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Neural Circuits for Social Cognition: Implications for Autism

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Abstract—Social neuroscience, the study of the neurobiological basis of social behavior, has become a major area of current research in behavioral neuroscience and psychiatry, since many psychiatric disorders are characterized by social deficits. Social behavior refers to the behavioral response with regard to socially relevant information, and requires the perception and integration of social cues through a complex cognition process (i.e. social cognition) that involves attention, memory, motivation and emotion. Neurobiological and molecular mechanisms underlying social behavior are highly conserved across species, and inter- and intra-specific variability observed in social behavior can be explained to large extent by differential activity of this conserved neural network. Human functional magnetic resonance imaging (fMRI) studies have greatly informed about the brain structures and their connectivity networks that are important for social cognition. Animal research has been crucial for identifying specific circuits and molecular mechanisms that modulate this structural network. From a molecular neurobiology perspective, activity in these brain structures is coordinated by neuronal circuits modulated by several neurotransmitters and neuromodulators. Thus, quantitative variation in the levels, release and/or receptor density of these molecules could affect the observed behavioral response. The present review presents an overall framework of the components of the social brain circuitry and its modulation. By integrating multiple research approaches, from human fMRI studies to animal models we can start shedding light into how dysfunction in these circuits could lead to disorders of social-functioning such as Autism.

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Key words: social, cognition, autism, oxytocin, dopamine, serotonin.

INTRODUCTION

Social behavior has become a major area of current research in neuroscience and psychiatry. Realization of the existence of a biological foundation for human social behavior dates back to the Greek philosopher Aristotle (384-322 BC) when he stated that ‘‘Man is, by nature, a social animal” (Aristotle, 328BC/1920). The term ‘social’ is attributed to a species where group living, from pairs to highly complex societies, was favored. But this social condition, although driven by innate, biological factors, is reached through a long evolutionary process influenced by environmental factors. In fact, one could argue that even an innate stimulus–response reaction has been shaped by environmental factors driving natural selection. Today, the field of neuroethology (i.e. the study of the neurobiological causes of behavior) understands that social behavior, and in fact any given behavior of a species, is the result of genetic, epigenetic and environmental factors (Hofmann et al., 2014).

Social behavior refers to the behavioral response with regard to socially relevant information, and requires the perception and integration of social cues through a complex cognition process (i.e. social cognition) that involves attention, memory, motivation and emotion. Group-living requires an interaction between the individual and the group and thus, an understanding of the social rules within that group. Indeed, one must process features and expressions of faces and bodies to infer identity, potential actions, social hierarchy and emotional status of a conspecific, all necessary to guide the appropriate behavioral response (Mitchell, 2009). Thus, social cognition is a device tuned to perceive and

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Abbreviations: (f)MRI, (functional) magnetic resonance imaging; (m) PFC, (medial) prefrontal cortex; ASD, Autism Spectrum Disorder; BLA, basolateral amygdala; CD38, cluster of differentiation 38; CPP, conditioned place preference; DA, dopamine; DAT, dopamine transporter; E/I, excitation/inhibition; GFP, green fluorescent protein; HVA, homovanillic acid; LS, lateral septum; MAO, monoamine oxidase; MSN, medium spiny neuron; NAcc, nucleus accumbens; OXT, oxytocin; PET, Position Emission Tomography; PVN, paraventricular nucleus; SERT, serotonin transporter; SN, substantia nigra; SON, supraoptic nuclei; UsV, ultrasonic vocalization; VTA, ventral tegmental area.

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process social relevant cues, integrate them with the internal physiological status of self, and produce a behavioral response adjusted to the specific situation of the moment. This process must in addition be dynamic and flexible, since the social context is continuously changing and updated with new information. The correct functioning of the social cognition system has tremendous implications for human health. Altered social response is present in many neuropsychiatric disorders such as Autism Spectrum Disorder (ASD), a disorder where social dysfunction is one of its primary diagnostic criteria (APA, 2013). Therefore, from a translational research perspective, there is increasing interest in understanding the neural circuits and molecular mechanisms that guide social behavior, and in identifying what goes awry in neuropsychiatric disorders characterized by social impairments. In fact, since any given behavioral response of a group is represented as a continuum, this question is currently contemplated within the study of inter-individual differences in social behavior. Comparative studies have pointed out that the neurobiological and molecular mechanisms underlying social behavior are highly conserved across species, and that the inter- and intra-specific variability observed in the social behavior response can be mostly explained by differential activity of a conserved neural network of cortical and subcortical structures that interact to integrate environmental and physiological cues, which in turn guide the behavioral response of an animal (Newman, 1999). Human functional magnetic resonance imaging (fMRI) studies have greatly informed about the brain structures and their connectivity networks that are important for social cognition. Animal research has been crucial for identifying specific circuits and molecular mechanisms that modulate this structural network. The present review presents an overall framework of the structure and function of the social brain circuitry, as inferred from animal research. By focusing on the conserved circuits between lower animals and humans, and on the behaviors these shared circuits regulate in those species, we are starting to understand their role in human pathological conditions. We focus on rodents because due to the ease of studying them in the lab and their technical amenability, they are currently the most used to enhance our understanding of the neurobiological basis of social cognition. We start by introducing the structural components of the social brain at a macroscopic scale, originally identified from human MRI studies. We then summarize recent findings in animal research at a circuit level, which give insight into the specific neuronal populations and molecular mechanisms modulating this structural network. Finally, we discuss how dysfunction in these circuits could lead to disorders of social-functioning such as Autism.

ANATOMICAL ORGANIZATION OF SOCIAL COGNITION

The so called ‘social brain’ refers to those brain structures that are engaged in social cognitive processes. Most of these regions were originally identified from lesion studies in humans with specific behavioral impairments. These regions have been supported, and new ones added, by an extensive number of human fMRI studies that have detected differential activation of specific brain regions during performance of social tasks (Kennedy and Adolphs, 2012). Historically, the ‘social brain’ comprises areas involved in perception and processing of faces (somatosensory and temporal cortices), attribution of emotion (amygdala) and executive function (prefrontal cortex) (Fig. 1). Thus, the somatosensory cortex (SSC) has been involved in the recognition of facial emotions (Adolphs et al., 2000), and the temporal cortex (TC) in the visual processing of faces (Tsao et al., 2006). The amygdala, conventionally linked to processing of fear-related stimuli or threat detection, is currently known to play an important role in social cognition (reviewed in Adolphs, 2010). In fact, several disorders characterized by dysfunction in social behavior have been linked to altered amygdala response to face-processing tasks, as measured by fMRI. For instance, a failure to engage the amygdala during face processing has been shown in Williams syndrome, a disorder characterized by abnormally high sociability (Paul et al., 2009); whereas increased activation has been found in autism (Kleinhans et al., 2010) and social anxiety disorder (Klumpp et al., 2010). The prefrontal cortex (PFC) is known to modulate decision making and executive control, to enable the choice of the most appropriate behavior at each moment, by integrating sensory and emotional cues (Nelson and Guyer, 2011). Accordingly, humans with damage to frontal areas often show behavioral impairments that include inflexibility, perseveration and social inappropriateness, isolation and apathy (Barrash et al., 2000) or psycopathological (i.e. antisocial) behavior (Anderson et al., 1999).

Despite this apparently functional specialization of different brain structures in separate behavioral domains, it must be noted that these structures are interconnected in a network of neural circuits, and it is the overall functioning of the network what will modulate the behavioral response (Kennedy and Adolphs, 2012). The recent explosion in the variety of techniques that can be applied in animal research (especially in rodents) allows for in-depth study of the neurobiological and molecular mechanisms that underlie social behavior. Results from these studies are pointing out that the regulation of social behavior is essentially driven by an evolutionary conserved neural network of cortical and subcortical structures. Recently, Kim et al. (2015) developed a method to map whole-brain activation, at the cellular level, as a response of behavioral paradigms in rodents. The method uses the immediate early gene c-Fos, a marker of neuronal activation, fused to a green fluorescent protein (GFP) and visualized by serial two-photon tomography. The cFOS-expressing neurons are automatically detected by their GFP expression, and their distribution and number transferred to a brain atlas. With this approach, the authors studied which neuronal populations were activated upon social interaction and showed that after 90 s of male–male non-aggressive social exploration the highlighted brain structures were mainly the