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Interactive Social Neuroscience to Study Autism Spectrum Disorder

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Individuals with autism spectrum disorder (ASD†) demonstrate difficulty with social interactions and relationships, but the neural mechanisms underlying these difficulties remain largely unknown. While social difficulties in ASD are most apparent in the context of interactions with other people, most neuroscience research investigating ASD have provided limited insight into the complex dynamics of these interactions. The development of novel, innovative "interactive social neuroscience" methods to study the brain in contexts with two interacting humans is a necessary advance for ASD research. Studies applying an interactive neuroscience approach to study two brains engaging with one another have revealed significant differences in neural processes during interaction compared to observation in brain regions that are implicated in the neuropathology of ASD. Interactive social neuroscience methods are crucial in clarifying the mechanisms underlying the social and communication deficits that characterize ASD.

INTRODUCTION

From birth, humans are innately social creatures and spend much of their time engaging with conspecifics. Continuous interactions with others shape the developing brain by providing necessary experience during sensitive periods [1,2]. Social interactions encompass a wide range of contexts, including verbal and nonverbal communication, cooperation and competition, and joint gaze and shared attention. In order to successfully interact with others, it is crucial to understand oneself, others, and relations between the two and the environment [3,4].

Autism spectrum disorder (ASD) is a neurodevelopmental disorder in which these relationships are compromised from early in life. ASD is characterized by difficulties in social communication and interaction; restricted, repetitive behaviors; and atypical response to sensory information [5]. Individuals with ASD have difficulty engaging and maintaining social interactions and relationships with others. The specific etiologies and neural bases of ASD remain largely unknown, though study of the "social brain" [2] holds promise for elucidating the underpinnings of core impairments [6]. Clinical and behavioral assessments, such as the Vineland Adaptive Behavior Scales [7], Autism Diagnostic Observation Schedule (ADOS) [8], Autism Diagnostic Interview — Revised (ADI-R) [9], and the Social Responsiveness Scale [10], focus specifically on the performance of individuals with ASD in the context of interactions with other people [11]. In contrast, with notable exceptions [12], most neuroscience research investigating ASD has entailed passive engagement with a computer monitor or speaker [13,14]. Since the social challenges experienced by individuals with ASD are most evident in naturalistic social interactions, insights derived from the study of social function in the absence of real or simulated interactions may have limited ecological validity [15,16].

For these reasons, we advocate for development of novel, innovative methods to study the brain bases of ASD in interactive social contexts. Recent innovations enable interactive social neuroscience experiments that use gaze-contingent and dynamic stimuli to simulate social interactions [17,18]; however, the influence of actual human interaction on brain activity in ASD remains poorly understood. With notable exceptions [12], most

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†Abbreviations: ASD, autism spectrum disorder; MNS, mirror neuron system; ToM, Theory of Mind; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; NIRS, near-infrared spectroscopy; fNIRS, functional near-infrared spectroscopy; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex.

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social neuroscience approaches study a single brain in isolation rather than during actual interactions with another person [13]. Individuals are typically isolated in a room or brain imaging facility and interact exclusively with a computer program [19]. Most current methods rely on viewing static pictures or videos of faces and other social stimuli. Although such approaches have provided critical information about brain response to conspecifics, they cannot capture the fast-paced, fluid nature of live social interactions [1,15]. Further, current methods do not consider how social perception, action, and cognition are regulated during live, dynamic interactions with real people [15]. Given that first-personal versus third-personal social participation modulates brain response [20,21], we consider this an important objective for ASD research. Lab approximations of social interaction in ASD often fail to elicit the degree of social impairment evident in naturalistic contexts [22]. Traditional experimental designs, in the interest of tight methodological control, may compromise ecological validity [23]. Given that the specific nuances of social interaction that present challenges for people with ASD remain undefined, we argue that measurement of neural response in actual interactive contexts is a necessary advance for ASD research, despite the challenges it presents in terms of methodological rigor and experimental control.

The objectives of this review are twofold. First, we aim to describe extant research in the emerging area of "interactive social neuroscience." We focus specifically on studies that involve concurrently recording brain activity from two interacting humans. Second, we highlight the applicability of such approaches to the study of ASD and neurodevelopmental disabilities affecting social behavior. We focus on specific neural social processes and neural circuitry that are understood to play a role in social behavior and that are implicated in ASD and review existing research applying these approaches to ASD. We organize this review according to the classification of dual brain recordings proposed by Liu and Pelowski, which are tiered according to a hierarchy of social complexity: 1) the social brain at rest; 2) shared attention; 3) social decision making; 4) transfer of information across brains through communication; 5) action and emotion synchrony; and 6) body-movement synchrony [24]. Given the novelty of this approach and the limited body of published research to-date, we highlight relevant methodological details.

SOCIAL BRAIN AT REST

Understanding the differences in resting state activity when alone versus with others can provide both information about the manner in which the presence of others modulates brain function and a baseline for understanding brain activity in more dynamic and complex social interactions. The "default network" [25], or the system of brain regions active when one is not performing an explicit task, overlaps with social brain systems [26]. In the only published study to examine the influence of the presence of another person on resting brain activity, Verbeke and colleagues recorded resting electroencephalograpy (EEG) in 35 participants with different, self-reported attachment styles under two conditions: alone and together [27]. During both conditions, participants viewed a white fixation cross for 2 minutes on a computer screen. During the together condition, participants sat beside each other, facing the computer screen. Study participants with a high anxious attachment style exhibited enhanced alpha, beta, and theta power in posterior brain regions when with another person compared to when they were alone. Additionally, Verbeke et al. found that enhanced alpha power, an index of inhibitory top-down control [28], was associated with anxious attachment scores. These differences were interpreted to reflect enhanced "tonic alertness," or nonselective readiness for perception and action, in the high anxious attachment participants. These pronounced differences in the resting brain when individuals are alone versus with another person suggest that the mere presence of another person influences baseline brain activity, even when interaction is not taking place.

These results are relevant to understanding social information processing in ASD. The presence of a potential social partner alters brain activity in preparation for social interaction, reflecting an alteration in the topography of salience of the environment [29]. A failure to adjust baseline brain activity in this way offers a potential explanation for the decreased responsivity to others in ASD. Individuals with ASD are impaired in many aspects of social attention and orienting [30,31], and a failure to prepare or raise their level of alertness in a social context may indicate a temporally early marker of social brain dysfunction that derails their ability to fully engage the social context. For these reasons, examination of modulation of resting state activity by the presence of others holds promise for understanding "social readiness" in ASD.

SHARED ATTENTION

A more complex interaction between two individuals involves exchanging information through eye gaze, such as establishing eye contact or sharing visual attention [4]. The neural correlates of mutual gaze have been investigated by dual functional magnetic resonance imaging (fMRI) research. In one such study, participants were shown another participant's eyes on the top half of the screen and two ball targets on the bottom half of the screen. Participants were instructed to direct their own gaze to a target based on the eye movement of their partner or by color changes in the target [32]. Activation in the right inferior frontal gyrus (IFG) was correlated among partners relative to non-partners [32]. The right IFG is involved in maintaining mental representations of the perspective of others [32]. It is also implicated in the mirror neuron system (MNS) [33], a collection of neurons that fire both when executing and observing actions that are

hypothesized to underlie imitation and action understanding [34]. The MNS, based in the superior temporal sulcus, region F5, and premotor cortex [35], has been suggested as critical to the development of imitation and empathy and the understanding of others in social interaction [4].

The MNS has also been implicated as a contributing source for social difficulties in ASD [36]. This experimental approach was also applied in a group of individuals with ASD paired with typically developing controls [13]. Behaviorally, ASD and control pairs exhibited more difficulty cueing and following gaze. With regard to brain activity, individuals with ASD showed reduced activity in the IFG, while controls paired with individuals with ASD showed increased activity in right frontal and bilateral occipital areas, interpreted as compensatory activation in response to impaired eye contact in the ASD-control pairs. These results suggest that brain activity during joint attention is guided by not only individual traits, but by the context of a given social interaction. Given that joint attention, establishment of eye contact, and gaze following are early developing, core symptoms of ASD, these results highlight the import of this approach in ASD [32,37]. These results also demonstrate that interactive social neuroscience approaches with participants with typical and atypical social development can provide novel information about both the clinical group (in this case, a hypoactive MNS) and the typically developing group (in this case, increased compensatory activity).

SOCIAL DECISION MAKING

A more complex form of interpersonal interaction involves social decision making. Studies of social decision making have used simultaneous recording of brain activity in cooperative and competitive contexts. Many of these studies have employed variants of the "Prisoner's Dilemma" or the "chicken game," based on the economic principle of game theory. In the Prisoner's Dilemma and chicken game, two names for the same widely used experimental paradigm, each participant must decide whether to cooperate with an opponent or defect in order to earn the highest score. If the two players cooperate, they both have small wins; if one cooperates and the other defects, the cooperator has a big loss and the defector has a big win; if both defect, they both have small losses [38]. "Tit-for-Tat," the optimal strategy, involves first cooperating and then imitating the opponent's previous move for all subsequent moves [38,39]. EEG studies using this paradigm with two participants reveal significantly higher power in the beta frequency band (13-29 Hz) during defection compared to cooperation [40]. Source localization analysis indicated that during defect conditions, participants displayed increased activation in regions of orbitofrontal cortex involved in decision making [40]. In another study applying the same approach, during the defect condition, partners demonstrated decreased correlation across participants in prefrontal cortical regions [41]. A fMRI study examined the role of interactivity on this paradigm by varying conditions such that participants believed they were either playing a computer (actually the case) or an opponent in another room. Activation in left amygdala was associated with cooperation when people believed they were playing against a human and defection when they believed they were playing against the computer [42]. Moreover, activation in the precuneus and deactivation in the ventromedial prefrontal cortex, regions both associated with Theory of Mind (ToM), or the ability to impute mental states to oneself and to others [43], were during application of a reciprocal tit-for-tat strategy, suggesting active mentalization [42].

Other experimental approaches have also provided relevant insight into the neural mechanisms of social interaction. Cui and colleagues applied a near-infrared spectroscopy (NIRS) task measuring cooperation versus competition based on synchronous and asynchronous timing of "go" actions between two players instructed to cooperate or compete with their partner. In the cooperation condition, participants were presented a hollow gray circle that was filled with a green circle as a "go" signal, at which point they each pressed a specified key. If the latency difference between the response times of the two participants was smaller than a specified threshold, both participants earned a point; if it was above the threshold, both participants lost a point. Participants had the objective of maximizing their points, and feedback was provided after each trial. In the competition condition, the task was identical, but participants were instructed to respond faster than their participant in order to win a point; the participant who responded slower lost a point. Behavioral responses were closer together during the competition condition, but players demonstrated greater inter-brain wavelet coherence in right superior frontal cortices only during cooperation conditions [44], suggesting that differential brain activity was driven by interpersonal context rather than task performance.

Another interactive experiment examined brain activity while players commanded ballistic shooting teams. Participants played the game under four varying levels of cooperation, with the goal of being the last remaining team: 1) two players took turns to command a single, six-character team against the computer; 2) players each controlled a three-character team, playing cooperatively while competing against two computer-controlled teams; 3) players each controlled a three-character team, paired with a computer-controlled team, competing against each other; 4) players each controlled a six-character team competing against each other. Increased interpersonal synchrony in beta and gamma EEG synchrony was found during competition compared to during team-play [45]. This synchrony during competition, rather than cooperation, may have reflected maintenance of closeness in the context of threat to a relationship or, alternatively, increased attention to the actions and reactions of another person as a strategy to support competition [45].

The contrasting results of these game-based social decision-making studies underscore the complexities of live social interactions. In the Cyberball paradigm [46], participants play an online game of catch with two other players, who are actually pre-programmed computer representations, and the participant is gradually excluded from the game when the other two players stop throwing the ball to the participant. In the context of Cyberball, adolescents with ASD are able to recognize that they are being excluded and report levels of ostracism comparable to typically developing peers [47]. Electrophysiological results, in contrast, reveal that in individuals with ASD, a late slow wave over medial-frontal scalp electrodes does not differentiate rejection from "not my turn" events as it does in typically developing peers [48], suggesting that individuals with ASD might have difficulty discerning among social contexts. These types of interactive approaches tap circuitry implicated in ASD. Difficulties with ToM are common in ASD [43], and the mentalizing network, based in the temporoparietal junction, posterior cingulate cortex, and medial prefrontal cortex (mPFC) [49], has been posited to underpin these difficulties [50]. Although not focused upon explicitly in these studies, social decision making involves reward systems. Reward processing in both social and nonsocial contexts is implicated in ASD [51]. In this way, social decision making paradigms offer valuable opportunities to understand the neural bases of ASD.

TRANSFER OF INFORMATION ACROSS BRAINS THROUGH COMMUNICATION

Dual brain recordings in the context of verbal communication have provided information about the neural underpinnings of interpersonal information transfer. Stephens and colleagues applied a paradigm in which a speaker told a 15-minute, non-rehearsed, real-life story while in an fMRI scanner, which was recorded and played back for a listener also being scanned. Temporal and spatial coupling of brain activity between the speaker and listener was observed in areas associated with production and comprehension of language, including the early auditory cortex, superior temporal gyrus, angular gyrus, temporoparietal junction, parietal lobule, IFG, and the insula [52]. Additionally, there was coupled activation in the precuneus, dorsolateral prefrontal cortex, orbitofrontal cortex, striatum, and medial prefrontal cortex, which are involved in the processing of semantic and social aspects of story [52]. To examine the possibility that these interparticipant correlations reflected low-level features of speech, a separate condition entailed a speaker telling a story in a language not understood by the listener; in this condition, spatial and temporal coupling was only found in early auditory cortices at lower thresholds. These results indicate that successful communication is associated with co-occurring patterns of temporal and spatial brain activity in the speaker and listener [52]. A second, live-interaction study used simultaneous fNIRS recording to compare face-to-face dialogue, face-to-face monologue, and back-to-back communication [53]. During the dialogue conditions, participants discussed a pre-selected hot news topic and subsequently evaluated the efficacy of their communication using a five-point scale. During the monologue conditions, one participant narrated his or her life experiences while the partner remained silent and did not use any nonverbal communication. To ensure that the partner was attending to the story, he or she was required to repeat the key points of the story after the monologue was completed. Wavelet coherence in left inferior frontal cortex was observed only during face-to-face dialogue.

This approach, recording brain activity during face-to-face conversations, has been applied to study autistic traits. Suda and colleagues measured brain activity using fNIRS during face-to-face conversation and examined variability as a function of autistic traits, as indexed by the Autism Quotient [54]. Participants and interviewers engaged in face-to-face conversation about food, taking turns speaking for 15 seconds. Synchronous activation of the prefrontal cortex and the superior temporal sulcus, both involved in social cognition, was negatively associated with level of autistic traits. These results suggest that interbrain synchrony is associated with sub-threshold autistic symptomatology. Given these results in a population without clinical impairment and the centrality of communication impairment to ASD [5], co-recording of brains during communication, face-to-face and otherwise, holds promise to characterize dysfunction during communication in ASD. The MNS has been suggested as a potential mechanism that allows for brain-to-brain coupling, the interbrain synchrony of the perceptual system of one brain to the output of another, enabling the brain to retrieve and understand information from the environment and act appropriately [19]. It is possible that effective interbrain synchrony is not formed in individuals with ASD, causing the observed difficulties in communication.

ACTION AND EMOTION SYNCHRONY

In addition to verbal communication, action and emotion synchrony between two brains can offer insight into nonverbal sharing of communication. As described above, the MNS is hypothesized to be central to the development of imitation, empathy, and the understanding of others in social interaction [4,35]. Difficulty recognizing emotions and accordingly adopting the appropriate synchronous neural response can impede effective social interaction [55]. While action synchrony has been studied using interactive methods, emotion synchrony has not been well-studied using these methods. Several studies have examined neural synchrony during group activities involving nonverbal forms of communication, such as team card games and playing music in unison. When four people played a card game in teams of two, EEG activity was localized to the anterior cingulate cortex (ACC) during anticipation of another player's impending play [56]. This

ACC activation was correlated with right prefrontal and parietal activity in the player who was about to play the card [56]. In this way, brain areas, such as the ACC, that are sensitive to the outcome of one's own actions [57,58] are also involved in evaluating the actions of a partner. In a dual-EEG study of two guitarists playing together, musicians demonstrated synchronized delta and theta oscillations during a preparatory period while listening to a metronome and when they started playing a short piece together [59].

Research has not yet investigated brain activity in individuals with ASD during these types of shared nonverbal communications. However, the brain regions implicated in these processes, such as the ACC and portions of the MNS, are also implicated in the neuropathology of ASD [60,61]. Studies of live interaction may help to clarify the role of these regions in the context of nonverbal communication in highly naturalistic contexts.

BODY MOVEMENT SYNCHRONY

Interactive neuroscience has also been used to investigate the neural bases of body-movement synchrony. When two individuals are walking together, it is common for their steps to naturally synchronize [62]. Such interhuman synchronization has been proposed as a means for understanding and relating to others [3]. Finger-tapping experiments have been used to study both the neural mechanisms and behavioral patterns associated with motor synchrony. In a dual-EEG setup in which participants executed self-paced finger tapping within and out of view of a partner, Tognoli and colleagues [63] found that a lateralized centro-parietal component of the EEG that spanned 9.2-11.5 Hz, which they identified as phi, was highly sensitive to social coordination during visual contact. In a similar finger-tapping task, in which participants either maintained synchrony, maintained asynchrony, or tapped at their own pace, MNS activity, reflected in lower (8-10 Hz) and upper (10-12 Hz) mu power, was associated with activity independent of and sensitive to different synchrony conditions, respectively [64]. In a separate study, functional near-infrared spectroscopy (fNIRS) task revealed increased wavelet coherence over premotor cortices during self-paced imitation, compared to stimulus-paced or individual tapping conditions [65]. One participant performed a self-paced finger-tapping task using different fingers while his or her partner imitated the finger tapping. In another finger-tapping task comparing the neural correlates of mutual coordination between two participants versus coordination with a metronome, stronger suppression of alpha and low-beta oscillations over motor and frontal areas was observed during the human coordination condition [66]. In the interactive condition, each participant received auditory feedback of his or her partner's finger tapping. In the computer-controlled condition, both participants received auditory feedback of steady computer-generated beats. Additionally, within the human pair, the leader showed stronger frontal alpha suppression, which was interpreted as reflective of planning.

Imitation and coordination of more complex hand motions have revealed similar results. Dumas and colleagues recorded EEG from two participants imitating one another perform random hand motions in the air viewed through a live-circuit video recording, with participants taking turns between the role of leader and imitator [67]. During imitation, interbrain neural synchronization was found in the alpha-mu band over right centro-parietal regions, reflecting MNS activity [67] and social coordination [63,67]. Interbrain synchrony in theta (4-7.5 Hz) and beta (12-30 Hz) has also been reported during movement imitation tasks [62]. Additionally, Ménoret and colleagues used dual EEG to record the neural activity of two participants while they were engaging in nonverbal social interaction with each other and with a robot. Participants each performed an action, such as moving a coffee cup and placing it in front of his or her partner. During the observation condition, the partner just observed the actions of the other person, while the partner performed a complementary action, such as placing the cup on a saucer, during the interaction condition. Each of those conditions was performed with a human actor and a robot actor. When interacting versus observing, with equal movement kinematics between conditions, beta suppression, associated with movement and action-perception, tends to be greater [68]. Additionally, motor-related potentials over fronto-central regions are enhanced during interaction, rather than mere observation, across both human and robot actors [68]. Further, in an fMRI study in which participants either imitate a hand gesture or perform a complementary action, the MNS is more active during complementary action, rather than mere imitation [69].

Difficulties in motor imitation and body-movement synchrony have been well documented in individuals with ASD [60]. Individuals with ASD have been found to demonstrate difficulty imitating others' actions [35], and imitation impairment has been correlated with autistic symptom severity, with individuals most severely impaired by autism demonstrating the poorest imitation abilities [70]. MNS activity in response to joint action in dyadic interactions has been observed in infants as young as 14 months of age [71], demonstrating that the action of the MNS emerges early in development and plays a crucial role in the understanding of others during interaction. By increasing ecological validity, interactive paradigms addressing MNS activity may offer greater sensitivity to clarify the controversial role of the MNS in ASD [72].

CONCLUSIONS AND OUTLOOK

Above, we have reviewed published research applying an interactive neuroscience approach to study two brains engaging with one another. Across varying levels of interactive complexity, these approaches reveal significant differences in neural processes during interaction com-

pared to observation. Interactivity modulates brain activity at rest, with even the physical presence of another person altering baseline activity. When sharing attention, shared gaze associates with enhanced activation in brain systems supporting mentalization. In the context of social decision making and transfer of information through communication, interpersonal interactions are reflected in concurrent patterns of brain activation, with increased brain-to-brain coupling and synchrony during interactions. During emotional and action synchrony and body movement synchrony, the MNS plays a critical role.

These findings suggest the utility of interactive techniques in better understanding social function and dysfunction in ASD. Many content areas described above have already been studied in ASD in the absence of interactive paradigms. Because these studies demonstrate novel findings with the element of interactivity added, parallel advances may result from the application of these approaches to ASD. This is supported by the observation that many of the brain regions selectively activated by interactivity, such as the ACC, the MNS, and mentalizing circuitry, are the very regions implicated in the neuropathology of ASD.

Although the research categories described here demonstrate relevance to ASD, other aspects of ASD may also be studied with interactive neuroscience approaches. Face perception and processing have been well studied in ASD [6], but little is understood about them in the context of two brains during a live interaction. Differential attention to social percepts, including biological motion, has been implicated in ASD as a potential cause of downstream social difficulties resulting from reduced neural specialization [73]. Further, reward processing has been associated with ASD [51]. Both of these domains of function could readily be studied with interactive neuroscience experiments.

The complexity of social interactions makes the study of two brains crucial for a deeper understanding of social function and dysfunction in human development. Difficulties in ASD manifest during social interaction, yet current methods provide limited insight into the dynamics of these interactions. We see these interactive social neuroscience methods as key in clarifying the mechanisms underlying the social and communication deficits that characterize ASD. A better understanding of these mechanisms offers great promise for the development of more effective interventions and treatments. However, it is important to acknowledge that the presence of a second person introduces multiple potential experimental confounds. First, live interaction creates variability in the experimental paradigm, which can make results more difficult to interpret. Second, when recording from two individuals simultaneously, it is possible that some correlated brain activity could be attributable to low-level sensory input, rather than social factors, per se. Third, various factors including age (same or different), gender (male or female), sexual orientation, relationship type, and closeness may impact results. Despite additional difficulty that the presence of a second person may introduce, many of these potential confounds can be controlled through experimental design. Importantly, while two-person interactive experiments are less controlled, it is in these uncontrolled contexts that individuals with ASD exhibit the most impairments, while single person experiments have historically yielded inconsistent findings [74-77] that are not always consistent with clinical characteristics. The inconsistent pattern of results in the literature suggests that it is unclear exactly how social contexts elicit vulnerabilities in ASD. By characterizing brain activity across the range of contexts we can identify those types of tasks most germane to eliciting, and thus understanding, social brain activity in ASD.

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