Neural and behavioral computations of social interaction in autism and beyond

By

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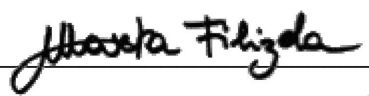
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Abstract

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Humans are inherently social creatures, and social connection is closely tied to our wellbeing. Nevertheless, significant variation exists in people's social perceptions and behaviors, especially amongst people with certain psychiatric and neurodevelopmental disorders, for whom social difficulties can cause substantial distress. In the following dissertation, I present three independent studies that offer unique insights into the complexities of social interaction across various populations, with a particular focus on autism spectrum disorder (ASD) and misophonia.

The first study investigates transdiagnostic symptom dimensions and their relationship to social controllability. Online participants self-reported symptoms across various psychiatric conditions, allowing us to identify latent dimensions. Unlike dimensions with high loadings of mood or social symptoms, the dimension with high loadings of misophonia and obsessive-compulsive symptoms was linked to inflated perceptions of the ability to control others and heightened aversion to unexpected events in uncontrollable social environments. Thus, our results implicate misophonic but not autistic traits in altered social controllability.

The second study evaluates the validity of such online self-report surveys for accessing research participants with ASD. We identified discrepancies in the social phenotypes of online participants with high self-reported autistic traits and in-person participants with clinically confirmed ASD diagnoses, suggesting they represent distinct groups. The study underscores the importance of maintaining separate interpretations of self-reported symptoms in individuals with and without an ASD diagnosis.

With this enhanced understanding of how social interaction tendencies differ between ASD and other groups, we finally turn to the brain. We present a review of the current literature implicating hippocampal alterations in the development of ASD, and proceed to evaluate the neural correlates of navigating social navigation in ASD, misophonia, and typical development. Findings revealed ASD-specific neural alterations, including hypoactivation of the left temporal pole during social interactions and increased task-associated functional connectivity between the parahippocampal place area and the inferior frontal gyrus. We additionally identified shared neural systems for tracking abstract social distances across all diagnoses. Overall, this dissertation contributes to a deeper understanding of social differences and their underlying neural processes, offering valuable insights for future research and intervention strategies.

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Attributions and Permissions

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Chapter 1. General Introduction

1.1 The Importance of Social Interaction

Social connection is central to the human experience. We owe much of our species'
intelligence to social interaction, as our need to manage the unpredictability of others'
actions is theorized to be one of the largest contributors to the evolution of our current
brains (the 'social intelligence hypothesis')[1–4]. The ability to understand the intentions of
others is essential for establishing cooperation, yet doing so is cognitively taxing. Unlike
much of the biological world, which follows clear patterns of action and reaction,
humans are fickle creatures. It's easy, for example, to understand why a plant grows
towards sunlight, but more difficult to understand why a person may choose to abruptly
leave a conversation. As we developed sociality, we also developed the ability to
understand and predict other's thoughts and behaviors, leading to a level of intelligence
that was previously unnecessary for adaptive survival[1]. Thus, social interaction played
an essential role in what makes us human.

In humans and non-human primates, social interaction also represents a basic need.
Social isolation during infancy has hugely detrimental effects on development. In the
1980s-90s, understaffing and underfunding in overcrowded Romanian orphanages led
to severe neglect[5]. Seminal work following the infants who experienced social
deprivation in these orphanages demonstrated the importance of early social contact:
the children showed severe developmental delays as well as long-lasting deficits in
cognitive and social functioning[6]. Harlow's work in non-human primates demonstrated

that infant rhesus monkeys separated from their mothers engaged in self-mutilation, reclusiveness, and refusal to eat, even once re-introduced to peers[7]. He also established the fundamental importance of social reward - socially deprived infant monkeys spent more time with soft cloth "mothers" than wire "mothers" that held milk bottles, suggesting a preference for the mere reminder of social comfort over basic food needs[8].

Extending beyond childhood, the use of solitary confinement in adult prisoners is considered the ultimate punishment, and is known to cause severe psychiatric harm including induced psychosis and loss of self[9]. Solitary confinement is considered by many to be a highly unethical form of torture, and has been described by those who have experienced it as "living death"[10]. In a less extreme example, social rejection by peers is often considered deeply traumatic[11], and the pain felt during social exclusion shares overlapping neural circuitry with physical pain[12]. On the other side of the same coin, as the removal of social interaction can cause psychiatric distress, the addition of social interaction can improve psychiatric outcomes. Greater frequency and quality of social interaction is protective against dementia[13,14], and social connectedness is associated with improved mental health[15]. Together, such findings establish clear ties between social interaction and overall wellbeing.

1.2 Disorders of Altered Social Behavior

Despite the importance of social interaction in all human lives, the details of how and why social behaviors are enacted are far from uniform. Social norms differ across

cultures and individuals. In countries such as Hong Kong and Japan, for example, loud slurping of food can be considered a polite acknowledgment of a well-cooked meal, whereas in many western cultures, audible eating sounds are often considered rude[16,17]. At a more granular level, individuals within cultures often differ in their social tendencies. At the far end of this spectrum, there are people who express reduced social motivation, exhibit impaired understandings of implicit social norms, and display atypical social behaviors. The resulting reduced social connectedness can have harmful effects on mental health. Many neurodevelopmental and psychiatric disorders are characterized by such social differences, including autism spectrum disorder (ASD).

ASD is a neurodevelopmental disorder affecting an estimated 1 in 36 children in the United States[18]. Symptom onset typically occurs within the first 2 years of life[19], though many cases go undetected until later in life, including well into adulthood[20]. ASD is characterized by difficulties in social communication as well as repetitive and restricted behaviors and interests[21]. As a part of their social communication difficulties, individuals with ASD often show impairments in flexible language, understanding of implicit or non-verbal social cues, and theory of mind, which refers to the ability to understand the intentions and feelings of others. Specific examples of social differences in ASD include inappropriate body language (i.e., standing too close to others), blunt language, reduced eye contact, difficulty initiating and sustaining reciprocal conversation, and reduced modulation of behavior across different social contexts[22,23]. Communication difficulties are most apparent during dynamic real-life interactions, likely because such instances reflect the most unpredictable social environments[24]. These social difficulties

can lead to problems establishing and maintaining relationships, and are associated with increased rates of peer victimization[25] and social isolation[26–29], contributing to high rates of depression and anxiety[29–33] in ASD. Though prior research has primarily focused on children and adolescents with ASD, the adverse effects of social difficulties may be even more consequential for autistic adults seeking to gain greater independence through employment, romantic partnership, and/or peer communities. Therefore, increasing our understanding of the social differences in adults with ASD is crucial for developing interventions aimed at improving quality of life.

Of course, autism is a highly heterogeneous spectrum, and individuals with ASD present with a variety of social profiles[34]. They differ, for example, in their levels of social motivation. The highly-cited "social motivation hypothesis" posits that ASD stems from a reduced desire for social experiences, rather than differences in social cognition[35]. In support of this, the authors present evidence of reduced orienting to social signals in ASD, ostensibly because they are seen as less rewarding, as well as reduced reporting of loneliness despite smaller social network sizes. However, while it is true that many individuals with ASD self-report reduced social motivation, there are also many that do not. For some individuals on the spectrum, reduced social initiation may not be a reflection of reduced desire to interact, but rather a consequence of social anxiety or reduced awareness of social norms[36]. Thus, though atypical social behavior is common across all individuals with ASD, there is heterogeneity in its manifestation. This makes it difficult to tease apart the social difficulties that are specific to ASD from those that may exist sub-clinically or be common to other disorders. To better

understand the heterogeneous social differences in ASD and properly inform treatment approaches, we must utilize appropriate comparisons.

While ASD is perhaps the most notable example, it is not the only condition characterized by atypical social behavior. Misophonia, for example, is a relatively newly-described condition involving extreme negative reactions to socially-produced sounds. Individuals with misophonia are often triggered by the sounds of people eating, breathing, or tapping repetitively. Reactions can include irritation, anger, and anxiety, which often lead to avoidance of social situations. The identity of the person producing the trigger sound appears to matter, as many people with misophonia report being more triggered by close friends and family members than by acquaintances[37]. Though not currently listen in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [21], misophonia has been widely documented in research. Indeed, there are numerous centers fully dedicated to studying misophonia across the world, including the Duke Center for Misophonia and Emotion Regulation, signifying growing global recognition. Research estimates that as much as 20% of the population experiences some form of misophonia, with a smaller percentage suffering from more severe cases that significantly impact their ability to maintain relationships and/or employment. In such cases, trigger avoidance can lead to extreme social isolation, which can have serious mental health consequences including suicidality[38].

Though research on misophonia has proliferated in the last 5-10 years, we still know very little about its mechanisms of action or overlap with conditions that involve similar

symptoms. Given the social nature of the trigger sounds and the auditory sensitivity seen in misophonia, there are clear similarities to ASD, which is characterized by symptoms in the social and sensory domains. Indeed, individuals with misophonia show higher rates of ASD traits compared to the general population[39,40]. Though they are considered distinct conditions, little is known about their similarities and differences in social cognition.

In the following dissertation, I aim to deepen our understanding of the behavioral patterns and neural processes associated with social differences in ASD and misophonia. Investigating multiple conditions improves the specificity of our findings, allowing us to gain a deeper understanding of the independent and shared factors that contribute to each diagnosis. In particular, I focus on investigating how individuals with ASD and misophonia understand and produce social actions during dynamic interactions, as these are the scenarios with which they struggle the most in real life.

1.3 Methods for Studying Dynamic Social Interaction

When studying social interaction, choosing the correct paradigms is paramount. Paradigms that are classically used to probe social behavior tend to be relatively passive, involving viewing of static images, and abstract, involving situations that are unlikely to be experienced in real life. Additionally, the majority of existing paradigms do not allow for proactive behavior on the part of the participant, as they do not respond (or appear to respond) dynamically to participants' choices. Though these paradigms can be helpful when looking to probe an isolated process, they are limited in their ability to

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mimic the complexities that the mind has to balance during everyday social experiences. Recently, researchers have begun developing and using "naturalistic tasks" that more closely match the intricate dynamics of the natural world. Such paradigms allow us to look at cognition outside of a vacuum, and are thus key to ecologically valid and replicable research. Proactive, naturalistic tasks are very useful for studying the processes that contribute to social interaction, as social situations present especially complex and unpredictable environments. This dissertation utilizes two naturalistic tasks – the social navigation paradigm and the social controllability paradigm, which both mimic real-life social interactions and respond (or appear to respond) dynamically to participants' choices.

The complexity of our tasks allows us to quantify nuanced social strategies that may be difficult to ascertain through observation alone. With computational approaches, we can use precise models to make sense of participant's decisions, such as how they respond to social norm violations. In addition to characterizing subtle distinctions in social behavior, this approach allows us to better understand the neural correlates of specific cognitive processes. We can specify a model that describes how an individual keeps track of evolving relationship dynamics, for example, and directly map it onto its neural substrates. These paradigms therefore confer advantages for probing both the behavioral and neural processes underlying social interaction.

1.4 Dissertation Overview

The studies outlined in this dissertation aim to deepen our understanding of divergences from normative social behaviors. The first study (**Chapter 2**) investigates the relationship between transdiagnostic traits and social controllability. Utilizing a large sample of online participants, we first identify latent dimensions consisting of shared self-reported symptoms across various psychiatric and neurodevelopmental disorders, including ASD and misophonia. Next, we investigate how each dimension (e.g., 'social avoidance') relates to the perception and exertion of social control. Because so little is known about how misophonia relates to other disorders like ASD, this study places particular emphasis on understanding the psychiatric correlates of misophonia symptoms.

Though such online approaches are well-suited for transdiagnostic questions, which require large datasets, they typically rely on self-report to measure symptom severity. In individuals with reduced symptom insight, including many with ASD, self-report may not match external perceptions. Accordingly, the second study (**Chapter 3**) considers the validity of online self-report surveys for accessing research participants with ASD. By comparing social behavior in online participants who self-report a high level of autism symptoms to in-person participants with clinician-confirmed ASD diagnoses, we can examine whether the two methods identify groups with comparable social phenotypes.

After detailing behavioral differences in online social interaction, I next present work investigating differences in the neural tracking of social signals across in-person patient

groups. Continuing the focus on ASD, **Chapter 4** outlines the potential involvement of the hippocampus in the pathophysiology of ASD. Traditionally thought to support memory and spatial navigation, the hippocampus has recently been implicated in more general abstract cognitive mapping, including the mapping of social relationships. Given the primary social symptoms and secondary memory and spatial reasoning differences seen in ASD, it appears that the proposed functions of the hippocampus have substantial overlap with the impaired functioning domains in ASD. Furthermore, hippocampal developmental reaches significant milestones by the age of 2, just as ASD symptoms typically appear. We thus establish the hippocampus is a prime candidate for neuroimaging research in ASD. The third and final study (**Chapter 5**) utilizes functional magnetic resonance imaging (fMRI) to investigate the role of the hippocampus and other key brain regions in social navigation in adults with ASD, misophonia (treated here as a clinical control group), and typical development (TD). By examining diagnostic similarities and differences in 1) overall neural activity during social interaction and 2) dynamic neural tracking of specific social representations, we gain a deeper understanding of the intricate processes underlying social cognition in each disorder.

Note: In recognition of divided preferences for person first (i.e., "person with ASD") or identity-first (i.e., "autistic person") language within the autism community, this dissertation uses a mix of both conventions.

Chapter 2. Disrupted computations of social control in individuals with obsessive-compulsive and misophonia symptoms

Adapted from iScience, 2022*

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*This text has been adapted from its published version to include additional supplemental figures that aid in contextualizing the findings within the context of the dissertation

2.1 Abstract

Misophonia is a condition in which certain sounds produced by other people lead to intense negative reactions. It remains unknown how misophonia relates to other psychiatric conditions or impairments. To identify latent constructs underlying symptoms, we conducted a factor analysis consisting of items from questionnaires assessing symptoms of misophonia and other psychiatric conditions. One thousand and forty-two participants completed the questionnaires and a social exchange task in which they either could ("controllable") or could not ("uncontrollable") influence future monetary offers from other people. We identified three symptom factors: one with socially avoidant symptoms (e.g., social anxiety and autism spectrum disorder symptoms), one with mood symptoms (e.g., anxiety and depression symptoms), and one with misophonia and obsessive-compulsive (OC) symptoms. Compared with individuals with low Miso-OC factor scores, individuals with high scores reported higher perceived controllability of their social interactions during the uncontrollable condition and stronger aversion to social norm violations in the uncontrollable compared with the controllable condition. The social and mood factors were unrelated to social control. Together, these results suggest misophonia, and OC symptoms share a latent psychiatric dimension characterized by aberrant computations of social controllability.

2.2 Introduction

Misophonia is a disorder in which sounds generated by other people - such as slurping, chewing, or clicking a pen - lead to intense, negative physical and/or emotional responses, including disgust, irritation, rage, or anxiety in the individual[41,42]. It is estimated that as much as 20% of the population may experience some form of misophonia, with a smaller subset experiencing a more severe form[41,42]. The heightened physiological responsivity and emotional reactivity experienced by misophonia patients in response to trigger sounds often correspond with high levels of distress and debilitating impairments in daily functioning, including strained relationships and isolation due to social avoidance[41,43].

The social nature of triggers in misophonia suggests that social impairments might play an important role in the aversive response[44,45]. Initial evidence suggests that negative reactions are associated with the perceived source of the sound rather than its particular acoustic properties[37]. For example, individuals with misophonia have reported that feelings of anger and distress often dissipate upon realization that a trigger sound is coming from a source other than another human, such as an animal, a machine, or themselves[37,46]. The specificity of misophonic reactions to social sounds may be related to the idea of agency, which refers to voluntary control over one's actions. Sounds produced by other people are uniquely intentional[47], and can be misattributed to the self, especially in psychiatric populations[48,49]. Misophonia may therefore involve impairments in agency discrimination and associated disruptions in perceived controllability.

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