructs “are responsible for generating activation of neural systems as appropriate for various contexts, and providing appropriate homeostatic regulation of such systems as energy balance and sleep.”

3.5.1 Arousal—In studies of arousal, which is distinct from both salience and anxiety, activation of the amygdala is linked with increased vigilance (Pessoa, 2011). After electrostimulation of a cat's amygdala Ursin and Kaada (1960) noted an “attention response” and orienting around the environment. Stimulation of the CeA's connection to the basal forebrain results in more activation of cholinergic neurons, including those that innervate the BLA (Fig. 2), increasing the signal-to-noise ratio therein (Davis and Whalen, 2001; Unal et al., 2015). In monkeys that have undergone neonatal removal of the amygdala there is an enhancement of CRF activity and HPA axis activation suggesting that early in development the amygdala acts as a brake on the arousal system but switches to an activator in maturity (Raper et al., 2014).

3.5.2 Circadian Rhythms—Coordinating biological activity to times of day and the light-dark cycle is a function of the superchiasmatic nucleus (SCN) and the rhythmic expression of ‘clock’ genes that serve as transcription factors (Reppert and Weaver, 2002). These same genes are expressed in other subordinate sites throughout the brain and body, including the amygdala (Harbour et al., 2014).

4. Amygdala dysfunction in Autism

The separation of a heterogeneous clinical population by biomarkers holds great promise in the treatment of many complex psychiatric disorders but particularly in autism (Clementz et al., 2016; Loth et al., 2016). Using biomarkers, such as characteristics of the amygdala, to

parcellate ASD allows the development of targeted therapies and facilitates overall understanding of autism.

4.1 Alterations in Development and Neurobiology

One of the hallmarks of autism is that it is a developmental disorder; though diagnosis typically occurs between 2-7 years, precursor symptoms can be identified even in the first six months of infancy (Hazlett et al., 2017; Jones and Klin, 2013; Mandell et al., 2005; Mazurek et al., 2014). In healthy subjects the amygdala continues to elaborate throughout childhood and adolescence, some connections with forebrain regions are still being strengthened even in adulthood, most notably with the mPFC (Chareyron et al., 2012; Ehrlich et al., 2012; Ernst et al., 2006; Lenroot and Giedd, 2006; Schumann et al., 2011). Indeed, the amygdala has more connections with distinct parts of the brain than almost any other region (Pessoa, 2014, 2008; Petrovich et al., 2001; Young et al., 1994). It is important then to see how exactly prominent characteristics of autism can be linked with altered amygdala development.

While many studies have found enlargement of the amygdala in autism, others have found no change, or a decrease in volume (Aylward et al., 1999; Haar et al., 2016; Nordahl et al., 2012; summary in Allely et al., 2013). We believe this is evidence of subgroups of individuals with autism, and that improvements in care and treatment require a close examination of these seemingly discordant findings, and replication with larger groups (Müller and Amaral, 2017). In addition to altered development in the amygdala, we will look at changes in connectivity with major neural networks, and how these variations compare symptomatically with damage to the amygdala that can come from UWD (section 2.2) or other sources.

4.1.1 Volume differences—Enlarged amygdala were among the first brain anomalies to be identified in individuals with autism (Bauman and Kemper, 1985; Kemper and Bauman, 1993; Schumann et al., 2004; Sparks et al., 2002). This increase is age dependent; Nordahl et al. (2012) found the amygdala was enlarged from 2-4 years and that the rate of increase year over year was higher in children with autism. An enlarged amygdala was also found to correlate with more severe symptoms in toddlers (Schumann et al., 2009). But from 8-14 years and older the increase slowed or reversed, no differences are seen between adolescents with typical development vs. those with autism (Barnea-Goraly et al., 2014).

This early overgrowth in the amygdala in children with autism could be related to later excessive pruning, accounting for volume differences seen between children, but not adults, with autism (Amaral et al., 2008). Dziobek et al. (2010) and Eilam-Stock et al. (2016) found no size differences in adult individuals with autism, although Murphy et al. (2012) found significant increases in amygdala volume in their comparison of individuals with Asperger's vs. typically developing controls. One important proviso is that there is a significant degree of heterogeneity. While Nordahl et al. (2012) found that on average children with autism had enlarged amygdala, there were a considerable number whose amygdala development was on par or decreased relative to typically developing individuals.

Does normalization of amygdala volumes in older adolescents and adult individuals with autism correlate with improvements in social abilities? Although adolescent subjects with autism's amygdala growth does not differ on the whole from typically developing subjects, increases in eye contact in those with autism correlates with increased amygdala size (Barnea-Goraly et al., 2014). In children with autism there is a positive relationship between amygdala volume, eye gaze, and response to joint attention, with smaller amygdala predicting less eye gaze, stronger symptoms, and non-response to bids for attention (Mosconi et al., 2009; Nacewicz et al., 2006). Unaffected siblings also have smaller amygdala and decreased eye gaze but they, like typically developing controls, do not show a relationship between amygdala volume and eye gaze (Dalton et al., 2007). Interestingly, Williams syndrome, a rare autosomal disorder characterized by mild to moderate cognitive impairments and hypersociability, is associated with an *enlarged* amygdala, along with an overall decrease in brain volume (Schumann et al., 2011). Ultimately, the change in size could be a consequence, rather than cause, of social interaction (Zalla and Sperduti, 2013). When the number of individuals in a monkey's social group was altered, the volume of the amygdala also changed (Sallet et al., 2011). If this translates to humans, then amygdala size during development could serve as a biomarker for effective therapeutic intervention.

A stereological comparison of cell types in the amygdala between those with autism and typically developing controls found that before 20 years of age there were no differences, but afterwards there was a significant drop in myelinating oligodendrocytes (Morgan et al., 2014). Thus, it is essential to look beyond gross anatomical differences of the amygdala to alterations in its activity, how it connects with other areas of the social brain, and what significance this has for the pathogenesis of autism.

4.2.1 Abnormal amygdala activity and social cognition—Social deficits are a second hallmark of ASD. The amygdala, along with regions like the superior temporal sulcus (STS) and OFC (Fig. 2), are an essential part of the neurobiological substrate of social cognition. Early neuroimaging of ASD individuals revealed decreased activation in the amygdala and frontal areas during social tasks such as reading the mind in the eyes (Baron-Cohen et al., 1997). Other studies revealed a lack of amygdala activity during the implicit processing of emotional facial stimuli (Critchley et al., 2000). Functional neuroimaging studies have found that abnormal amygdala activation in ASD is, reminiscent of SM, related to decreased eye fixations to faces (Dalton et al., 2005; Kliemann et al., 2012).

In addition to a lack of amygdala activation, individuals with autism show a significant reduction in functional connectivity between the amygdala, principally the BLA, with cortical, visual, and parietal regions involved in perception during resting state (Rausch et al., 2016). This reduction in functional connectivity was also seen between the amygdala and the salience network including the insula (Von Dem Hagen et al., 2014). However, there are a number of attentional and social deficits in ASD, independent of the amygdala, and it's bilateral destruction is insufficient to produce autism, as determined by clinical measures (Paul et al., 2010; Wang et al., 2014).

4.1.3 Damage to the amygdala—In comparative studies between people with autism and focal amygdala lesions (Section 2.2) there are several similarities in their behavioral phenotypes: abnormal social judgment regarding the rating of trustworthiness and approachability in faces, difficulties in identifying emotional features from facial expressions, impairments in judging faces with negative affect such as fear and anger, and abnormalities in attributing social meaning to ambiguous and moving shapes (Adolphs et al., 2001; Klin, 2000; Pelphrey et al., 2002). What's more, individuals whose amygdala are removed due to a tumor or refractory epilepsy also display significant deficits in Theory of Mind tasks, but only if the damage occurred in their childhood (<16 years old, Shaw et al., 2004). Loss of the amygdala from UWD appears to impair the saliency network's (Section 3.3.1) ability to prioritize emotionally charged inputs (Hurlemann et al., 2007). This phenomenon is similar to the weak central coherence model of autism from Happé and Frith (2006): a focus on details rather than the whole.

This suggests autism does not arise exclusively from the functioning of the amygdala, as a complete lesion would be expected to result in the most severe social dysfunction (Paul et al., 2010). It suggests instead a change in *how* the amygdala develops and functions is responsible, and that modeling these developmental disruptions can be a useful way to understand autism.

4.2 Valproic acid and autism

Valproic acid (VPA) is the most widely prescribed anti-epileptic drug in the world, as well as a potent teratogen (Perucca, 2002). VPA exposure during pregnancy is linked with fetal valproate syndrome (FVS) characterized by dysmorphic facial features, spina bifida, lower IQ, delayed language, and autism in approximately 9% of those exposed (Ardinger et al., 1988; Clayton-Smith and Donnai, 1995; Jäger-Roman et al., 1986; Rasalam et al., 2005; Williams et al., 2001; Williams and Hersh, 1997). FVS is thought to result from the effects of VPA on the developing central nervous system in the 1st trimester of pregnancy (Binkerd et al., 1988; Christianson et al., 1994; but see Rouillet et al., 2013). VPA is to date the only environmental agent so strongly linked to autism (Bromley et al., 2013; Christensen et al., 2013; Ornoy et al., 2015)

How exactly the epigenetic changes wrought by VPA contribute to FVS and autism is still unknown. By promoting the acetylation of histones, VPA makes DNA more accessible to transcription factors, altering the course of development, and ultimately the neural systems underlying cognitive and social domains (for review see Chomiak et al., 2013). Much of the work in explicating this process has been done in animal models: As originally developed by Rodier (1997) fetal exposure to VPA resulted in rats that were less sociable and more anxious, a finding that has been replicated many times (K. C. Kim et al., 2011; Mabunga et al., 2015; Markram et al., 2008; Rouillet et al., 2013 but see Cohen et al., 2013; Štefánik et al., 2015). VPA exposed rats also display hyperserotonemia, one of the oldest known biomarkers of autism (Anderson et al., 2011, 1990; Hranilovic et al., 2007; Narita et al., 2002; Takahashi et al., 1976).

The amygdala is significantly altered along several dimensions following prenatal VPA exposure. In rats, VPA changes the volume of the amygdala and drastically alters dendritic

arbors of principal neurons, following a progression that is comparable to humans, with initial overgrowth of spines at the time of weaning, followed by a retraction in the fully-grown rat (Amaral et al., 2008; Bringas et al., 2013; Sosa-Díaz et al., 2014). This may be related to increases in the excitability of LA neurons, facilitating LTP, and contributing to behavioral alterations in the model (Lin et al., 2013). VPA exposure changes the expression of many amygdala genes including *Homer1*, a notable finding as overexpression of *Homer1* in the amygdala leads to a reduction in social interaction and impaired fear conditioning (Banerjee et al., 2016; Oguchi-Katayama et al., 2013). We have also observed that VPA exposure in the rat significantly increased OTR expression in the female, but not male, CeA (authors, unpublished).

Two caveats: First, though rodent models of autism are crucial for better understanding the neurobiological mechanisms of social functioning, most of the behavioral tests that are used in these experiments do not mirror the complexity of social dysfunction seen in ASD. The autism phenotype is heterogeneous and not restricted to a lack of social approach, the gold standard measure in the majority of animal studies (Moy et al., 2004; Tordjman et al., 2007). Second, the use of a teratogen as the agent for creating autism-like symptoms must be reconciled with autism's high heritability (Hallmayer et al., 2011). But the fact that this model is not the product of a single gene mutation makes it in many ways more representative of the broad swath of individuals whose autism is not related to any known monogenic cause. Autism is associated with higher rates of de novo protein truncating mutations, and more severe autistic symptoms and intellectual disability are associated with the highest rates of mutations (Kosmicki et al., 2017).

4.3 Autism, anxiety, and oxytocin

Besides the core social symptoms in ASD, there are several medical, neurological, and psychiatric comorbidities, including disorders of: anxiety, depression, obsessive-compulsiveness, sleep, irritability, and hyperactivity. Anxiety disorders in particular are much more common in individuals with autism than in the general population, with estimates ranging from 40-55% of young people with autism also exhibiting one or more anxiety disorders (van Steensel et al., 2011; White et al., 2009). Currently, there are two FDA approved drugs (risperidone and aripiprazole) for comorbid symptoms of irritability. There are no approved treatments for the social dysfunctions of ASD or for anxiety disorders in these individuals.

In addition to reducing fear and anxiety (Section 3.1.2) intranasal OT has been shown to promote social functioning, gaze to the eyes, and theory of mind, in both typically developing individuals, and those with autism, as well as activity in, and functional connectivity between, key brain regions involved in social and emotional processing, such as the amygdala (Andari et al., 2016, 2010; Aoki et al., 2014; Auyeung et al., 2015; Gordon, 2014; Guastella et al., 2010; Watanabe et al., 2016, 2015, 2014). A recent meta-analysis reported significant associations between ASD and the OXTR SNPs rs7632287, rs237887, rs2268491 and rs2254298 (LoParo and Waldman, 2015). Importantly, one of these SNPs (rs237887) was found to be strongly associated with recognition memory in individuals with ASD, their parents and their siblings, suggesting a critical role of the OT system in social

recognition (Skuse et al., 2014). We have also demonstrated that the administration of intranasal OT triggered reciprocal cooperation between individuals with ASD and partners in an interactive social game (Andari et al., 2010). Finally, OT differentially altered BOLD activity in the amygdala during an interactive social game, reducing it with an equitable partner but increasing it with an untrustworthy one (Andari et al., 2016).

More research is needed to better understand the mechanism by which OT affects social cognition in these individuals, and whether it can also be a treatment for co-occurring anxiety (Andari, 2016).

5. Conclusion: synthesis of RDoC, the amygdala, and autism

While we have described each of the domains and constructs of RDoC, and their associated neural networks, as independent systems, they exist in dynamic equilibrium. Evaluating competing needs: fear of punishment vs. possibility of reward, or interest in complex systems vs. in conspecifics, is one of the essential tasks of the brain across all species and all levels of development. Disruption of this mechanism, manifested in one construct or many is, in a sense, the definition of mental illness; especially so in autism.

Consider an amygdala dependent ability that cuts across several RDoC domains: disambiguation. It is a difficult task, though one that typically developing individuals accomplish with relative ease: **Attention** must be switched across multiple contextual levels, salient details extracted and judged. The challenge increases if the information is **social** in nature, given the unwritten mores and subtleties of that domain. Imagine how, **stressful**, and **frustrating** that task would be, and how little **motivation** to pursue it, were it not intrinsically **rewarding**. Mental bandwidth is not limitless and, once exhausted, individuals with autism might retreat to spaces where cause and effect are clear, and where they have control over the stimuli they experience i.e. stereotypes.

This line of thinking about autism has several implications. It explains some discordant fMRI findings in the amygdala: hypoactivation when bandwidth demand is low and potent stimuli such as the eyes are unengaged, hyperactivation otherwise, such as when the subject is specifically instructed to look at the eyes (Baron-Cohen et al., 1999; Critchley et al., 2000; Dalton et al., 2005; Kleinhans et al., 2010; Kliemann et al., 2012; Schultz, 2005; Zürcher et al., 2013). The highest degree of amygdala activation, and association with symptom severity, occurs when judging ambiguous expressions (Swartz et al., 2013; Tottenham et al., 2014). Madarasz (2016) directly studied the role of the amygdala in disambiguation by examining changing cue contingencies; neurons in the LA not only store sensory associations, they update dynamically when new information is presented. Kim et al. (2016) found two populations of genetically distinct, positive and negative valence responding neurons in the BLA that not only independently drove or repressed behaviors, but mutually inhibited one another. Meanwhile, Burgos-Robles et al. (2017) demonstrated that when rats were faced with competing fear and reward signals it was a connection from the BLA to the prelimbic mPFC that predicted animal's behavior, and that that outcome could be biased towards or away from freezing by activation or inhibition of that connection. Together these studies suggest a potential neurological substrate involving the amygdala that may account

for why some individuals with autism have difficulty discerning important details within complex inputs and committing to a course of action.

As the classification of the amygdala as a single brain structure was questioned decades ago, there are calls now to abandon ASD as unsuitable for neurobiological research (Davis and Whalen, 2001; Swanson and Petrovich, 1998; Waterhouse et al., 2016). We, like Müller and Amaral (2017), think this is unwarranted. Instead, by embracing RDoC, grasping how variations from neuron to brain are reflected dimensionally across domains of behavior, in typically developing and individuals with autism, we can fulfil the promise of individualized medicine, finding optimal outcomes for everyone with this disorder. We conclude that there are likely dysfunctions in the amygdala of many, but not all, individuals with autism, and that investigation of this relationship remains a very fruitful area of research.

In addition to adoption of RDoC, four specific issues in this field call out for further study: 1) Much of autism research (and biomedical research generally) is done in males, and while a gender disparity in autism does exist, bias in subject selection may serve to exaggerate it (Beery and Zucker, 2011; Giarelli et al., 2010; Mandy et al., 2012; Robinson et al., 2013; Stone et al., 2004; Werling and Geschwind, 2013a, 2013b). Evidence strongly suggests the amygdala is sexually dimorphic, and this may be related to the higher incidence of ASD in males but more studies in females with ASD are needed to explore this possibility (Baron-Cohen et al., 2011, 2005).

2) Most neuroimaging studies of individuals with autism look at only a single time point, while the few longitudinal studies have only 1-4 years between measurements (Courchesne et al., 2011; Hazlett et al., 2017; Mosconi et al., 2009; Nordahl et al., 2012). Since amygdala connections are elaborated well into the second decade of life, imaging studies are clearly needed on this timescale, especially if monitoring the size and growth trajectory of the amygdala could serve as a biomarker for effective therapeutic intervention (Ernst et al., 2006; Lenroot and Giedd, 2006; Ruggeri et al., 2014; Uddin et al., 2011).

3) While fMRI studies are useful for finding large scale changes in activity and connectivity, experiments using implanted electrodes would reveal precisely how information flow between the amygdala and social brain is altered (Rutishauser et al., 2013). Since electrophysiological studies in humans are necessarily in populations with significant comorbidities, such as epilepsy, this is one area that animal models, e.g. VPA, would prove useful (Jeffrey et al., 2013; MacFabe et al., 2007; Meletti et al., 2012; Mormann et al., 2015; Rutishauser et al., 2015; Sato et al., 2011).

4) Promising therapies, such as oxytocin, can be fully realized only through a detailed understanding of how exactly they do, or do not, work in the brains of individuals with autism, especially in critical areas like the amygdala (Bales et al., 2013; Young and Barrett, 2015). To translate research on the effects of acute administration of intranasal OT into clinical therapeutics, it will be necessary to adopt a precision medicine approach to determine OT's targets in autism. More studies and replications of OT treatment's effect on functioning and development, particularly with chronic vs. acute exposure, are needed.

It is our hope that researchers can move to address these and other significant gaps in knowledge, deepening our understanding of a remarkable brain area, and improving the wellbeing of millions of individuals with neuropsychiatric disorders.

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Highlights

- A novel approach for categorizing numerous amygdala functions with RDoC criteria
- Advances in understanding of the amygdala, autism, and their interrelation.
- Oxytocin and VPA: two tools for discerning dysfunction in autism and the amygdala

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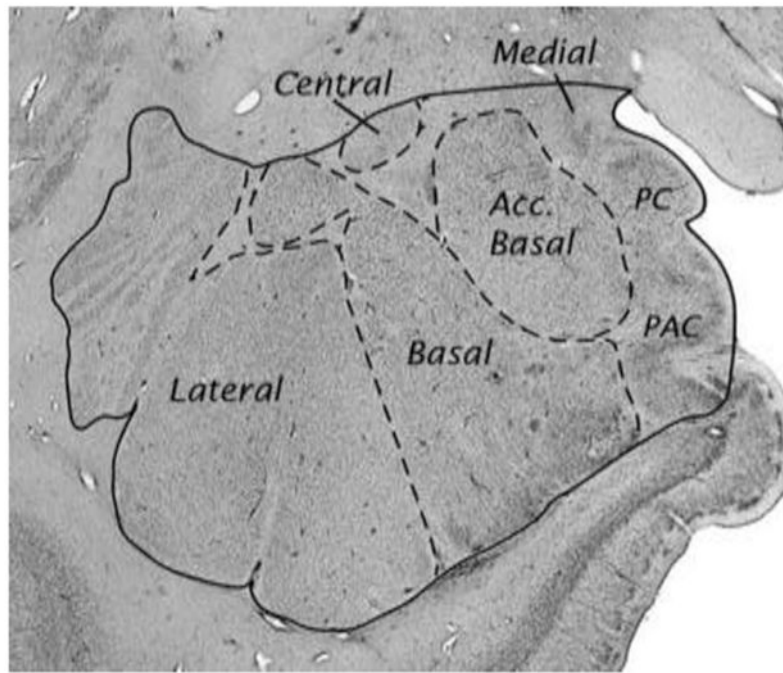


Figure 1:
The human amygdala, *from* Schumann 2011.

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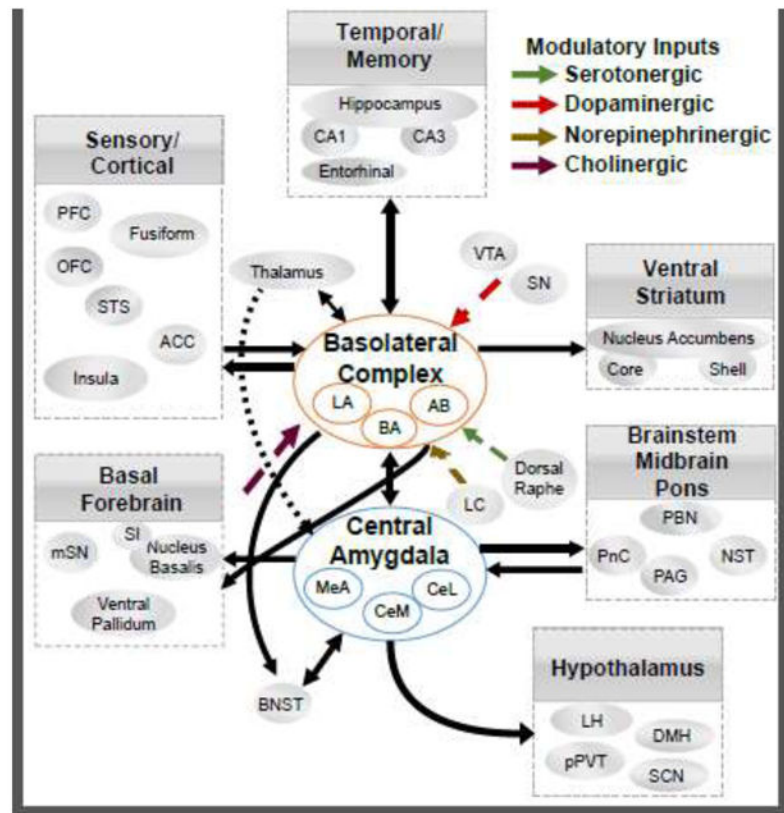


Figure 2: Components, inputs, and outputs of the amygdala.

The BLA has bidirectional connections to sensory and cortical areas including the Insula, Fusiform gyrus, Prefrontal Cortex (PFC), Orbital Frontal Cortex (OFC), Anterior Cingulate Cortex (ACC), and Superior Temporal Sulcus (STS), as well as temporal memory areas including CA1 and 3 of the Hippocampus, and Entorhinal cortex. The BLA innervates the Ventral Striatum, including the Nucleus Accumbens core (NAcc) and shell (NAcs), and the Bed Nucleus of the Stria Terminalis (BNST) which is also connected with the CeA. Monoaminergic modulation of the BLA comes from the Dorsal Raphe, Ventral Tegmental Area (VTA), Substantia Nigra (SN), and Locus Coeruleus (LC). The CeA is connected to the Basal Forebrain including the Medial Septal Nucleus (mSN) and the Substantia Inominata (SI), which contains the Nucleus Basalis and together with the Ventral Pallidum (innervated by the BLA) provides cholinergic input to the BA. The CeA also connects to regions in the brainstem, midbrain, and pons, such as the Parabrachial nucleus (PBN), Caudal Pontine Reticular Nucleus (PnC), Periaqueductal Gray (PAG), and Nucleus of the Solitary Tract (NTS). The CeA projects to regions of the hypothalamus including the Dorsomedial Hypothalamic Nucleus (DMH), Posterior Paraventricular Thalamus (pPVT), Lateral Hypothalamus (LH), and Superchiasmatic Nucleus (SCN). Dashed line from Thalamus to CeA indicates a small number of direct projections there vs. substantial innervation of the LA.

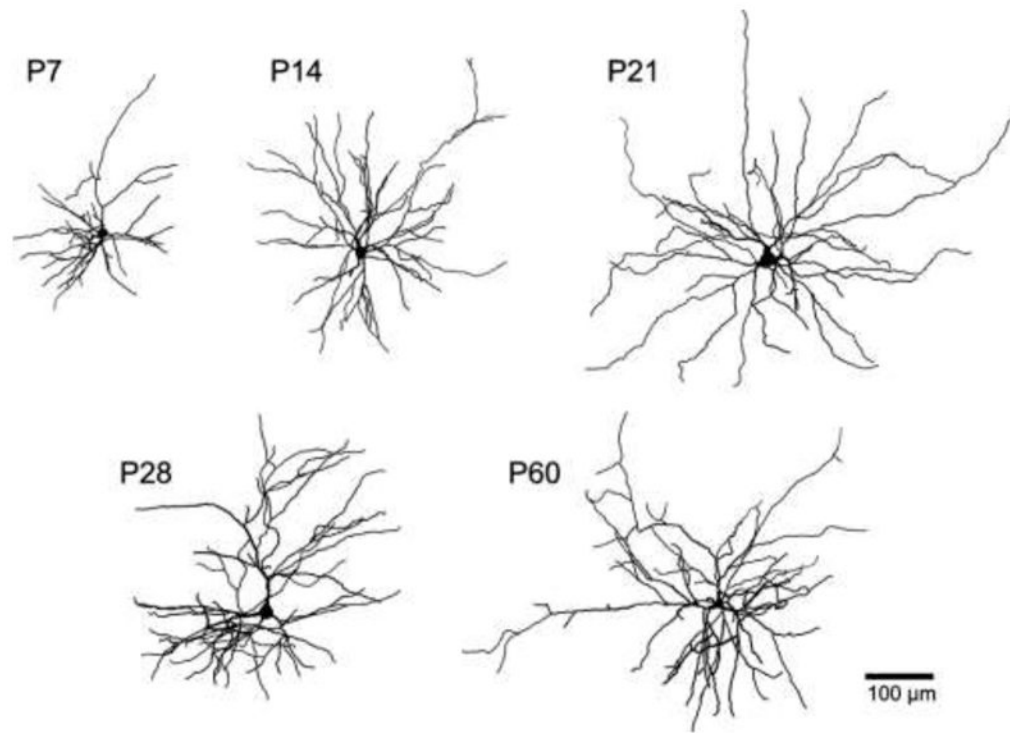


Figure 3:
Developmental expansion of BLA dendritic arbors, *from* Ryan 2016.