Neurobehavioral Consequences of Disrupted-In-Schizophrenia-1 (DISC1) Overexpression in a Transgenic Rat Model

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Zusammenfassung

Das Verständnis, wie molekulare Mechanismen das Sozialverhalten beeinflussen, ist von zentraler Bedeutung, um Grundlagenforschung der Neurowissenschaften mit den klinischen Symptomen psychiatrischer Störungen zu verknüpfen. Bei der heterogenen Ausprägung der Schizophrenie ist diese Verknüpfung besonders wichtig, da Beeinträchtigungen im Sozialleben gegenüber aktuellen Behandlungsmethoden weiterhin resistent sind. Unter den molekularen Faktoren, die an der Pathophysiologie beteiligt sind, hat sich das Gen *Disrupted-in-Schizophrenia-1* (DISC1) als konvergenter Schlüsselfaktor herausgestellt, der die dopaminerge Signalübertragung und synaptische Organisation beeinflusst. Diese Arbeit beschreibt die neurobehavioralen Folgen einer Überexpression von DISC1 in einem transgenen Rattenmodell (tgDISC1), wobei ein besonderer Schwerpunkt auf der Rolle des sozialen und belohnungsbezogenen Verhaltens liegt.

In zwei Studien an tgDISC1-Ratten zeigten Verhaltens-, pharmakologische und neurostrukturelle Analysen selektive Störungen bei der Bewertung sozialer Signale und deren Modulation durch dopaminerge Signalübertragung. tgDISC1-Ratten zeigten intaktes soziales Interesse, aber beeinträchtigtes soziales Belohnungslernen. Zudem entwickelten sie keine Präferenz für das Interagieren mit einem unbekannten Artgenossen gegenüber einem bereits bekannten – diese Beeinträchtigung konnte durch die Gabe eines Dopamin-Antagonisten mit limbischer Spezifität behoben werden. Damit übereinstimmend wurden mittels Diffusions-Tensor-Bildgebung mikrostrukturelle Veränderungen innerhalb mesolimbischer Knotenpunkte festgestellt. Diese Ergebnisse verknüpfen etablierte molekulare Störungen mit ihren funktionellen Ausprägungen im Sozialverhalten.

Eine dritte Studie an nicht-transgenen Ratten untersuchte ergänzend die neurochemischen und mechanistischen Grundlagen des sozialen Belohnungslernens und analysierte, wie soziale Informationen das eigene Verhalten beeinflussen. Die Ergebnisse zeigen, dass dieser Prozess stark von der Bekanntheit zwischen Individuen abhängt und durch neuromodulatorische Einflüsse von Oxytocin geprägt ist, was das Verständnis der neuronalen Grundlagen sozialer Kognition und Belohnungslernen erweitert.

Zusammenfassend integriert diese Ausarbeitung molekulare und verhaltensbezogene Ansätze, um aufzuklären, wie konvergierende neurobiologische Mechanismen das Sozialverhalten steuern. Somit wird eine translationale Verbindung zwischen den Neurowissenschaften und der sozialen Dysfunktion bei psychiatrischen Erkrankungen hergestellt.

Abstract

Understanding how molecular mechanisms shape social behavior is central to linking basic neuroscience with the clinical phenomena observed in psychiatric disorders. In the heterogeneous presentation of schizophrenia, this link is especially crucial as symptoms affecting social functioning remain particularly resistant to current treatment. Among the molecular factors implicated in its pathophysiology, Disrupted-in-Schizophrenia-1 (DISC1) has emerged as a convergent key factor, influencing dopaminergic signaling, neurodevelopment and synaptic organization. Hence, this thesis outlines the neurobehavioral consequences of DISC1 overexpression in a transgenic rat (tgDISC1) model of sporadic schizophrenia, with a particular focus on the role of social and reward-related behavior.

Across two complementary studies in tgDISC1 rats, behavioral, pharmacological and neurostructural analyses revealed selective disruptions in the valuation of social cues and their modulation by dopaminergic signaling. tgDISC1 rats showed intact baseline sociability but impaired social reward learning and failed to prefer novel over previously encountered conspecifics. The later phenotype was rescued by amisulpride, a selective dopamine antagonist with limbic specificity. Consistent with this, diffusion tensor imaging identified microstructural alterations within mesolimbic key nodes. By anchoring value processing within dopaminergic signaling, these findings connect established molecular disturbances in schizophrenia to their functional manifestations in social behavior and reward valuation.

In a third study, complementary research in non-transgenic rats provides insight into (fundamental) mechanistic and neurochemical determinants of social reward learning by focusing on underlying mechanisms that govern how social information guides own behavior. The results demonstrate that this process is strongly sensitive to familiarity between individuals and shaped by neuromodulatory influences of oxytocin, offering a broader perspective on the neural foundations of valuation and social cognition.

In conclusion this work integrates molecular and behavioral perspectives to elucidate how converging neurobiological pathways govern social reward learning, providing a translational link between basic neuroscience and the social dysfunction in psychiatric conditions.

Chapter 1 - Introduction

Psychiatric disorders remain among the leading causes of disability worldwide, largely because mechanistic understanding has lagged behind clinical description. Schizophrenia, for example, is characterized by profound disruptions in everyday adaptation and social functioning, yet treatments remain only partially effective. Addressing this gap requires approaches that link molecular mechanisms to behavioral outcomes. As a first step, this thesis begins with an overview of dopamine, one of the most consistently implicated systems in schizophrenia and psychiatric disorders more broadly.

The Dopamine System

Dopamine (DA) is a key neurotransmitter in the mammalian (central) nervous system. Within the brain, the DA system is widespread, but highly organized into distinct canonical pathways (Björklund & Dunnett, 2007; Wise, 2004). Most prominent are the midbrain dopaminergic cell bodies, distinct in the Ventral Tegmental Area (VTA) and Substantia Nigra (pars compacta; SNc) (Kwon & Jang, 2014; Ungerstedt, 1971). From there, axonal projection pathways emerge, aiming at various areas.

The mesocorticolimbic pathway contains VTA-originated DA neurons targeting the Nucleus Accumbens (NAc), amygdala, septal nuclei, olfactory tubercle, and certain areas of the Medial Prefrontal Cortex (mPFC; De Keyser et al., 1990). Furthermore, it is often subdivided into the mesolimbic pathway, which comprises DA neurons of the VTA that extend their projections to the NAc, located within the Ventral Striatum (VS), as well as amygdala and septal nuclei (Björklund & Dunnett, 2007). The mesolimbic pathway is described as a critical reward-pathway in the brain (Ikemoto, 2010; Russo & Nestler, 2013; Voorn et al., 1989). In extension, there is the mesocortical pathway which comprises VTA neurons targeting parts of the mPFC exclusively (De Keyser et al., 1990; Lindvall et al., 1978). It is important to note that this categorization is not uniform across the literature, simply because the term "limbic (system)" itself is referring to a vague and abstract definition (Roxo et al., 2011). For the context of this dissertation, the above-mentioned definition of “mesolimbic” system is applied.

Lastly, a major dopaminergic projection contains cells from the SNc targeting the dorsal part of the striatum, referred to as nigrostriatal pathway (Björklund & Dunnett, 2007). Though this description of major DA pathways is widely accepted and used in

neuroscience, advancing technologies continuously allow for more precise, even short-circuit architecture and regional differences (Chen et al., 2023; Morales & Margolis, 2017; Roeper, 2013; Yang et al., 2018).

Actions of dopaminergic neurons are mediated by G-Protein coupled receptors, which range from D1-receptors (D1R) to D5 receptors (D5R) (Sibley et al., 1993). These receptors can be categorized into two subgroups: D1-type receptors (including D1R and D5R), which stimulate neuronal activity, and D2-type receptors (comprising D2R, D3R and D4R), which inhibit neuronal activity (J.-M. Beaulieu & Gainetdinov, 2011; Missale et al., 1998). In addition, DA signaling is regulated by autoreceptors, which are located at presynapses in projection terminals and somatodendritic at cell bodies in the midbrain. They belong to the family of D2-type receptors and, as most commonly and best described, consist of D2R (L'Hirondel et al., 1998). They coordinate DA synthesis, release and reuptake (Anzalone et al., 2012; Benoit-Marand et al., 2001).

Dopaminergic Control of Behavior

The DA system has a broad variety of behavioral control in humans and animals alike. The most prominent domain covers reward-related behavior (Matsumoto & Hikosaka, 2009; Schultz, 2015; Schultz et al., 1997)(Box 1). Early experiments suggested a uniform response of DA neurons to rewards, or associated stimuli, and silencing upon aversion (Mirenowicz & Schultz, 1996). However, more recent findings and methodological developments show an intriguing heterogeneity in DA signaling, even within subregions of anatomical structures (de Jong et al., 2019; Klawonn & Malenka, 2018; Lammel et al., 2013; Matsumoto & Hikosaka, 2009). This work demonstrates that DA neurons are not uniform in their coding properties: while some populations primarily signal rewarding outcomes, others are selectively engaged by aversive events, and still others encode motivationally salient stimuli independent of valence (Lammel et al., 2013; Morales & Margolis, 2017). Hence, rather than acting as a uniform reward-signal, DA transmission flexibly encodes the value of rewards, thereby affecting decision-making (Yawata et al., 2012, Box 1).

In the mesolimbic system, DA has been suggested as a neuronal representation for subjective reward value (Castrellon et al., 2019; St. Onge et al., 2012), as differences in D2R availability were found to predict how strongly rewards are coded, both in humans (Dang et al., 2018) and, more vaguely, in animals (Tournier et al., 2013). Altered DA

signaling can therefore shift reward preferences, thereby, biasing decision-making toward higher or lower valued outcomes (Balleine et al., 2009). As a consequence, DA is directly connected to motivation and goal-directed behavior (Ferguson et al., 2020; Grace et al., 2007). These influences ultimately converge on the control of movement, ensuring that motivational states are expressed through appropriate approach or avoidance, as exemplified by the profound motor impairments that arise when DA pathways are disrupted (Frank & Hutchison, 2009; Halbout et al., 2019). Hence, DA is understood as a key modulator of valuation, motivation, and action, thereby enabling individuals to convert perceived (reward) information into adaptive behavior (Kwak & Jung, 2019).

As DA builds the basis for coordinating engagement with the environment, it has an innate and complex link to the modulation of social behavior, from insects to fish, to mammals (Gunaydin et al., 2014; Kawamichi et al., 2016; Scaplen & Kaun, 2016). Beyond guiding the pursuit of individual rewards, DA contributes to how organisms engage with conspecifics, thus influencing sociability, affiliation, and the motivation to interact (Bicks et al., 2015; Padilla-Coreano & Martínez-Rivera, 2025; Walsh et al., 2022). Consistent with this, studies in rodents have demonstrated that VTA DA neurons are activated during interactions with conspecifics, whether familiar or unfamiliar, supporting the idea that social contact itself is processed as a rewarding and salient stimulus (Solié et al., 2021). Moreover, dopaminergic activity has been shown to facilitate the learning of socially derived cues, allowing animals to extract information from conspecifics about both, external conditions (e.g., food availability) and internal states such as distress or arousal (Choleris et al., 2011; Li et al., 2025; Lichtenberg et al., 2018; Paraouty et al., 2021; Suzuki & Lucas, 2015; Willuhn et al., 2014). Consistent with this, impaired social behavior has been obserbed in experimental animal models with altered dopaminergic signaling (Homberg et al., 2016).

Similarly, in humans, the dopaminergic system has been implicated in the modulation of social preferences (Soutschek et al., 2017), social decision-making such as cooperation and trust (Bellucci et al., 2020; Rutledge et al., 2015), and in the reinforcement of prosocial behaviors including generosity and reciprocal exchange (Moll et al., 2006; Phan et al., 2010). As an experimental example, Soutschek et al. (2017) found that pharmacological reduction of D2R/D3R signaling would reduce prosocial choices in an economic game, directly linking DA transmission to human social decision-making. Thus, by assigning value to social stimuli, DA shapes how individuals' approach (novel)

partners, establish relationships and even use information acquired from others to guide own behavior (Insel & Fernald, 2004; Sotoyama et al., 2022).

DA modulates reward and social behaviors in concert with other neurotransmitter and hormonal systems rather than acting in isolation. In main parts of the mesolimbic DA system, e.g., the VTA, NAc and the amygdala, DA receptors often co-localize with Oxytocin (OXT) receptors (OXTR) and they strongly regulate each other's signaling through forming heterocomplexes (Borroto-Escuela et al., 2022; de la Mora et al., 2016; Jurek & Neumann, 2018; Petersson & Uvnäs-Moberg, 2024; Rappeneau & Castillo Díaz, 2024; Roeling et al., 1993; Romero-Fernandez et al., 2013). For instance, OXT release in the VTA activated DA neurons (Xiao et al., 2017) and subsequently led to heightened DA in the NAc (Shahrokh et al., 2010). Similarly, activation of DA terminals in the main OXT hub, the periventricular nucleus, increased circulating OXT levels (Scott et al., 2015), underscoring their tightly linked signaling. Thus, it is reasonable that OXT takes a part in DA shaping behavioral responses (for review see Petersson & Uvnäs-Moberg, 2024).

In summary, DA exerts a profound influence over both reward-related and social behaviors, enabling organisms to evaluate stimuli, assign value, and translate motivational and social signals into adaptive actions. These functions are yet further fine-tuned through interactions with other neuromodulators (e.g., OXT), reflecting DA's broad role in shaping complex behavioral coordination. Importantly, the very processes by which DA regulates valuation, motivation, and sociability are among the most disrupted in psychiatric disorders. Dysregulated dopaminergic signaling has been consistently implicated in schizophrenia, affective disorders, addictive behavior and autism spectrum disorder (ASD), underscoring its position as a cornerstone of psychiatric pathophysiology. Thus, the same mechanisms that allow DA to flexibly adapt behavior to environmental and social demands can, when dysregulated, contribute to maladaptive cognition and behavior.

Box 1. Definitions

Reward: Denotes the positive affect that an individual associate with an object, action or internal state. It represents an outcome that elicits approach behavior, reinforces learning and supports motivation through its capacity to signal beneficial consequences (Berridge & Kringelbach, 2015; Schultz et al., 1997).

Value: Designates the evaluative or motivational weight assigned to an option, stimulus or action. It expresses how strongly something is preferred, desirable or worth pursuing and thereby guides choice and behavior (through distinct underlying neural and psychological processes) (Balleine et al., 2009; Rangel et al., 2008).

Social Interest: Encompasses the motivation and tendency of individuals to seek out, approach, and engage with conspecifics (apart from being driven by aggression or reproduction) (Moy et al., 2004).

Social Novelty Preference: Refers to an individual's tendency to preferentially investigate a novel conspecific over a familiar one, when given a choice (Moy et al., 2004).

Social (Reward) Learning, Social Transmission: Defines the process by which animals acquire behaviors or preferences through (positive) social interactions and reinforcement (For systematic review on Social Reward see Stijovic et al., 2024, for review on Social Learning see Reader, 2016).

Social cognition: Conceptualizes the emotional and cognitive processes that enable people to understand other's (social) behavior (Adolphs, 2009; Javed & Charles, 2018; Mancuso et al., 2011).

Social functioning: Describes an individual's capacity to engage in social interactions and to maintain interpersonal relationships across different (societal) roles (Abel et al., 2021; Burns & Patrick, 2007; Ro & Clark, 2009).

Schizophrenia

While it is acknowledged to a growing extent that many disorders have fluid boundaries, and are more of a spectrum than fitting into rigid categories, for further use, the term "schizophrenia spectrum disorder" will be shortened to schizophrenia for simplicity (American Psychiatric Association, 2013).

Schizophrenia (SZ) is a severe psychiatric condition with a complex and heterogeneous presentation. The condition was first described by Emil Kraepelin and Eugen Bleuler, independently, in the end of the 19th century. Kraepelin conceptualized the disorder as *dementia praecox*, underlining the early cognitive deterioration and functional decline in patients (Kendler, 2020). Later, Bleuler coined the term "schizophrenia" (from ancient Greek: "split mind") to capture what he considered the core feature in patients: a fragmentation of thoughts, affect and cognition (Kyzirdis, 2005). Those early descriptions reflect the striking abnormalities in behavior and experiences reported by patients, ranging from disturbances in perception and reasoning to difficulties in sustaining social relationships and daily functioning.

SZ occurs at relatively stable rates worldwide, throughout various populations, which suggests an inherited vulnerability with a stable gene frequency (Castillejos et al., 2018). Though the disorder has a marked genetic component, cases can still arise sporadically. The onset typically manifests in early adulthood and psychiatric comorbidities, such as depression or addiction, are frequently observed, adding further to the complexity of the clinical picture (Buckley et al., 2009; A. I. Green et al., 2003).

Although SZ has been studied for more than a century, its underlying mechanisms remain elusive. Rather than resulting from the dysfunction of a single gene or pathway, the disorder is increasingly understood as the outcome of multiple genetic risk factors, probably interacting with environmental influences to disrupt neuronal trajectories (Karl & Arnold, 2014; Owen & O'Donovan, 2017). These interactions converge on widespread alterations in molecular networks, making SZ a phenotypically diverse and mechanistically complex disorder (Orsolini et al., 2022). Among the many neurobiological hypotheses, dysregulation of DA has been particularly influential in framing SZ research.

The Dopamine Hypothesis of Schizophrenia

The DA hypothesis of SZ posits that dysregulated dopaminergic activity contributes significantly to the disorder's pathophysiology (Seeman et al., 1976). Initially, this hypothesis suggested that excessive DA transmission in the striatal pathways underlies positive symptoms such as hallucinations and delusions (Seeman et al., 2005). This notion was supported by findings that drugs that increase DA release, like amphetamines, can induce psychosis-like behavior (Helmeste & Seeman, 1982; van Rossum & Hurkmans, 1964), and that antipsychotic medications, which block D2R, alleviate these symptoms (Seeman & Lee, 1975).

Through time, the DA hypothesis of SZ has been revised several times (Davis et al., 1991; Howes & Kapur, 2009). Subsequent refinements to the hypothesis introduced the concept of a dual dopaminergic dysfunction: hyperdopaminergia in the striatal pathways and hypodopaminergia in the prefrontal cortex. This imbalance is thought to contribute to the positive and affective symptoms of schizophrenia, respectively (Davis et al., 1991). Supporting this, post-mortem analysis of brain tissue and imaging studies in patients have provided converging evidence for DA abnormalities, including altered presynaptic DA synthesis and release, as well as changes in D2R or dopamine transporter (DAT) availability, although findings remain heterogeneous across studies (for review see Weinstein et al., 2016). Still, the complex symptomatology cannot be explained by DA dysregulation alone: for instance, some patients exhibit minimal response to antipsychotic medications and accumulating evidence indicates that interactions with other neurotransmitters such as OXT, serotonin and glutamate are highly influential (Iasevoli et al., 2023; G. P. Reynolds, 2021; Rosenfeld et al., 2011). Rather than negating the DA hypothesis, such findings have prompted its refinement and integration with models that incorporate additional neurotransmitter systems.

In summary, the DA hypothesis embodies one of the earliest efforts to provide a foundational framework for SZ and ongoing research continues to refine our understanding. Given that DA disturbances are consistently present in SZ patients (Weinstein et al., 2016), and antipsychotic drugs continue to act on DA as their primary target, DA signaling remains a plausible and promising focus for advancing our understanding of the intricate neurobiological facets in SZ.

Symptom Classes

Current classification of SZ by the International Classification of Diseases (ICD) embrace distinct clinical categorization by the existence of positive symptoms (e.g., hallucination, delusions), negative symptoms (amotivation, anhedonia, apathy and blunted affect, Kirkpatrick et al., 2011), and cognitive symptoms (memory, attention, and executive functions deficit) (Tamminga & Holcomb, 2004). In addition, motor symptoms including abnormal involuntary movements, parkinsonism, catatonia or psychomotor slowing are very frequently observed in schizophrenia (Walther & Strik, 2012).

Negative Symptoms: Reward & Social Impairments in Schizophrenia

While the hallmark positive symptoms in SZ usually begin in late adolescence and occur episodically (Nazeer & Calles, 2015), negative symptoms, such as social deficits and mild cognitive impairments, often emerge in prodromal stages and are more difficult to capture.

From early on, the classification of negative symptoms in SZ patients has emphasized *apathy* (reduced motivation) and *anhedonia* (inability to feel pleasure), and these features remain central to clinical assessment and self-reporting questionnaires (Andreasen, 1989; Chapman et al., 1980). However, this classical view has been challenged by findings that patients report normal levels of in-the-moment pleasure and show preserved hedonic responses to rewarding stimuli (Cohen & Minor, 2010; Kring & Caponigro, 2010; Kring & Elis, 2013; Strauss et al., 2011). This dissociation has broadened scientific attention toward aberrant reward-related processes (Strauss et al., 2014; Ziauddeen & Murray, 2010). Converging evidence suggests that patients have difficulties in updating or retrieving a mental representation of value (Fulford et al., 2018; Martinelli et al., 2018; Strauss et al., 2014; Ziauddeen & Murray, 2010). Functional imaging corroborates such findings, revealing attenuated VS activation during reward processing (Esslinger et al., 2012) and corresponding impairments in reward-related decision-making (Catalano & Green, 2023; Strauss et al., 2011). This evidence suggests that, while hedonic responses remain intact, value-based modulation of behavioral output, e.g., decision-making, reward anticipation or novelty-responding (Heerey & Gold, 2007; Strauss et al., 2011, 2014) may be compromised in SZ (Winton-Brown et al., 2014). Importantly, this dissociation likely contributes to the clinical presentation of apathy,

understood as diminished (goal-directed) motivation, even though hedonic responses to stimuli remain largely preserved (L. L. Wang et al., 2021).

Social functioning (Box 1) may provide a particularly sensitive context in which these valuation deficits manifest. Despite preserved social interest (Blanchard et al., 2015, Box 1), individuals with SZ often struggle to recognize and interpret social cues such as facial expressions, gestures (Billeke & Aboitiz, 2013; Corrigan & Nelson, 1998) and other's intentions, difficulties that also appear during passive observation of other's interactions (Cavieres et al., 2023). Thus, patients appear limited in their ability to benefit from positive social interactions (Campellone et al., 2018; Catalano et al., 2018, Box 1). For instance, it was demonstrated that patients exhibited dysregulated social reward learning, when emotional facial expressions (such as smiling faces) served as affective cues, indicating a reduced capacity to learn from rewarding social feedback (Liu et al., 2022).

Unsurprisingly individuals with SZ report marked difficulties in participating in society and maintaining relationships (Weittenhiller et al., 2021), and thus have smaller social networks (Gayer-Anderson & Morgan, 2013). Nevertheless, they describe comparable interest in social activities and value social relationships as highly as healthy control individuals (Blanchard et al., 2015). Improving social functioning is therefore rated among a top priority for therapy outcomes (Barnett et al., 2022).

These findings suggest that, rather than reflecting reduced capacity to enjoy social interactions (Mote & Fulford, 2020), social impairments in SZ involve more nuanced disruptions in the mechanism of social-affiliative-behavior. Whether such impairments reflect a domain-general disruption in reward mechanisms or, instead, a domain-specific vulnerability of social rewards, remains a matter of debate. Some studies support a common dysfunction in reward valuation and learning (Butler et al., 2020; Hanssen et al., 2020), whereas others suggest that social rewards may be differentially affected and constitute a partly distinct domain of impairment (Campellone et al., 2018; Catalano et al., 2018, 2020). In either case, these reward-related alterations interact with broader impairments in social cognition and theory of mind (Lemmers-Jansen et al., 2023, Box 1), as well as with deficits in effort-based decision-making that reduce investment in social exchanges (Barch & Dowd, 2010), further compounding difficulties in maintaining successful social interactions. Collectively, this constellation of deficits fosters

withdrawal and isolation (Schlosser et al., 2014) despite preserved social desire. Importantly, this line of research also strengthens the need to distinguish between *primary* social symptoms, reflecting innate aspects of the disorder, and *secondary* symptoms that arise as consequences of other factors such as socially adverse experiences, medication side-effects or co-morbidities (Carpenter et al., 1988; Gayer-Anderson & Morgan, 2013).

In summary, although hedonic experiences (Gard et al., 2014), and even the recollection of positive emotions (Trémeau et al., 2010), are largely preserved in SZ, patients nonetheless exhibit pronounced impairments in social functioning (Cohen & Minor, 2010; Høegh et al., 2022). This paradox indicates that reduced social engagement cannot be explained by diminished innate interest alone, challenging the broad conceptualization of anhedonia as a negative symptom. Instead, it underscores the need to move beyond broad labels such as "anhedonia" and instead differentiate between *primary* and *secondary* symptoms (Catalano et al., 2020; M. F. Green et al., 2015; Kalin et al., 2015; Weittenhiller et al., 2021). Importantly, manifestations of social impairments and withdrawal may emerge more than a decade before first hospitalization (Velthorst et al., 2016), offering potential value as early indicators of risk (Cornblatt et al., 2012) and underlining their central role in defining negative symptoms.

Taken together, reward and social dysfunctions illustrate the heterogeneity of negative symptoms in SZ. Patients may present only selected deficits, or multiple domains may be affected simultaneously, making the clinical picture highly variable. Previous attempts to utilize further subtypes of SZ have been dropped from current ICD-11 due to poor stability and limited utility, underscoring the need for refined approaches. Advancing both clinical assessment and mechanistic understanding beyond broad labels of apathy and/or anhedonia will be crucial for capturing the complexity of negative symptoms and for guiding more targeted interventions.

Current Treatment of Schizophrenia

Current medications for SZ treat symptoms of patients, but they do not provide a cure. Positive symptoms remain the primary therapeutic target (Arranz & De Leon, 2007).

Antipsychotics

The first generation of antipsychotics (FGA, or "typical" antipsychotics) acts mainly through D2R antagonism (Seeman et al., 1976). While effective in controlling psychosis, their potent blockade of DA signaling can induce severe side-effects: previously described motor symptoms of SZ are even worsening under chronic medication, termed extrapyramidal symptoms (Walther & Strik, 2012). Progress in drug discovery introduced the second-generation antipsychotics (SGA, "atypical" antipsychotics), which act on a broader range of targeted receptors beyond DA (Mauri et al., 2014). All SGAs bind to DA as well as serotonin receptors but to varying extends and kinetics/dynamics, depending on the drug (Mauri et al., 2014). Many further extend their receptor profiles to muscarinic receptors, α-adrenergic receptors, or histamine receptors (Miyamoto et al., 2012). This broader pharmacology reduces the risk of extrapyramidal symptoms compared to FGAs, but at the cost of introducing significant metabolic side effects such as weight gain and insulin resistance (Carli et al., 2021). Thus, while SGAs improved tolerability for many patients, they brought new challenges in long-term management.

Crucially, both drug classes share major limitations. Negative symptoms and cognitive impairments largely persist after remission of the psychotic symptoms. As a result, antipsychotics are frequently prescribed in combination with antidepressants in an effort to address these domains. Psychosocial interventions and psychotherapy can complement pharmacological therapies, but still patients continue to face difficulties in motivation, social functioning, and everyday adaptation even when psychosis is stabilized (Barlati et al., 2024). Thus, the treatment of negative symptoms in particular remains a critical and unresolved challenge.

Taken together, while antipsychotics remain the cornerstone of SZ treatment, they provide an incomplete symptomatic relief, rather than a cure. Importantly, a considerable proportion up to one quarter of first-episode patients do not respond adequately to antipsychotic medication, placing them at risk for treatment-resistant SZ (Diniz et al., 2023; Siskind et al., 2022). Combined with the considerable side-effect burden (Carli et

al., 2021; Pillinger et al., 2020), these limitations highlight the urgent need for a better fundamental understanding of the precise mechanisms in etiology of disease.

Biomarkers

The limited efficacy of current treatments has underscored the lack of mechanistic understanding (and common paths) in SZ etiology and the high demand for approaches that move beyond symptom control. One promising strategy is to classify patients into meaningful subgroups using shared biological diagnostic markers (biomarkers, Cagney et al., 2017). Biomarkers are objectively measurable biological characteristics that serve as indicators of underlying pathological condition, disease processes or therapeutic effects of interventions (Atkinson et al., 2001). Clinically, such a characteristic may include genetic variants, plasma parameters or neurobiological traits which can further be detected by imaging or histological techniques (Aronson & Ferner, 2017).

In other fields of medicine, biomarkers already provide the basis for ascribing patients into biologically meaningful subgroups and guiding targeted therapies, for example, amyloid-β and tau levels in Alzheimer's disease (Jack et al., 2018) or oncogenic mutations in cancer (Collins & Varmus, 2015). By contrast, no biomarker has yet reached routine clinical application within the broad field of psychiatry. For SZ, several candidates have been proposed, including striatal DA synthesis capacity and VS activation as imaging-based markers (Howes et al., 2012; Radua et al., 2015), inflammatory cytokines in cerebrospinal fluid (CSF) or plasma (Frydecka et al., 2018; Romeo et al., 2018) and genetic risk variants identified by genome-wide association studies (GWAS) (Trubetskoy et al., 2022).

By increasing diagnostic precision, particularly in predicting treatment response, biomarker-based approaches hold potential to overcome the limited efficacy of current pharmacological options available (Kapur et al., 2012). Yet, it is unlikely that a single marker will provide sufficient specificity to cover the puzzled molecular underpinnings of SZ. Instead, clinical applications should rely on combined markers, each contributing modest effects, to create diagnostically meaningful tests (Chan et al., 2015). Ultimately, biomarker research aims to delineate neurochemical alterations within more homogenous SZ subgroups, thereby refining our understanding of shared etiological pathways.

Disrupted-In-Schizophrenia-1

The Disrupted-In-Schizophrenia-1 (*DISC1*) gene was first identified through a balanced translocation of the chromosomes 1 and 11, which distorted the *DISC1* locus and thus reduced its expression (St Clair et al., 1990). This translocation was inherited alongside multiple major psychiatric disorders, including SZ, depression and bi-polar disorder, within a large Scottish family, establishing *DISC1* as a milestone genetic finding in psychiatric research (Millar et al., 2000). Although the gene was named *Disrupted-in-Schizophrenia-1*, this designation is somewhat misleading, as subsequent research has implicated *DISC1* in the etiology of multiple psychiatric disorders beyond SZ (Porteous et al., 2011).

DISC1 Protein and Functions

DISC1 encodes a scaffold protein of the same name, which interacts with a large variety of signaling proteins and, as such, regulates numerous cellular processes (Brandon & Sawa, 2011; Camargo et al., 2006; Lipina & Roder, 2014). During neurodevelopment, DISC1 plays crucial roles in neuronal migration, neurite outgrowth and synapse formation (Brandon & Sawa, 2011; Tropea et al., 2018). It further regulates dendritic branching, axonal development and synaptic plasticity, underlining its importance for the establishment of neuronal circuitry (Kvajo et al., 2011; Soares et al., 2011; Tropea et al., 2018). In the adult brain, DISC1 is expressed in multiple (sub)cellular compartments, including the nucleus, centrosome, cytoplasm, axons and synapses, consistent with its multifaceted roles in neuronal signaling (Devine et al., 2016; Tropea et al., 2018).

Given its broad interaction profile, DISC1 has been studied across several neurotransmitter systems, with DA signaling emerging as particularly prominent: DISC1 regulates both pre- and postsynaptic aspects of DA function via interactions with transporters, receptors and associated signaling proteins (Dahoun et al., 2017; Tropea et al., 2018).

Interactions with Dopamine Signaling

As a scaffold protein, DISC1 modulates signaling of several neurotransmitter systems, including DA, glutamate and γ-aminobutyric acid (GABA) (Tropea et al., 2018). Among these, DA signaling has received particular attention. At the presynaptic level, DISC1

plays a central role in vesicle transport by coordinating and strengthening the complexes of motor proteins, cargo adaptors, and microtubules (Flores et al., 2011; Kamiya et al., 2005). Importantly, it further contributes to the coordination and synchronization of exocytosis, the process of releasing neurotransmitter out of the vesicles into the synaptic cleft for signal transmission (Maher & Loturco, 2012; Tang et al., 2016). Moreover, DISC1 influences DA homeostasis by regulating expression, trafficking and membrane availability of DAT, thereby affecting extracellular DA concentrations (Dahoun et al., 2017; Niwa et al., 2010).

Postsynaptically, DISC1 is enriched in the postsynaptic density, where it functions as a molecular hub, enabling other messenger-proteins to interact with and/or activate each other (Hayashi-Takagi et al., 2010; Tropea et al., 2018). Of particular importance, DISC1 interacts directly with D2R, forming physical complexes that enhances glycogen synthase kinase-3 (GSK3) signaling and consequently prevents agonist-induced D2R internalization (Su et al., 2014). By this interaction, DISC1 modulates the Akt-GSK3 pathway, a signaling cascade important in regulating DA transmission (J. M. Beaulieu et al., 2005). In addition, DISC1 affects downstream processes such as cAMP/PKA signaling and ERK/MAPK activation, thereby influencing synaptic plasticity and neuronal excitation (Niwa et al., 2016; Park et al., 2017). Based on this evidence DISC1 has emerged as a key role in regulating DA signaling at the postsynaptic membrane.

In summary, DISC1 modulates DA signaling at multiple levels, from presynaptic release and extracellular clearance to postsynaptic receptor signaling. This complex regulation positions DISC1 as a central hub for protein-protein interactions and as an important integrator of DA dependent signaling pathways.

DISC1 in Psychiatric Pathology

While the findings from above underscore DISC1 as a critical molecular hub, its role as a risk factor in psychiatric diseases has been less straightforward to demonstrate. Large-scale GWAS have failed to identify common variants in the *DISC1* locus as robust risk factors for SZ - and the chromosomal translocation remains unique to the Scottish pedigree (Trubetskoy et al., 2022). Consequently, the classification of *DISC1* as a risk factor for SZ is still debated (Porteous et al., 2014; Sullivan, 2013).

Nonetheless, various association studies across different populations worldwide have linked *DISC1* variants (and its interactome) to SZ, as well as affective disorders, maintaining considerable interest in the gene (Bradshaw & Porteous, 2012; Cannon et al., 2005; Talib Norlelawati et al., 2015; Thomson et al., 2014). Converging support also comes from pre-clinical models - including knock-out (KO), knock-down and missense variants - which consistently demonstrate striking dopaminergic alterations and behavioral phenotypes in multiple domains crucial for SZ symptomatology and beyond (For review see Lipina & Roder, 2014 and Tomoda et al., 2016).

While genetic mutations of *DISC1* gained much attention in psychiatric research, DISC1 protein-level pathologies have been less frequently studied. Insoluble DISC1 protein aggregates have been observed in post-mortem brain tissue and, more recently, in CSF samples from patients with SZ and other psychiatric disorders (Leliveld et al., 2008; Pils et al., 2023). Those pathological aggregations are proposed to result in a loss-of-function, by sequestering DISC1 away from its normal interaction partners, alongside a toxic gain-of-function, by recruiting soluble DISC1 into further aggregation (Atkin et al., 2012; Leliveld et al., 2008, 2009; Ottis et al., 2011). The identifications of these aggregates have led to the concept of "DISCopathies", which frames DISC1 protein disturbances and aggregation as a potential biomarker for subgrouping psychiatric patients (Korth, 2009). Although still a relatively recent concept, it underscores the potential relevance of DISC1 protein dysfunction in SZ.

As an experimental outset to investigate the involved mechanism in-vivo, a translational rat model was generated that mimics DISC1 overexpression and aggregation, enabling the study of its impact on DA signaling and behavior.

Transgenic DISC1 Rat Model

The transgenic DISC1 (tgDISC1) rat provides a versatile platform to study how alterations in DISC1 signaling contribute to the pathoetiology of psychiatric disorders. The model expresses the full-length non-mutant human *DISC1* gene at modest levels, aiming to recapitulate protein misassembly phenomena observed in samples from SZ patients (Trossbach et al., 2016). Since its development, the tgDISC1 rat consistently displayed cellular, neurochemical and behavioral alterations that converge on

dopaminergic dysfunction, a central feature of SZ and other mental disorders (Seidisarouei et al., 2022; Trossbach et al., 2016; Uzuneser et al., 2019; Wang et al., 2017; A. L. Wang et al., 2019).

At the cellular and neuroanatomical level, the model exhibits a profound impact on the DA system. tgDISC1 rats show an increased expression of D2R as well as an increased DAT translocation to the plasma membrane, hence decreasing the DA availability in the synaptic cleft (Trossbach et al., 2016). Neurochemical profiling revealed reduced DA levels in the striatum, PFC, amygdala and hippocampus, alongside alterations in other transmitter systems such as noradrenaline, serotonin and acetylcholine (Trossbach et al., 2016; Uzuneser et al., 2019; Wang et al., 2017).

With regard to neuroanatomy, dopaminergic pathways are altered by a reduced number of SNc neurons, diminished nigrostriatal fiber density and an enlargement of the striosomal compartment in the dorsal striatum (Hamburg et al., 2016). In the cortex, the distribution of parvalbumin-positive (PV^+) interneurons shows a migration-related shift toward deeper layers in somatosensory areas (Hamburg et al., 2016), strongly suggesting a developmental miswiring of cortical-subcortical circuits. Proteomic and bioinformatic analysis further points to widespread synaptic dysregulation, including alterations in actin cytoskeleton regulation, axon guidance and DARPP-32-mediated DA signaling (Sialana et al., 2018). Taken together these findings suggest that DISC1 overexpression affects not only DA levels but also impairs molecular networks that support synaptic plasticity and connectivity.

Ultimately, these neurobiological disturbances are reflected in distinct behavioral phenotypes. tgDISC1 rats display a hyper-exploratory phenotype with augmented investigation of novel objects and enhanced rearing (Trossbach et al., 2016; A. L. Wang et al., 2019). While spatial and object learning remain intact (Uzuneser et al., 2019; Wang et al., 2022), impairments are evident in learning of motor coordination (Trossbach et al., 2016). Moreover, their above outlined abnormal DA homeostasis translates into a hypersensitivity to the psychoactive stimulant amphetamine (Trossbach et al., 2016) underscoring a mechanistic role of DA dysfunction that bridges molecular pathology with behavior. Interestingly, assessment of aged tgDISC1 rats (14-15 months) revealed emerging problems in long-term memory and attentional deficits, while short-term memory remained intact. Crucially, these deficits were rescued by intranasal DA

administration, stressing dysfunctional DA signaling as a mechanistic contributor (Wang et al., 2017).

Taken together, the tgDISC1 rat integrates molecular and cellular neuropathology with a subtle, yet robust phenotype in the positive domain and cognitive symptoms, which widely converges on DA dysfunction. Beyond central phenotypes, peripheral transcriptional profiling has revealed dysregulated immune-related gene networks, overlapping with changes reported in a subset of SZ patients (Trossbach et al., 2019). This finding highlights the model's potential to reflect biomarker-defined subgroups. Against this background, extending the negative symptoms in the tgDISC1 rat represents a promising next step: for now, results concerning social behavior are inconsistent, with reports ranging from diminished interaction to unaltered functioning (Seidisarouei et al., 2022; Uzuneser et al., 2019; Wang et al., 2022). The present work therefore focuses on characterizing male tgDISC1 rats in regard to social and reward-related behavior as a potential proxy for negative symptoms, with the goal of advancing the model's translational relevance in a biomarker-related framework.

Chapter 2 - Research Objectives

As outlined in the preceding chapter, mechanisms underlying SZ are complex across etiologic, symptomatic and therapeutic domains. There remains an urgent need for more precise treatment, ideally guided by reliable biomarkers. In this context, the tgDISC1 rat is of particular relevance as a model for sporadic SZ, characterized by modest DISC1 overexpression, resulting in protein aggregation and disrupted DA homeostasis. In the following studies, the model is characterized in terms of social and reward-related behaviors. In addition to behavioral testing, we sought to investigate neuronal mechanism and consequences of DISC1 overexpression. To this end, we employed minimal to non-invasive, translationally relevant approaches, including subcutaneous pumps to mimic continuous drug administration and in-vivo imaging to detect neuropathological hallmarks of DISC1 dysfunction. Further, complementary research in non-transgenic rats provides insight into (fundamental) mechanistic and neurochemical determinants of social behavior in a social reward learning-task.

Together, this thesis aims to disentangle DISC1-related pathophysiology through an integrative analysis across all three levels of translational validity (construct, face, predictive) while extending the investigation beyond the transgenic model to illuminate the broader neurobiological mechanisms underlying the integration of social reward.

■ Study 1 presents behavioral data from tgDISC1 rats. At baseline, they revealed intact social interest toward an unfamiliar conspecific, comparable to wildtype littermates. However, tgDISC1 rats failed to develop a clear preference for interacting with an additional, novel social stimulus. Importantly, this altered behavior was reversed by continuous administration over two weeks of amisulpride, a relatively selective D2R/D3R antagonist, delivered via subcutaneously implanted osmotic pumps. In contrast, the same treatment paradigm with clozapine did not normalize behavior.

■ Study 2 examined social reward learning in tgDISC1 rats using a paradigm designed to assess how social cues influence the valuation of rewards, serving as a proxy for social information integration (“social transmission”). In addition, we used an in-vivo imaging approach to uncover microstructural alterations in tgDISC1 rats in key subcortical structures, many parts of, or related to, the mesolimbic DA system.

■ Study 3 did not focus on the phenotype of tgDISC1 rat. Here, instead, we aimed to broaden our understanding of the neurobehavioral mechanisms (and principles) recruited for social transmission. Specifically, we examined the role of familiarity between interacting individuals, which emerged as a critical mediator of the strength of social transmission. Further, pharmacological manipulation of OXT signaling modulated the magnitude of this effect in a familiarity-dependent manner, stressing its contribution to the intricate puzzle of social reward processing.

Finally, Chapter 4 synthesizes the findings from the preceding studies, discussing potential mechanisms and neural circuits affected by the DISC1 overexpression and underlying the observed behaviors. Their implications for translational research including human studies and the identification of SZ subgroups, are considered. Additionally, mechanistic insight into social reward learning is discussed, in the light of potential translational use. Methodological limitations are outlined, alongside future research directions, building on the knowledge generated in this work.

Please note that the subsequent sections summarize my own research articles. Accordingly, parts of the text are identical to the respective manuscript. Individual author contributions are specified at the beginning of each summary. Original figures from the publications are included to facilitate comprehension and, in some cases, figures were reorganized for clarity and consistency within the summaries. No other modifications were made. The original articles are provided in the appendix.

Chapter 3 - Summary of Research Projects

Study 1 - Amisulpride restores social deficits in a rat model of schizophrenia featuring DISC1 protein aggregation

José Dören[*], Else Van Gerresheim, Sandra Schäble, Svenja Troßbach, Ann-Christin Langen, Heike Schneider, Werner Steimer, Tobias Kalenscher[§], Carsten Korth[§*], *submitted to Schizophrenia*, Amisulpride restores social deficits in a rat model of schizophrenia featuring DISC1 protein aggregation

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Please note that this section summarizes my own research, therefore certain parts of the text closely correspond to the original manuscript. Selected figures from the publication are included for illustration. The full article is provided in the appendix.

The pharmacological treatment of negative symptoms in SZ remains a serious challenge since they impede social reintegration after positive symptoms disappear upon antipsychotic therapy. Among the negative symptoms, impairments in social functioning such as social withdrawal and lack of social adaption are key since they shape compliance with therapy and social interactions in therapeutic settings (Correll & Schooler, 2020; Nuss & Tessier, 2010). Importantly, SZ patients report improvement of social functioning as one of the top goals for therapy (Barnett et al., 2022) and show equal interest in social contact as healthy individuals (Blanchard et al., 2015), a paradox that underscores the limited understanding of negative symptoms in SZ.

The basis of these social impairments remains insufficiently studied, in part because they may arise as secondary consequences, as described in the introduction. Therefore, we aimed to expand the phenotyping of the tgDISC1 rat in the social domain. We employed the 3-Chamber task (Fig.1), a well-established paradigm with high translational validity for SZ since it probes dimensions directly relevant for diagnostic criteria – namely the willingness to engage in social contact or the preference of social novelty (Ang et al., 2021; Moy et al., 2004). In this paradigm, the first trial assesses social interest by measuring the propensity to engage in social interaction with an unfamiliar conspecific. The second trial quantifies social adaptability by testing the ability to shift preference toward a novel social partner when an additional, unfamiliar conspecific is introduced. In addition, we conducted multiple control tasks to ascertain that the phenotype observed in the 3-Chamber task could not be explained by differences between genotype in anhedonia, working memory, or preservative behavior, such as rigid exploration pattern (Fig. 1). These tasks revealed no genotype-dependent differences.

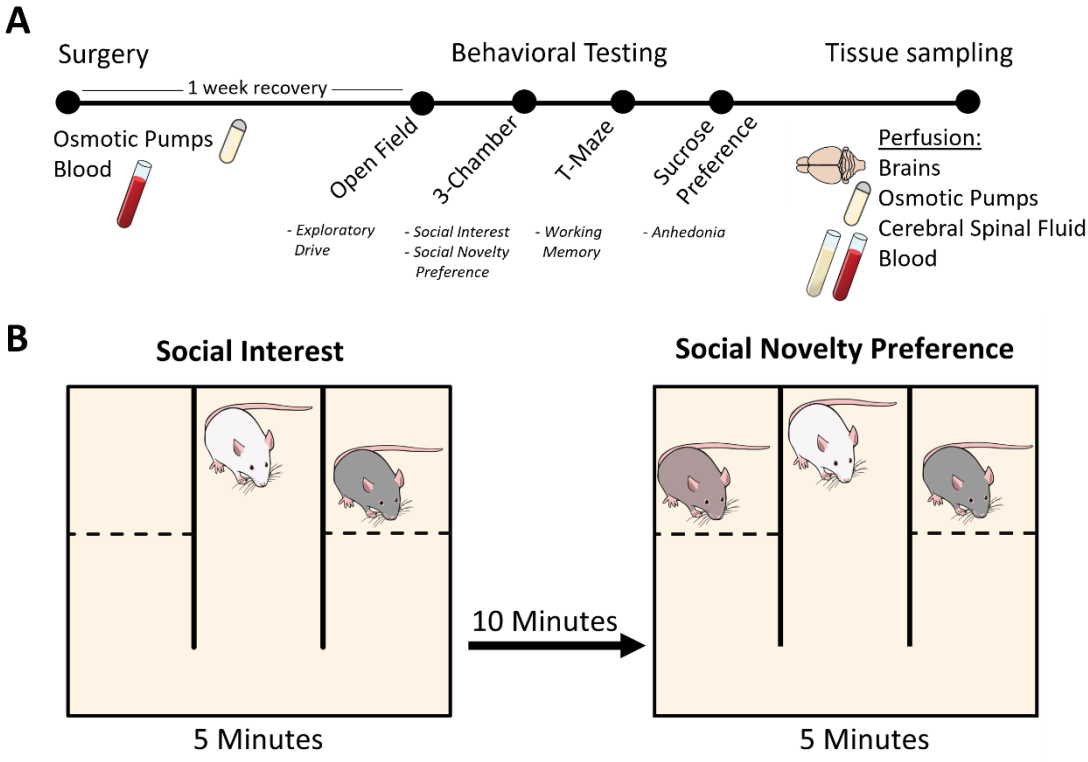

Figure 1 ***Study Overview*** ***A*** *Experimental design* ***B*** *Simplified illustration of the 3-Chamber task and apparatus. Dashed lines represent the bars which separated the subject animal (white) and demonstrators (grey). Demonstrators were aged- and sex-matched and of the same strain (colors differ for visualization).*

As results of the 3-Chamber task, we found comparable levels of social interest between tgDISC1 rats and wildtypes, reflected by the time spent interacting with an unknown conspecific in an otherwise empty apparatus. However, tgDISC1 rats were deficient in social novelty preference, as indicated by reduced interaction with a newly introduced conspecific during the second trial.

This pattern suggests that the tgDISC1 rat model is not characterized by generally diminished social motivation, but rather a context-specific bias toward engaging with previously encountered individuals, when given the choice. The tgDISC1 rat may therefore mirror the challenges faced by individuals with SZ and other psychiatric disorders, where a reluctance to engage in novel social interactions may co-exist with preserved social interest (Morrison et al., 2017; Weittenhiller et al., 2021): if patients place less value on interacting with novel individuals, this may lead to rigid or maladaptive responses to new group dynamics, consistent with descriptions of reduced social effort or impaired social skills in individuals with SZ (Fulford et al., 2018). Moreover, persistent engagement with familiar partners reduces opportunities for forming

new social connections, a critical aspect of adaptive behavior in dynamic social environments. In line with this, people with SZ have reported smaller social networks (Gayer-Anderson & Morgan, 2013). Consequently, difficulties in adapting to novel contexts and the tendency to over-focusing on familiar individuals may reinforce each other, sustaining the hallmark of social anhedonia in schizophrenia despite preserved social motivation for social contact.

Thus, we aimed to establish a pharmacological rescue of the deficits observed. For this purpose, we employed osmotic pumps. These are subcutaneously implanted reservoirs that allow continuous delivery of a steady drug dose, thereby mimicking medication in patients. We tested two SGA compounds with distinct receptor profiles: amisulpride, a rather selective D2R/D3R antagonist, and clozapine with a rather broad, but unspecific receptor profile. Each drug was tested in different groups in different concentrations (“low”,” high” for amisulpride, “low”,” medium” for clozapine). The results showed, that the observed deficit in social novelty preference was rescued by application of amisulpride (0.2 and 0.8 mg/kg/day for two weeks), but not by clozapine (Fig. 2).

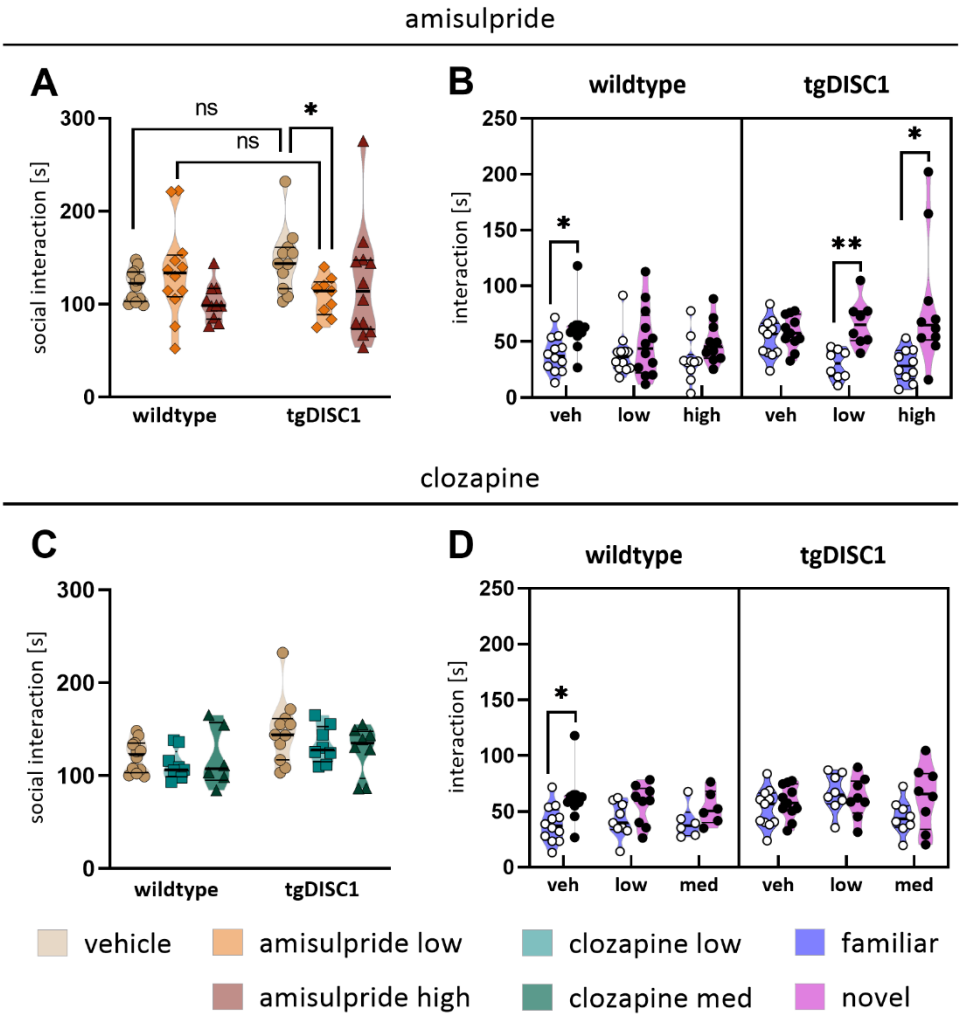

Figure 2 ***Effects of amisulpride or clozapine treatment on social behavior in the 3-Chamber task. A*** *Duration of social exploration during the social interest trial in the 3-Chamber task. Results of post-hoc group comparisons are visualized. ns = not significant.* ***B*** *Social novelty preference in tgDISC1 and wildtype rats following amisulpride treatment. Social novelty preference was measured as an increased interaction duration [s] with the novel conspecific compared to a familiar one. A linear mixed-effects model revealed significant 3-way interactions (novelty * genotype* dose). Post-hoc two-sided t-test showed a significant preference for the novel conspecific in wildtype vehicles (adjusted p = 0.018), whereas this preference was absent int vehicle-treated tgDISC1 rats (adjusted p = 0.431), indicating impaired social novelty preference in tgDISC1 animals. Notably, further post-hoc tests revealed intact social novelty preference in tgDISC1 rats after treatment with either dose of amisulpride. veh = vehicle* ***C*** *Duration of social exploration during the social interest trial in the 3-Chamber task. No significant effects were revealed in the analysis.* ***D*** *Social novelty preference in tgDISC1 and wildtype rats following clozapine treatment. A linear mixed-effects model revealed no significant effects. med = medium; veh = vehicle. Data are presented as median ± quartiles. *p < 0.05, **p < 0.01*

Notably, by contrast, amisulpride rescued, rather than diminished, social novelty preference in tgDISC1 rats, presumably because D2R/D3R antagonism leads to more efficient regulation of DA signaling in the case of D2R overexpression, as seen in tgDISC1 rats (Trossbach et al., 2016).

In summary, we conclude that amisulpride pharmacotherapy may improve social deficits in a subset of SZ patients characterized by aberrant DISC1 signaling, a subgroup for which DISC1 aggregation has previously been proposed as a potential biomarker.

Building on those implications, the next study aimed at broadening the characterization of impaired social behavior in tgDISC1 rats beyond novelty preference, despite intact social interest, which may help understanding trouble in social settings in SZ patients.

Study 2 - Social Reward Learning Deficits and Concordant Brain Alterations in Rats Overexpressing Disrupted-In-Schizophrenia 1 (DISC1)

Dören, J. [*§], Kupriyanova, Y. [§], Schäble, S., Troßbach, S., McGuire, B., Vernon, A. C., Roden, M., Korth, C., & Kalenscher, T. (2025). Social Reward Learning Deficits and Concordant Brain Alterations in Rats Overexpressing Disrupted-In-Schizophrenia 1 (DISC1). The Journal of Neuroscience, e1067252025.

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Please note that this section summarizes my own research, therefore certain parts of the text closely correspond to the original manuscript. Selected figures from the publication are included for illustration. The full article is provided in the appendix.

Impaired social skills are a frequently described feature of patients with SZ (Fulford et al., 2018). Consistently, patients show pronounced difficulties in interpreting social cues during interactions, resulting in limited integration of social information (Billeke & Aboitiz, 2013; Kohler et al., 2003). One explanatory account proposes that these deficits arise from socially acquired information being insufficiently valued or incorporated into one's own behavior (Heerey et al., 2008). To test whether, such impairments manifest in the context of modest DISC1 overexpression and aberrant DISC1 signaling, we examined tgDISC1 rats in a Social Transmission of Food Preference (STFP) (Galef et al., 1984) paradigm specifically modified to probe social reward learning (Fig. 3) (Noguer-Calabús et al., 2022).

In this paradigm, (observer) rats first reveal a preference for one out of two flavored rewards over a time course of three days. Following this, they interact with an unfamiliar individual (demonstrator), which has been fed with the food the observer rat did not prefer. Information about the demonstrator's diet is transmitted via semiochemicals in their breath – and is thus, detectable for the observer. After the social interaction, the observer's preference for the two flavored rewards is tested again. A shift toward increased consumption of the previously non-preferred food is taken as a proxy for social reward learning. This is measured by a Preference Index (PI) (Noguer-Calabús et al., 2022)

$$\text{Preference Index} = \frac{(\text{preferred [g]} - \text{nonpreferred [g]})}{(\text{preferred [g]} + \text{nonpreferred [g]})}$$

The PI ranges from -1 to 1 and reflects the relative preference in relation to the total amount consumed: -1 indicates exclusive consumption of the previously non-preferred food, 1 indicates exclusive consumption of the innately preferred food and 0 shows indifference between the options. This approach allowed the direct testing of whether the tgDISC1 phenotype extends beyond deficits in social novelty and also includes impairments in socially mediated reward learning.

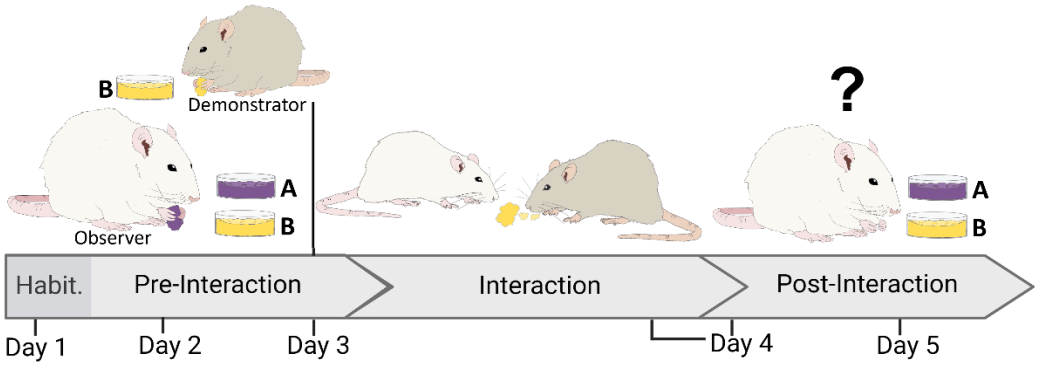

Figure 3 ***Study Design.*** *Illustration of the experimental adaption of the Social Transmission of Food Preferences-Paradigm by Galef et al. (1989) to assess the social influence on revaluation of food rewards (Noguer-Calabús et al., 2022). In the example, the observer rat prefers flavor A over B.* ***Habituation & Pre-Interaction Preference Testing:*** *During the Habituation & Pre-Interaction Testing phase, observer rats were presented with two weighed cups on three consecutive days, each containing a different type of flavored pellets (A or B). The testing lasted for 6 hours each day. After completing testing on Day 3, individual preferences of the observer were quantified by weighing the amount consumed of each respective reward. On Day 3, demonstrators were single housed and provided with a hanging feeder overnight containing the pellets that were not preferred by their assigned observers. Demonstrators were age- and sex-matched, unfamiliar wildtype rats of the same strain (for visualization purposes, colors differ).* ***Social Interaction:*** *On Day 4, each matched pair of demonstrators and observers were allowed to interact freely for 20 minutes.* ***Post-Interaction Preference Testing:*** *Immediately after the Social Interaction, observer rats were returned to their individual cages and provided with two cups, each containing one of the two pellet types. As in the Pre-Interaction Testing, the cups were removed after 6 hours to assess observers' preferences. This procedure was repeated the next day. Habit. = Habituation. Illustrations were sourced from SciDraw and adapted by the author.*

We found that tgDISC1 rats failed to update their reward preferences based on socially transmitted information, whereas wildtype rats increased consumption of the food demonstrated by the conspecific (Fig. 4). Importantly, behavior during the social interaction did not differ between genotypes: tgDISC1 rats and wildtypes initiated social contact to a comparable extend, ruling out insufficient interaction as a confounding factor.

Further, in a series of control tasks, tgDISC1 rats showed intact olfaction as well as the ability to discriminate between odors. Moreover, a separate batch of tgDISC1 rats showed normal performance in non-social reward learning and subsequent reversal learning, suggesting, at least partly preserved cognitive flexibility and a rather nuanced deficit in social reward learning. Hence, for tgDISC1 rats, the social context emerged as a limiting factor for the modulation of flexible behavior.

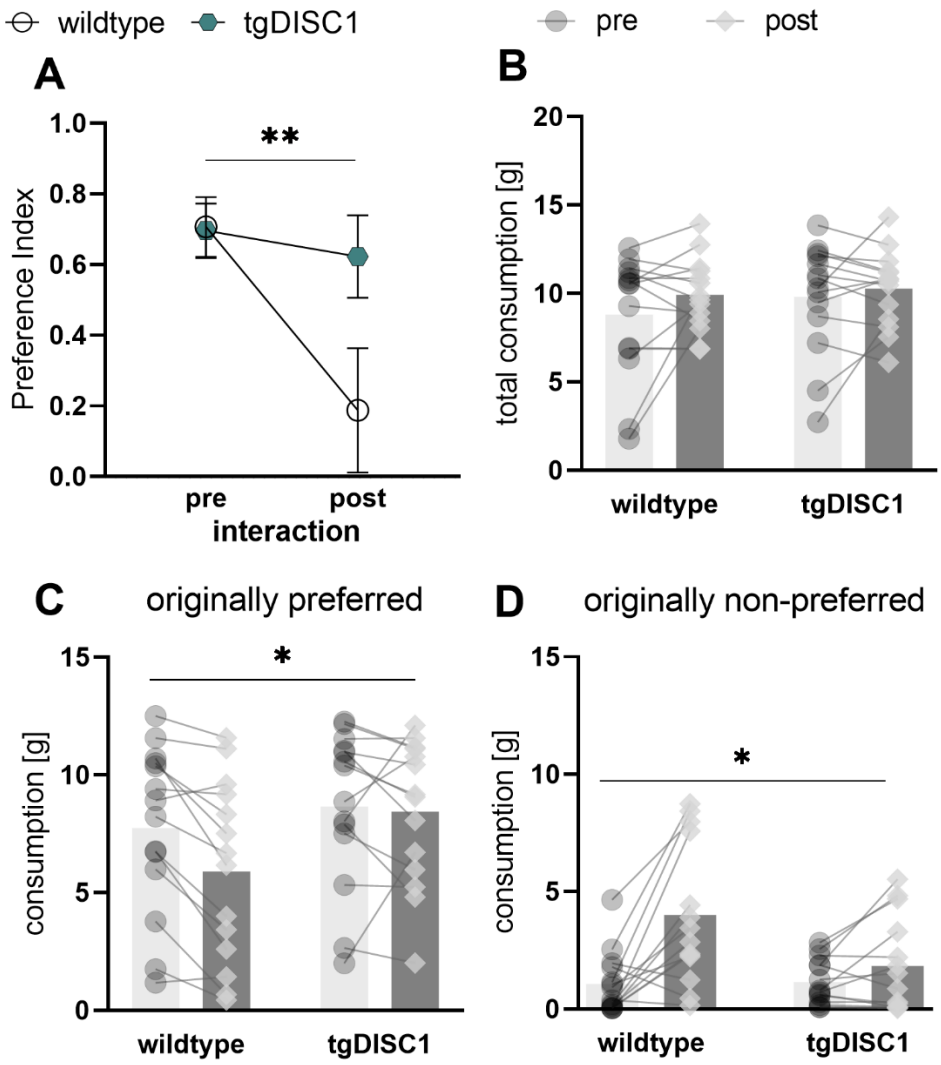

Figure 4 ***tgDISC1 rats show no revaluation of reward values after social contact with a demonstrator****. **A** Preference index (PI). The PI indicating the strength of preference for one reward over the other, for both genotypes and before (pre) vs. after (post) Social Interaction. **B** Total pellet consumption over the course of the STFP. No change in the total consumption of flavored pellets, regardless of the flavor (in grams) from pre- to post-interaction for both genotypes. **C** Consumption of originally preferred food: wildtype, but not tgDISC1 rats decreased their mean consumption of the originally preferred food type (in grams) from pre- to post-interaction. **D** Consumption of the originally non-preferred food: Wildtype, but not tgDISC1 rats, increased the consumption of the originally non-preferred food type (in grams) from pre- to post-interaction.Data are means ± standard error of the mean (SEM.). *p < 0.05 and **p < 0.01 for contact*genotype interaction.*

Further, we aimed to characterize the tgDISC1 model on a neural bases for a better understanding of underlying traits influencing their phenotype. A behaviorally naïve batch of rats was used to investigate such neuropathologies, in order to avoid any confounding factors, like neuroplasticity, induced by prior behavioral testing. We used in-vivo Diffusion-Tensor-Imaging (DTI) which quantifies microstructural integrity,

based on the directionality and magnitude of water diffusion in tissue (Basser et al., 1994; Le Bihan et al., 2001). Within the central nervous system, this is shaped by the morphology of neurites, glia cells and myelin sheaths (Budde et al., 2011; Salo et al., 2021). The index to measure this is called Fractional Anisotropy (FA), which can range from 0 to 1 (Pierpaoli & Basser, 1996). Strictly organized diffusion, as an indicator of microstructural brain integrity, corresponds to higher FA values. On the other hand, a lower FA value is considered to indicate less integrity, reflecting neuropathology in white and gray matter structures.

We checked integrity in regions previously implicated in social reward learning using the (original) STFP paradigm. tgDISC1 rats exhibited alterations in several brain structures, including the NAc, SNc, Basolateral Amygdala (BLA), Cortical Amygdala (CoA) and Thalamus (Fig. 5). Those results point to network-level alterations rather than selective local impairments. This is in accordance with previous rodent studies demonstrating that processing socially acquired information relies on distributed neural circuits. For instance, a well-characterized BLA–prelimbic cortex–NAc circuit is critical for integrating social cues into reward-based decisions in mice (Kietzman et al., 2022), a process closely mirrored by the STFP paradigm. In tgDISC1 rats, FA reductions these same regions - many of which are downstream targets of mesolimbic DA - may reflect the underlying vulnerability of this circuitry to disturbed DISC1 signaling. Since both animal and human studies have demonstrated a central role for DA in social reward processing, revaluation, and decision-making (Burke et al., 2017; Castrellon et al., 2019; Dang et al., 2018), it is plausible that the impaired social reward learning observed in tgDISC1 rats reflects dysregulated mesolimbic DA signaling.

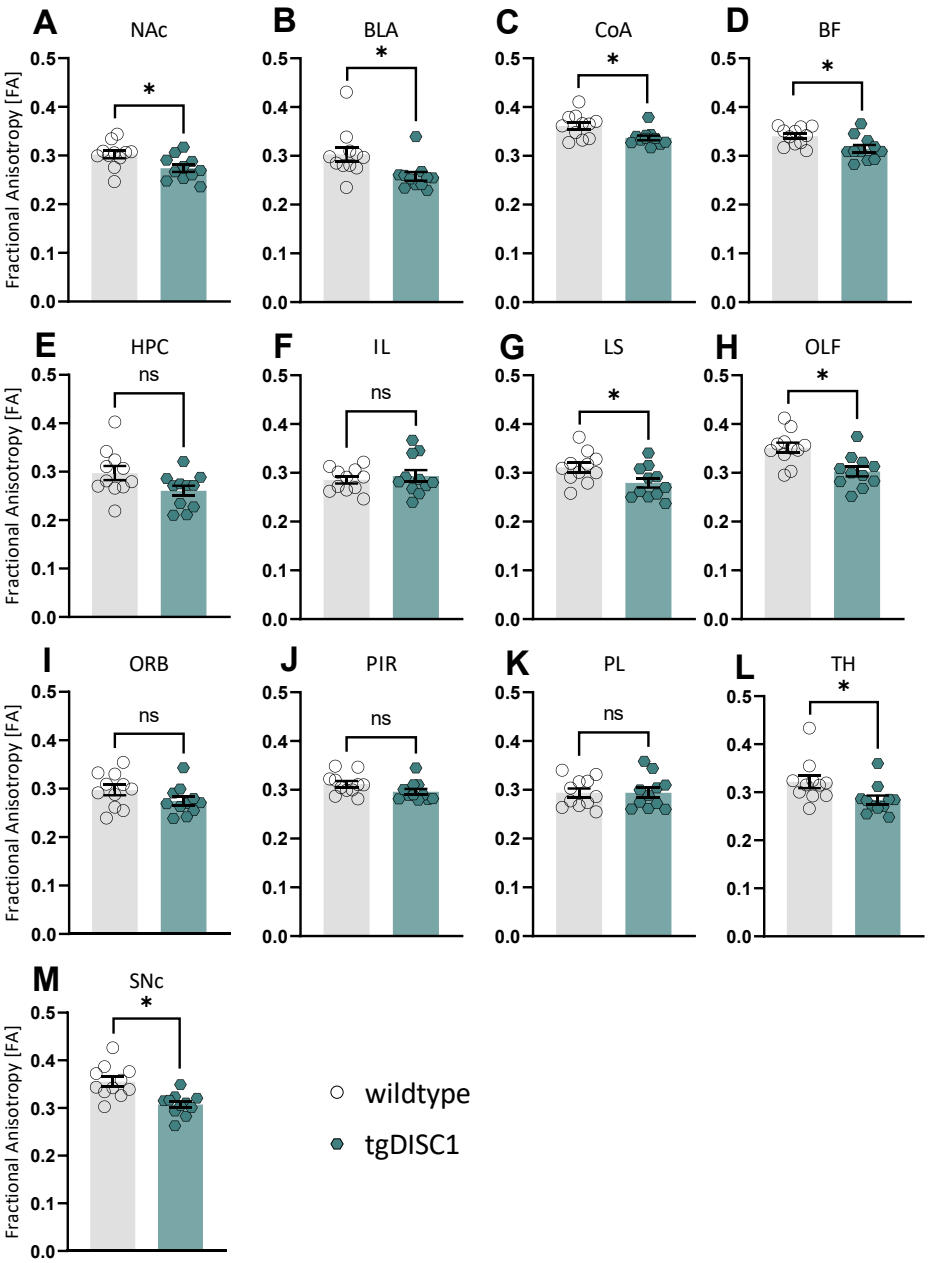

Figure 5 ***Changes in Fractional Anisotropy (FA) observed in tgDISC1 rats compared to wildtypes.*** *Abbreviations: Nucleus Accumbens (NAc), Basolateral Amygdala (BLA), Cortical Amygdala (CoA), Hippocampus (HPC), Infralimbic Cortex (IL), Lateral Septum (LS), Basal Forebrain (BF), Olfactory Areas (OLF), Orbital Cortex (ORB), Piriform Cortex (PIR), Prelimbic Cortex (PL), Substantia Nigra pars compacta (SNc), Thalamus (TH). Data are means ± SEM; ns = non-significant; *p < 0.05*

In SZ patients, DTI studies revealed similar alterations, including reduced FA values in the amygdala, thalamus and NAc (Cuesta et al., 2021; Hashimoto et al., 2009; Kalus et al., 2005; Spoletini et al., 2011). Importantly, these findings have been interpreted as impaired modulation of dopaminergic relay stations (Kalus et al., 2005) and disturbed information flow between limbic and cortical systems (Spoletini et al., 2011).

In conclusion, this study has a 2-sided approach: on the one hand we show that DISC1 overexpression impairs social—but apparently not general—reward learning in rats and on the other hand it is linked to specific microstructural alterations in a fine-grained network of subcortical regions. Together, these results strengthen the face validity of the tgDISC1 model by linking behavioral deficits to neuropathological signatures of DISC1 dysfunction. Moreover, the identification of circuit-level alterations offers potential for biomarker development, which may aid in defining SZ subgroups characterized by aberrant DISC1 signaling.

In the next study, the focus shifted away from the translational properties of the tgDISC1 model toward a mechanistic dissection of social reward learning itself - a domain sparsely investigated in animal research. We relied on the same STFP paradigm used in Study 2, but focused on how social context, i.e. the familiarity between observer and demonstrator rats, would shape the integration of social information. As a pharmacological entry point, we manipulated OXT signaling in observer rats, given its well-established role as a modulator of social behavior and as a social reinforcement signal (Dölen et al., 2013). By integrating contextual and neurochemical dimensions, this approach aimed to refine the mechanistic understanding of social reward learning.

Study 3 - Oxytocin effects on socially transmitted food preferences are moderated by familiarity between rats

Noguer-Calabús, I*., Schäble, S., Dören, J., & Kalenscher, T. (2024). Oxytocin effects on socially transmitted food preferences are moderated by familiarity between rats. Psychopharmacology, 1–12. https://doi.org/10.1007/S00213-024-06682-X

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Please note that this section summarizes my own research, therefore certain parts of the text closely correspond to the original manuscript. Selected figures from the publication are included for illustration. The full article is provided in the appendix.

In this study, we applied the same STFP paradigm for social reward learning as described in the previous study 2 (Fig. 3) but importantly, testing was restricted solely to non-transgenic rats. Our aim was to expand understanding of contextual factors underlying social reward learning by probing the role of familiarity between observer and demonstrator rats. During the social interaction on day 4, observer rats were exposed either to an unfamiliar, sex- and age-matched conspecific ("out-group") as a demonstrator, or their cagemate ("in-group"), with whom they have been housed together before the separation for the STFP procedure (Fig. 6).

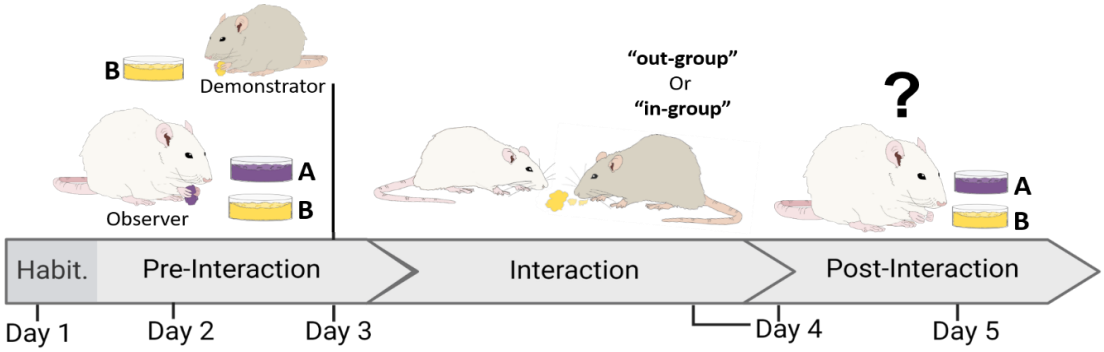

Figure 6 ***Study Design.*** *The Social Transmission of Food Preferences (STFP) paradigm was conducted identically to the procedure shown in Fig. 3. During social interaction on day 4, observer rats were paired either with an unfamiliar, sex- and age-matched conspecific ("out-group") or with their former cagemate ("in-group") as demonstrator, thereby manipulating demonstrator familiarity as an experimental variable in the STFP. All rats were of the same strain (for visualization purposes, colors differ). Habit. = Habituation. Illustrations were sourced from SciDraw and adapted by the author.*

We found that observer rats showed a stronger shift in preference – that is an increased consumption of non-preferred food - when the demonstrator was unfamiliar. In contrast, information provided by cagemates exerted less influence on the magnitude of reward revaluation (Fig. 7). Importantly, interaction times did not differ between the familiarity conditions and therefore cannot account for the observed differences in STFP. Together, these findings establish demonstrator familiarity as a key factor shaping the strength of social reward learning.

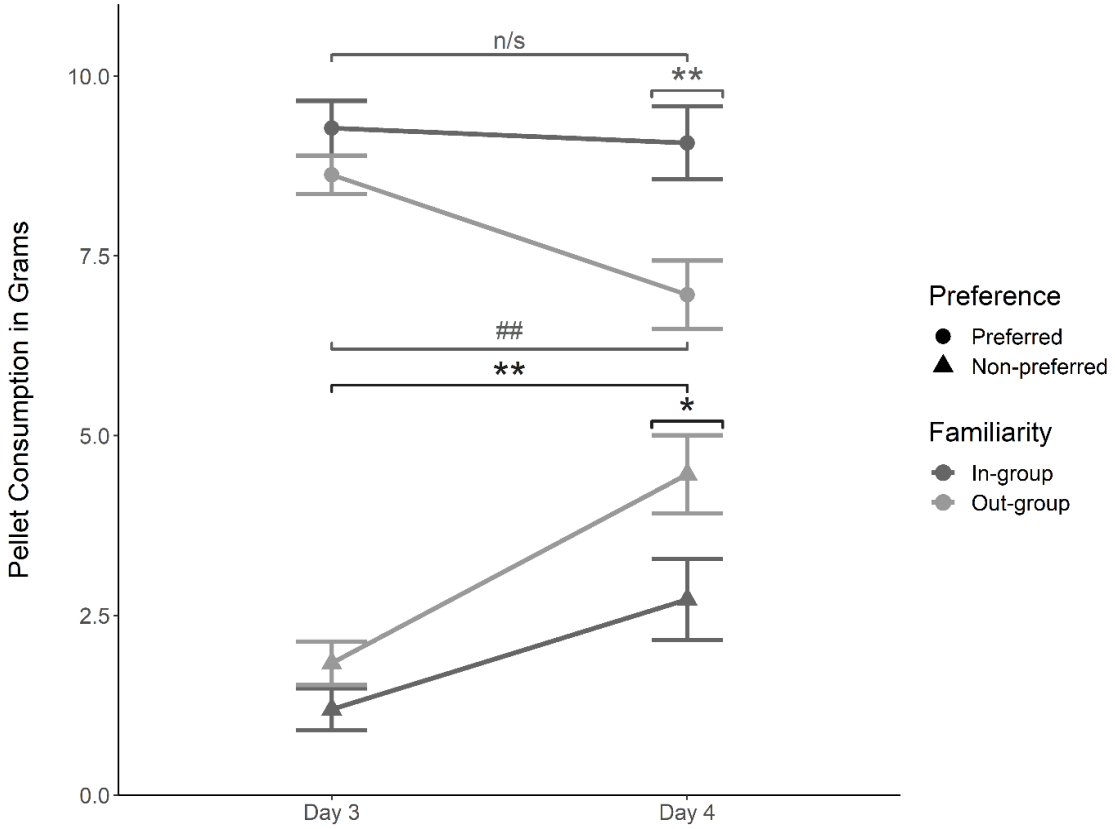

Figure 7 ***Socially transmitted food preferences are modulated by familiarity.*** *Mean ± SEM of the pellets (originally preferred, circle; originally non-preferred, triangle) consumed on days 3 (pre-social interaction) and day 4 (post-social interaction) by observers who interacted with a familiar demonstrator (in-group (n = 31), black) or an unfamiliar one (out-group (n = 40), light gray). The change in consumption of the originally non-preferred pellets pre- vs. post-interaction was stronger in the out-group than the in-group, and a change in consumption of the originally preferred pellets was only found in the out-group. * p < .05; ** p < .01; ## out-group p < .01, n/s in-group p > .05*

To begin uncovering the neurobiological mechanisms underlying this effect, we focused on OXT, a key modulator of social behavior (Dölen et al., 2013; Hung et al., 2017). To this end, observer rats received systematic injections of either a vehicle solution or one of two OXT doses ("low" or "high"), prior to encountering either their cagemate or a stranger as demonstrators (Fig. 8).

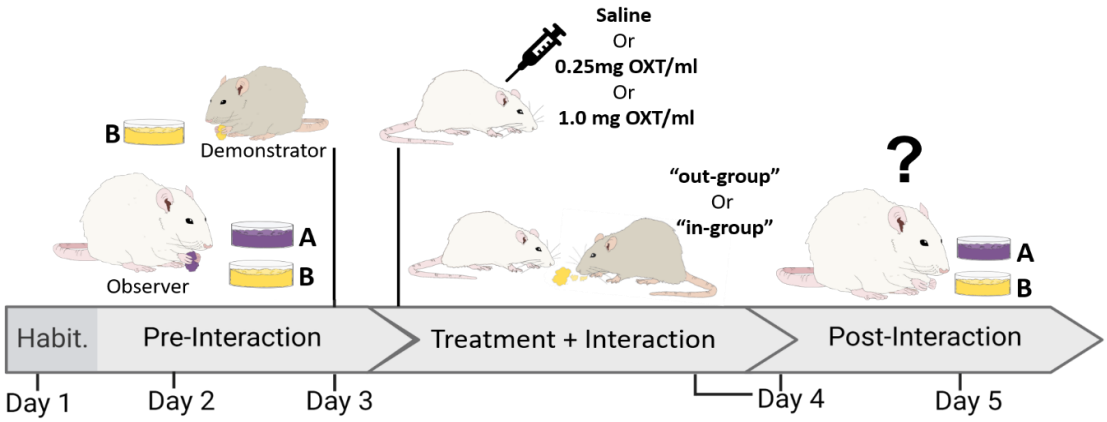

Figure 8 ***Study design with pharmacological manipulation.*** *The experimental design was identical to that shown in Fig. 6, but expanded by systematic injections administered to observer rats on day 4 prior to the social interaction. Animals received either Saline or one of two oxytocin (OXT) doses before encountering their cagemate ("in-group") or an unfamiliar, sex- and age-matched conspecific ("out-group") as demonstrator. All rats were of the same strain (for visualization purposes, colors differ). Habit. = Habituation. Illustrations were sourced from SciDraw and adapted by the author.*

Strikingly, the effects of OXT were familiarity-dependent: in the out-group, treatment with high-dose OXT prevented the increase in consumption of the previously non-preferred food, thereby abolishing social transmission of information (Fig. 9). In the in-group condition, by contrast, OXT-treated observers at both doses consumed the previously non-preferred food at levels comparable to vehicle controls.

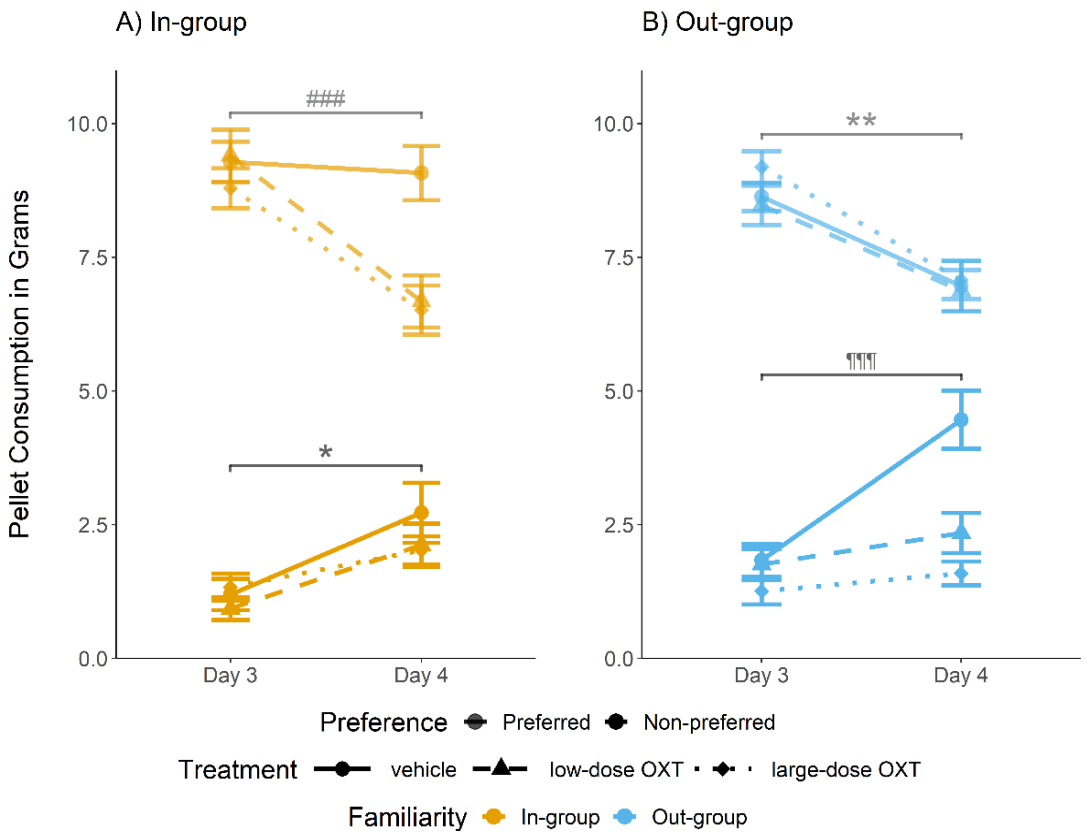

Figure 9 ***Acute oxytocin (OXT) and intergroup effects on socially transmitted food preference (STFP).*** *STFP in the in-group (panel A), and the out-group (panel B). In both panels, the pellet consumption (mean ± SEM) of the vehicle group is represented by the solid line and circle symbols, the low-dose OXT group by the dashed line and triangles, and the large-dose OXT group by the dotted line and squared symbols. The originally preferred pellets (upper lines) are indicated in a slightly transparent hue, and the originally non-preferred pellets (lower lines) are in an opaque hue. In the in-group (panel A), rats in all treatment conditions increased their consumption of the originally non-preferred pellets after social interaction on day 4, thus exhibiting STFP. Unlike rats in the vehicle group, rats that received OXT injections prior to social interaction decreased the consumption of the originally preferred pellets. In the out-group (panel B), OXT administration prevented the increased consumption of the originally non-preferred pellets observed in the vehicle group, thus blocking STFP. However, there were no differences between treatment conditions in the consumption of the originally preferred pellets, which decreased between days 3 and 4. * All treatments $p < .05$; ** all treatments $p < .01$; ### OXT-treated groups $p < .001$; ¶¶¶ vehicle group $p < .001$*

Thus, both behavioral and pharmacological manipulation revealed familiarity-dependent variation in the STFP task, underscoring the complexity of factors that shape social reward learning. In conclusion, an intricate picture emerged with familiarity being a significant driver for differences in STFP magnitude and OXT having a moderative add-on effect.

Chapter 4 - Discussion

The studies compiled in this dissertation collectively address the neurobiological mechanisms that govern social and reward-related behavior. Building on this shared framework, the first two studies employed the tgDISC1 rat - a model with relevance for sporadic SZ - to examine how altered DISC1 signaling influences social adaption and reward learning, while the third study extended this approach to non-transgenic rats to delineate contextual and neurochemical determinants of social reward learning. Together, these investigations provide complementary perspectives on how social cues and information are evaluated and integrated into own behavior, thereby linking mechanistic insights from animal models to processes that are clinically relevant to human psychiatric research.

Behavioral Consequences of DISC1 Overexpression

tgDISC1 rats display a selective alteration in social reward valuation. While overall social motivation was preserved, they failed to adequately respond to social novelty as they formed no preference for a newly encountered conspecific. Further, they did not adjust their flavor preference in the STFP task. These findings suggest that DISC1 overexpression disrupts how social experiences are assigned value, rather than reducing social interest per se.

This dissociation between intact sociability and impaired novelty preference is consistent with prior findings in genetic DISC1 mouse models. For instance, dominant-negative DISC1 mutants and DISC1 knock-in mice with a rare mutation both showed intact social interest but impaired novelty preference (Kaminitz et al., 2014; N. S. Kim et al., 2021; Mahoney et al., 2024). In several cases, the altered phenotype was driven by increased exploration of the familiar conspecific, not by missing interest in the novel partner, closely matching what was observed in tgDISC1 rats. Such convergence across species and genetic variants strengthens the interpretation that impaired social novelty valuation represents a robust feature of DISC1 dysfunction.

Further, the phenotype observed in the STFP paradigm provides an additional indication of altered reward valuation in the social context. tgDISC1 rats were able to assign value to a set of flavors - thus forming a preference for one over the others - but

did not re-evaluate their choice based on socially transmitted information, whereas wildtype rats reliably updated their preferences. Empirical evidence in wildtype rats suggests that information transmission and the respective behavioral adaption in STFP paradigms rely on unconscious processes (Burne et al., 2010; Valsecchi & Galef, Jr., 1989). Thus, its disruption in tgDISC1 rats indicates that DISC1 may regulate basic evolutionary conserved mechanisms of integrating social information into own behavior. While comparable paradigms have not (yet) been widely applied in other DISC1 models, there is converging evidence from mice with striatal D2R overexpression – a molecular trait also present in tgDISC1 rats - who similarly failed to utilize reward-predictive cues to adjust performance (Ward et al., 2015). This overlap strengthens the view that DISC1 overexpression converges on dopaminergic mechanisms, particularly D2R function, as key drivers of altered social reward valuation.

Although the studies in this thesis were not designed to provide full phenotyping of general reward functions in tgDISC1 rats, applied control tasks across various domains showed no evidence for broader deficits. tgDISC1 rats readily expressed an innate preference for a flavor in the STFP, they discriminated odors (Study 2), and preferred larger over smaller rewards in the RMDT - even adapted flexibly during reversal learning. These findings argue against a generalized impairment in reward processing, at least in the paradigms employed. Instead, it is conceivable that social context places an additional demand on neural circuity, for instance by recruiting broader circuit-networks, and that this complexity makes reward valuation in social domains particularly vulnerable to DISC1 dysregulation. This perspective may contribute to the ongoing debate of whether reward dysfunction in SZ emerges from general dysfunctions or separates from pronounced deficits in social contexts.

Taken together, DISC1 overexpression produces a reproducible and selective impairment in integrating social novelty and socially transmitted information. The consistency with other DISC1 models and the mechanistic overlap with D2R overexpressing models strongly suggests that DISC1 plays a critical role in encoding how social cues acquire value. Interestingly, in addition to our results matching with previous reports of genetic DISC1 rodent models, a recent study in transgenic fruit flies expressing human full-length DISC1 show impaired social structures and interaction networks, which closely resembles phenomena postulated by this thesis (Samardžija et al., 2024).

Mechanistic Interpretation of Behavioral Findings

Building on the behavioral alterations described above, the present methodological approaches provide mechanistic insight into the circuit- and molecular-level consequences of DISC1 overexpression. The findings of this thesis corroborate earlier reports of dopaminergic alterations in tgDISC1 rats (Trossbach et al., 2016) and extend them by highlighting the mesolimbic pathway as a potential critical site of dysfunction. Evidence for this conclusion derives from three complementary lines of investigation: 1) behavioral readouts pointing to DA-dependent alterations in social behavior, 2) neurostructural analyses revealing changes in subcortical integrity, and 3) pharmacological rescue experiments demonstrating selective efficacy of a limbic-targeted antipsychotic. Together, these converging approaches suggest that DISC1 overexpression renders particular vulnerability within mesolimbic circuitry, thereby linking the observed behavioral phenotype to a defined neurobiological substrate.

Behavioral Evidence: Mesolimbic Control of Social Novelty and Social Transmission

In the broad picture of social behavior, DA wildly contributes to sociability (Molas et al., 2024), motivation and approach toward conspecifics (Dai et al., 2022). More selectively, DA has been associated with the two behaviors impaired in tgDISC1 rats: social novelty preference (Millan et al., 2007; Molas et al., 2017, 2024; Watson et al., 2011) and the mechanisms underlying social transmission (Choleris et al., 2011; Matta et al., 2017; Wong et al., 2012).

Evidence indicates that these behaviors depend on distinct but partly overlapping neural systems: during the initial encounter with an unknown conspecific, extracellular DA levels rise in both, the mPFC and the NAc, reflecting general novelty detection (De Leonibus et al., 2006; Molas et al., 2024). However, in situations where both, a familiar and a novel conspecific, are present, increased DA release is restricted to the NAc, highlighting this region's selective role in encoding social novelty value (De Leonibus et al., 2006). Optogenetic studies corroborate this interpretation, demonstrating that NAc activity, rather than mPFC signaling, is critical for distinguishing (novel) conspecifics (Gunaydin et al., 2014). The role of DA in STFP is less well established, yet several convergent findings implicate the NAc in this process: recently, a lesion study demonstrated that integrity of the NAc is crucial for the STFP employed in Study 2

(Noguer-Calabús et al., 2022). In support, studies indicate that the NAc, in close interchange with the amygdala, supports the updating of stimulus value based on socially acquired cues, which represents the core mechanism underlying STFP designs (Cardinal et al., 2002; Hall et al., 2001; Mannella et al., 2013). In contrast, evidence for frontal cortical involvement is limited: for instance, a study using a neuronal activity-marker found little engagement of frontal regions following socially transmitted reward information in rats (Agee et al., 2023).

Taken together, these findings suggest that DA release in the NAc plays a more prominent role in regulating social behaviors than DA signaling in the mPFC, at least for the experimental designs employed here (Gunaydin et al., 2014; but see Huang et al., 2020). Disruption of subcortical mesolimbic pathways may therefore represent a plausible mechanism underlying the altered social behaviors observed in tgDISC1 rats. At the same time, the contribution of prefrontal regions cannot be excluded as a contributing factor, given the close anatomical and functional interconnectivity of mesolimbic and cortical circuits (Haber & Knutson, 2010; Hui & Beier, 2022). This interdependence complicates the attribution of the observed phenotype to a single pathway, yet the evidence presented here indicates that mesolimbic dysfunction represents a characteristic feature of the tgDISC1 model.

Neurostructural Alterations: Network-level Disruption of Mesolimbic Pathways

Examination of microstructural integrity in tgDISC1 brains revealed several regions showing significant alterations compared to wildtypes (Study 2). Rather than reflecting a single localized defect, these findings point toward a network-level dysfunction. Notably, the affected areas were part of, or closely connected to, the mesolimbic DA system. Such a pattern is in line with the established role of DISC1 in neurodevelopment (Kamiya et al., 2005) and, more specifically, in the development of dopaminergic circuits (Dahoun et al., 2017; Hamburg et al., 2016; Su et al., 2014). This pattern suggests that DISC1 misassembly due to overexpression may primarily disrupts the organization of subcortical gray matter structures. Supporting this interpretation, prior studies have reported deficient subcortical DA signaling in genetic DISC1 models (Jaaro-Peled et al., 2013), as well as structural changes in striato-nigral circuitry following D2 receptor overexpression (Cazorla et al., 2014).

Additional evidence comes from DTI studies in rodents, which have linked alterations in subcortical structures such as the SNc, amygdala and thalamus to modulation of social behavior (S. Kim et al., 2012). The overlap between these regions and alterations detected in tgDISC1 rats therefore provides converging support for mesolimbic structural vulnerability as a substrate of the selective impairment in social reward valuation: for instance, mechanistic evidence showed that impaired pruning of synapses in the NAc would increase exploration of a familiar conspecific at the expense of social novelty preference (Kirkland et al., 2024), while reduced amygdala activation has been linked to deficient integration of social information in the STFP (Huang et al., 2014). Interestingly, no significant microstructural alterations were detected in cortical regions, with the exception of the CoA. While this observation requires further investigation, it is consistent with previous findings of preserved cortical thickness (Hamburg et al., 2016) and partly preserved cognitive functions in tgDISC1 rats, including working memory and reversal learning (Uzuneser et al., 2019; but see Wang et al., 2017). Collectively, these findings reinforce the notion that DISC1 overexpression preferentially disrupts subcortical networks, implicating (meso)limbic dysfunction as a core feature of the model.

Regional Distinction in Dopamine Projections and Pharmacological Rescue

Pharmacological rescue of the social novelty preference deficit in tgDISC1 rats through the D2R/D3R antagonist amisulpride (Study 1) provides a window into plausible regional vulnerabilities of DISC1-related DA dysfunction. Due to the methodological constrains in the application of clozapine in Study 1, conclusions are restricted to the amisulpride condition.

Amisulpride possesses several mechanistic features that distinguish it from other SGAs. It exhibits functional limbic selectivity (Kiss et al., 2019; Möller, 2003; Natesan et al., 2008) and acts on dopaminergic transmission in a dose-dependent manner (Schoemaker et al., 1997). Several experimental studies in rodents demonstrated that, at low doses, amisulpride promotes DA release by disinhibiting presynaptic autoreceptors (Perrault et al., 1997), thereby increasing extracellular DA (Di Giovanni et al., 1998; Schoemaker et al., 1997). In contrast, only at substantially higher concentrations are postsynaptically receptors engaged (Bressan et al., 2003; Schoemaker et al., 1997). This pharmacodynamic profile positions amisulpride as a compound capable of (selectively)

modulating presynaptic D2R/D3R control of DA signaling, particularly within limbic circuits (Di Giovanni et al., 1998; Möller, 2003).

The functional selectivity of antipsychotic compounds has been attributed to regional heterogeneity across dopaminergic projection targets, regarding DA release capacities, synthesis as well as re-uptake mechanisms (Kapur et al., 2001; L. M. Reynolds & Flores, 2021). Mesolimbic terminals contain a dense population of D2 autoreceptors that tightly regulate DA synthesis and release (Ford, 2014; Galloway et al., 1986; Nolan et al., 2020; Wolf & Roth, 1987). Similarly, DAT are highly expressed, constituting the principal mechanism for DA re-uptake and thus the temporal coordination of dopaminergic signaling (Holloway et al., 2019). Notably, autoreceptors have been shown to influence DAT membrane expression (Bolan et al., 2007; Cass & Gerhardt, 1994; Ford, 2014; Lycas et al., 2022), suggesting a coupled regulatory mechanism between autoreceptors activity and DA clearance efficiency by DAT. Such interdependency may render mesolimbic terminals particularly sensitive to pharmacological agents targeting presynaptic D2 autoreceptors. In contrast, mesocortical projections show sparse autoreceptors expression and low DAT density (Bannon et al., 1982; Bannon & Roth, 1983; Chiodo et al., 1984; Holloway et al., 2019). Consequently, extracellular DA in the cortex is primarily cleared through enzymatic deactivation rather than re-uptake, rendering cortical terminals relatively resistant to autoreceptor-mediated modulation (Zald, 2023). Thus, the balance between autoreceptors and DAT regulation is understood as a defining feature of mesolimbic versus mesocortical DA signaling (Holloway et al., 2019; Zald, 2023).

Within this framework, the molecular phenotype of tgDISC1 rats - characterized by increased expression of both D2R and DAT (Trossbach et al., 2016) - may suggests a state of excessive dopaminergic self-inhibition (Fig.10B): enhanced autoreceptors signaling would elevate DAT surface availability, accelerating DA clearing and producing a locally hypodopaminergic tone, particularly within circuits with heightened DA abundance such as the (ventral) striatum (Holloway et al., 2019; Sulzer et al., 2016). This mechanism would offer a plausible substrate for the observed behavioral deficit and its pharmacological rescue by amisulpride. In tgDISC1 rats, amisulpride treatment may counteract this imbalance by blocking presynaptic D2 autoreceptors, thereby relieving inhibitory feedback on DA release, speculatively promoting DAT internalization. The

resulting prolongation of synaptic DA signaling would normalize dopaminergic transmission at postsynapses and restore the capacity to encode the value of social novelty (Fig. 10D).

While this mechanism remains speculative and requires experimental validation, it provides a coherent framework to interpret the bidirectional effects observed in tgDISC1 and wildtype rats upon amisulpride treatment. In wildtype animals, amisulpride abolishes social novelty preference, likely due autoreceptors blockade, possibly alongside DAT internalization, leading to excessive mesolimbic DA (Fig. 10C). Indeed, increased DA in the NAc has been shown to prevent preferring social novelty (He et al., 2024), supporting the notion that this behavior is critically D2R dependent (Millan et al., 2007; Molas et al., 2024). Importantly, D2R-antagonism does not affect total time of investigation, but specifically shifts the allocation of novelty versus familiarity (Watson et al., 2011). Consistent with this, low D2R availability has been linked with increased novelty-seeking in both animals (Tournier et al., 2013) and humans (Zald et al., 2008).

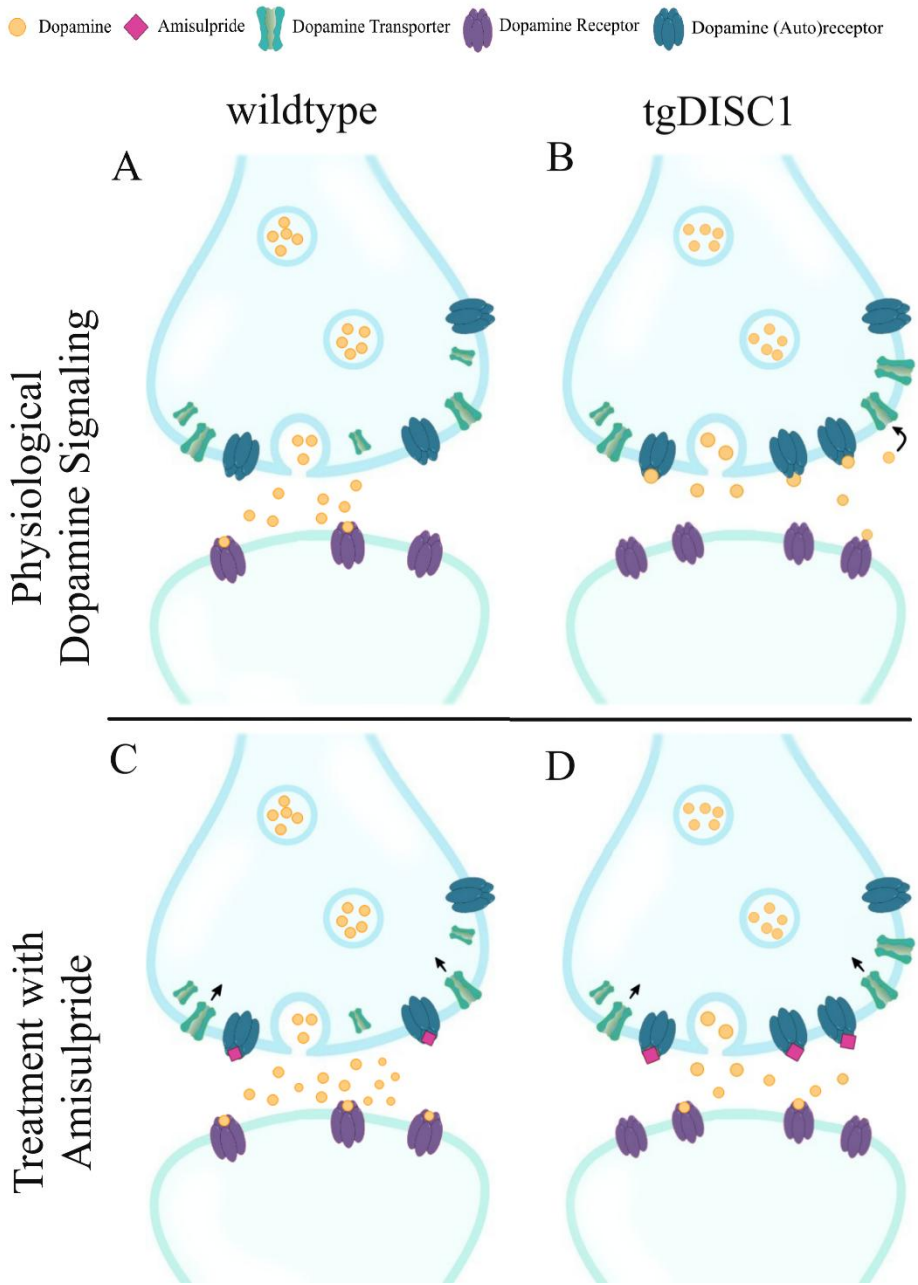

Figure 10 ***Functional framework for divergent mechanisms of amisulpride application in wildtypes and tgDISC1 rats.*** ***A*** *Schematic illustration of physiological dopamine transmission in wildtypes.* ***B*** *Hypodopaminergic state in tgDISC1 rats due to overexpression of Dopamine D2 receptors (D2R) and elevated Dopamine Transporter (DAT) translocation to the plasma membrane.* ***C*** *In wildtype rats, application of D2R antagonist amisulpride and its interaction with D2R receptors on the presynapse (autoreceptors) favor a hyperdopaminergic state, speculatively through stimulating DAT internalization.* ***D*** *Amisulpride application in tgDISC1 rats possibly enhances dopamine transmission in the synaptic cleft by blocking presynaptic autoreceptors.*

Together, these observations suggest that D2 (auto)receptor signaling and DAT regulation jointly determine the dopaminergic value of social novelty. In tgDISC1 rats, pathological upregulation of this system may produce rather selective hypofunction, which can be transiently normalized through targeted pharmacological disinhibition, as exemplified by amisulpride.

Interim Summary - tgDSC1 Rats

In conclusion, tgDISC1 rats displayed intact basic sociability but consistent impairments in social reward valuation, evident across both the social novelty preference and the STFP task. These behavioral alterations were accompanied by microstructural changes which indicate that mesolimbic projections may represent a key site of vulnerability to DISC1 misassembly, as those regions show abnormalities in DTI of tgDISC1 rats. The data expand the understanding of the cellular and receptor-level mechanisms contributing to the behavioral phenotype of the model. Specifically, they point toward future work clarifying whether D2R overexpression may preferentially occur pre- or postsynaptically. Given that the D2-type is the only DA receptor subtype expressed as autoreceptors, and the D2R-subtype is specifically elevated in tgDISC1 rats, it remains a promising candidate for targeted investigation. Furthermore, the observation that DISC1 aggregation may serve as a molecular biomarker, and that tgDISC1 rats successfully respond to treatment with amisulpride, strengthens the predictive validity for negative symptom-related dysfunction.

Finally, the identification of mesolimbic vulnerability provides a feasible mechanistic framework for understanding how DISC1 misassembly contributes to the emergence of social impairments. This integrative view links molecular aggregation, circuit-level dysregulation and behavioral output, offering a promising translational perspective on the pathophysiology of SZ and related disorders.

Neuromodulatory Convergence in Social Behavior

Although Study 3 was not conceived with a translational framework in mind, it provides mechanistic insight into how OXT shapes social reward learning. In this experiment, systematic OXT administration selectively disrupted social transmission when the demonstrator was unfamiliar, but not when the cagemate demonstrated the information to be transmitted. These findings indicate that OXT acts as a context-sensitive modulator of social information use, underscoring that neuromodulatory influences on social behavior cannot be dissociated from the context in which they occur.

Considering the close functional relationship between OXT and DA, these results may be worth interpreting in the context of dopaminergic mechanisms known to be differentially engaged by familiarity versus novelty. DA release in the NAc is robustly enhanced by novel stimuli, but decreased when stimuli become familiar, suggesting that DA's contribution to reward learning itself is likely context-dependent. This matches with findings in mouse models, where deficits in social novelty preference, caused by diminished DA-induced OXT release, could be rescued by OXT administration in a DA-receptor dependent manner (Fujiwara et al., 2016, 2021). Conversely, pharmacological DAT inhibition restored social novelty preference only, when OXT receptor (OXTR) signaling was intact (Fujiwara et al., 2021). Such evidence points to a bidirectional dependency between DA and OXT systems.

The relevance of these findings becomes apparent when placed alongside the tgDISC1 phenotype: tgDISC1 rats exhibit impairments in social novelty preference and in the integration of socially acquired information – interestingly, these two domains converge in Study 3, where social transmission itself was revealed to be familiarity dependent. Thus, while the primary interpretation of tgDISC1 deficits center upon dopaminergic imbalance due to elevated D2R and DAT expression (and the resulting hypodopaminergic state) (Trossbach et al., 2016), it is plausible that secondary disturbances in OXT signaling contribute to these impairments. Consistent with this interpretation, rodent models with OXT and OXTR KO, as well as mice with experimentally induced OXT disturbances, all fail to form a social novelty preference, despite intact social interest – closely mirroring the tgDISC1 phenotype. Thus, Study 3, while not designed for translational application, complements the tgDISC1 work by stressing that disruptions in

either DA or OXT systems are sufficient to impair social behavior, and that their interaction may be crucial for intact function.

Taken together, these findings support the idea that tgDISC1 rats may not only model dopaminergic disturbances but could also reveal downstream consequences for OXT signaling. Investigating OXTR function and signaling in tgDISC1 rats may therefore illuminate how DISC1 misassembly alters the processing of social cues, and potentially identify intervention points at the DA-OXT axis/intersection. This perspective is of particular relevance as DA-OXT interactions gain increasing attention in psychiatric research (Baskerville & Douglas, 2010) and OXT-based interventions are already in focus for ameliorating social deficits in ASD. This interpretation is consistent with the finding that in individuals with SZ, higher plasma OXT levels predicted more accurate integration of social cues (Strauss et al., 2015) and elevated circulating OXT was associated with stronger prosocial behavior (Rubin et al., 2010).

By integrating the findings from Study 3 with those from the tgDISC1 experiments, a coherent picture emerges in which DA-OXT interplay may constitute a common mechanistic substrate of social dysfunction. Notably, in patients with SZ, OXT influences appear relatively specific to social cognition, with little effect on general cognitive performance (M. F. Green et al., 2015; Meyer-Lindenberg et al., 2011; Rimmele et al., 2009). Moreover, social context itself profoundly modulates affective state and social motivation (Badal et al., 2021), suggesting that neuromodulatory effects of OXT are inseparable from the environments in which social information is processed. Together these insights underscore the clinical relevance of context-sensitive neurochemical interactions and strengthen OXT as a potential therapeutic target for ameliorating social impairments across psychiatric conditions.

Limitations

Like any experimental work, the present studies were conducted within methodological and conceptual constraints. Acknowledging these boundaries is important for interpreting the findings in their proper context as well as for identifying directions future research should address.

General Methodological and Conceptual Limitations

A first consideration concerns the restriction to the use of male animals only. While this choice reduced variability across cohorts, it inevitably limits the generalizability of the findings. Addressing sex as a biological variable will be an important step in future research, expanding prior work in tgDISC1 rats (Uzuneser et al., 2019).

Second, in Study 2, while amisulpride produced a clear behavioral rescue, the intervention with clozapine remained inconclusive, due to the emerging problems in drug application. Refining the parameters for optimized solubility and thus continuous drug infusion via osmotic pumps will be essential to assess whether broader antipsychotic mechanisms can normalize the tgDISC1 phenotype.

Relatedly, the present work focused primarily on behavioral and imaging outcomes, whereas complementary, biochemical analysis are missing. Measures, such as receptor or transporter expression following pharmacological treatment in tgDISC1 rats would provide a crucial mechanistic bridge between behavioral rescue effects and underlying neurochemical features. However, those data are not yet available at the time point writing this thesis.

Lastly, from a methodological perspective, it is important to note that “familiarity” was operationalized differently across the studies presented here: as repeated encounter with the same partner in Study 1 versus pre-existing demonstrator-observer relation in Study 3. Although driven by paradigm-specific necessity, these differences should be considered when comparing those results. Therefore, employing experimental paradigms using tgDISC1 rats and their respective cagemates will help to clarify role of familiarity, and potentially social bonding, in shaping their behavior. In the 3-Chamber task, for instance, the absence of a social novelty preference might become even more pronounced when given the choice between interacting with an unfamiliar conspecific or their own cagemate. In contrast, speculation on the role of familiarity in the STFP paradigm remains

limited by the lack of task performance in tgDISC1 rats and is therefore not elaborated further here.

Reconciling Divergent Findings on tgDISC1 Social Behavior

A further limitation stems from prior work using the tgDISC1 model in social experiments, which yielded findings that appear to be contradictory to those presented here. This research reported reduced social interest in tgDISC1 rats in a multi-level decision-making task, which was carefully coined as "social anhedonia" (Seidisarouei et al., 2022). At first sight, this contrasts with the intact baseline social interest and selective alterations described in this thesis.

However, the studies differ in crucial ways: in the previous study, social contact was placed in direct competition with sucrose rewards – after an extended training phase in which animals learned about the hedonic value of different sucrose concentrations. Such a design may strongly shape motivational priorities toward consummatory rewards and may thereby reduce the relative value of a novel social stimulus. By contrast, the present work assessed social behavior in contexts where such direct competition in motivational states was absent.

Importantly, it was shown that the repeated exposure to sucrose rewards strongly influences the D2R density in the NAc and dorsal striatum (Bello et al., 2002). Such plasticity may have divergent mechanistic consequences depending on genotype, given the D2R overexpression in tgDISC1 rats. Thus, tgDISC1 rats may be more sensitive to the reinforcing, or "addictive", nature of repeated exposure to a highly rewarding consummatory stimulus.

Viewed in this light, these results are not necessarily contradictory but may instead be complementary – they suggest that tgDISC1 rats do not display a global deficit in social interest but instead a shift in motivational balance, as they may preferentially upvalue consummatory rewards along the training phase and thus display "social anhedonia" when social and hedonic stimuli compete on the test trial. This perspective integrates both sets of findings into a broader framework of altered reward valuation (upon social context) in tgDISC1 rats.

Future Outlook

The behavioral tasks applied in this thesis provide a foundation for identifying mechanisms underlying the tgDISC1 phenotype, and several avenues for future research emerge from the present findings.

First, given that tgDISC1 rats failed to adapt their preference in the STFP task and that amisulpride successfully rescued social novelty preference, testing whether the same intervention can normalize STFP performance would be of considerable interest. Such experiments could clarify whether mesolimbic dysfunction underlies both phenotypes and would extend current knowledge of tgDISC1-associated disruptions. This hypothesis is supported by reports that amisulpride was reported to modulate subcortical brain nuclei connectivity (Grimm et al., 2020), and the large brain network disturbance discovered in tgDISC1 rats (Study 2). Since integrating social cues represents a complex phenomenon rarely probed in animal models, pharmacological modulation in this domain could provide valuable translational insight.

Further, expanding the insight on DA-OXT interactions in tgDISC1 rats may provide a promising avenue for understanding their genuine social phenotype. Oxytocin-based pharamcological interventions may exert therapeutic effects by modulating dopaminergic signaling at critical mesolimbic nodes, as shown previoulsy (Fujiwara et al., 2016, 2021).

Second, the role of mesolimbic DA dysfunction in aversive contexts warrants further investigation. DA activity signals both reward and aversion depending on regional inputs (de Jong et al., 2019), suggesting that tgDISC1 rats may also display altered responses in aversive learning paradigms. Social defeat, early separation, or prolonged isolation could be particularly informative, as such conditions probe social processing in negatively valanced contexts. This line of inquiry is highly relevant given that traumatic or aversive experiences constitute crucial risk factors for psychiatric illness in humans and may interact with DISC1-related vulnerability as a "second hit."

Finally, methodological extensions of the structural work would offer additional opportunities. DTI, traditionally applied to assess white matter integrity, is increasingly used to characterize gray matter microstructure. DISC1 plays an established role in pre- and postnatal dendritic development (Kamiya et al., 2005), and dysregulated signaling could therefore contribute to altered dendritic morphology detectable with advanced

diffusion models. Neurite Orientation Dispersion and Density Imaging (NODDI) represents one promising approach, as it captures dendritic branching and density more directly. Applying such methods could refine the link between DISC1-associated neurodevelopmental changes and the microstructural differences observed here. Employing NODDI in the regions identified as altered in our DTI analyses may further help elucidate our observed behavioral phenotype – notably, inhibiting synaptic plasticity during neurodevelopment increased familiar exploration during the social novelty preference trial (Kirkland et al., 2024) and recently, a critical window in neurodevelopment was proposed for social reward learning, based on synaptic plasticity (Nardou et al., 2023).

In summary, future work should expand on the present findings by probing pharmacological rescue in complex social behaviors, exploring aversive learning paradigms, and employing advanced imaging techniques to capture neuropathological alterations with greater specificity. Together, these approaches hold the potential to deepen our understanding of how DISC1 overexpression shapes social reward processing across developmental, circuit, and molecular levels.

Chapter 5 - Conclusion

The findings gathered throughout this thesis demonstrate that modest overexpression of human no-mutant DISC1 protein in rats leads to selective alterations in social reward learning and associated reward-signaling, reflecting dysfunctions in how social cues are valued and used to guide adaptive choices. The specificity of this behavioral phenotype, together with its reversal by a D2R/D3R antagonist and the microstructural alterations in limbic key nodes, point toward a conceivable dopaminergic dysregulation centered on limbic control. At a broader level, these data underscore the need to view dopaminergic dysfunction in SZ not as a uniform abnormality but as a circuit-and context-dependent phenomenon. Thus, distinct symptom domains may ultimately arise from differential vulnerability for disruptions across DA projection sites, explaining why tgDISC1 rats show a rather selective impairment in social novelty preference and social reward learning.

Complementary work further indicates that social reward learning is strongly sensitive to familiarity between individuals and shaped by neuromodulatory influences of OXT, offering a broader perspective on the neuroscientific foundations of social cognition. While the present work centers on the dopaminergic mechanism, the tgDISC1 rat may, in future studies, also serve to explore how highly interconnected systems such as DA and OXT jointly influence the valuation of social information. Such investigations could refine our understanding of how coordinated neuromodulator orchestration regulates complex social behaviors.

In conclusion, the tgDISC1 rat constitutes a highly integrative framework in which molecular, structural and behavioral alterations converge on pathophysiological domains relevant to primary negative symptoms of SZ. Its translational value lies not only in reproducing a feature of impaired social cognition and dopaminergic control, but also in offering a foundation for biomarker-guided patient stratification and precision treatment approaches: within a biologically defined SZ subgroup, aggregated DISC1 protein and disrupted DISC1 signaling may even present with prominent presynaptic dysregulation and selective responsiveness to compounds with a high affinity for D2R/D3R, such as amisulpride. In patients, assessing whether DISC1-related molecular perturbations translate into behavioral dysfunctions may help identify vulnerabilities in domains where reward-related and social processes intersect.

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Appendix

Eigenständigkeitserklärung

Ich, José Dören. Geboren am 02.02.1996, versichere an Eides Statt, dass diese Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.

Düsseldorf, 28.10.2025 _____

José Dören

Study 1 - Original Paper

Pharmacological rescue of social deficits in rats featuring Disrupted-in-Schizophrenia-1 (DISC1) protein aggregation

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Abstract

The pharmacological treatment of negative symptoms in schizophrenia remains a major unmet need. Among these symptoms, impairments in social functioning – manifesting as reduced adaptability and social withdrawal – are particularly disabling, as they persist beyond remission of positive symptoms and impede social reintegration. To address the neurobiological basis of such social deficits, we employed the tgDISC1 rat, a translational model overexpressing the human non-mutant Disrupted-in-Schizophrenia-1 (DISC1) gene. This overexpression results in DISC1 protein aggregation and signaling disturbances – molecular features found in a subgroup of schizophrenia patients identified by elevated DISC1 aggregates in cerebrospinal fluid. Behaviorally, the tgDISC1 rats exhibited a selective loss of social novelty preference in the 3-Chamber task while maintaining intact social interest, indicating a specific deficit in social adaptability rather than social motivation. Here, we tested whether continuous administration of atypical antipsychotics amisulpride or clozapine would rescue social deficits in tgDISC1 rats. Both drugs were delivered subcutaneously via osmotic pumps, to mimic continuous medication in patients. Treatment with amisulpride (0.2 and 0.8 mg/kg/day for two weeks) fully restored social novelty preference, whereas clozapine had no effect. Control tasks for anhedonia, short-term working memory, and explorative behavior confirmed that their phenotype was not secondary to global motivational or cognitive impairments. Together, these findings demonstrate that amisulpride, a selective D2/D3 receptor antagonist, rescues social adaptability deficits linked to aberrant DISC1 signaling. The results highlight dopaminergic modulation of social adaption as a promising therapeutic target and suggest that amisulpride may be particularly effective in biomarker-defined schizophrenia subgroups characterized by DISC1 aggregation.

Introduction

Schizophrenia is a complex psychiatric disorder characterized by a spectrum of positive symptoms that include psychotic episodes, negative symptoms and a variety of subtle cognitive impairments. Among the negative symptoms, deficits in social behavior significantly impact patients' quality of life and functional outcomes (Correll & Schooler, 2020; Nuss & Tessier, 2010). Although the exact mechanisms underlying social impairments in schizophrenia are not yet fully understood, dopaminergic dysregulation is widely recognized as a key contributing factor (McCutcheon et al., 2020). In particular, the Dopamine-2-Receptor (D2R) is a prominent candidate of interest, as its activity was found to predict social behavior across a variety of species, including humans (Chen et al., 2024; Ike et al., 2023; Martinez et al., 2009; Morgan et al., 2002; Soutschek et al., 2017). A wide range of studies, including PET-scans as well as post-mortem tissue analysis, revealed disrupted D2R patterns and even a correlation of striatal expression with reported negative symptoms in schizophrenia patients (Goldsmith et al., 1997; Kubota et al., 2017; Seeman, 2013). Thus, the D2R is a strong candidate, not only for psychosis, but also to investigate formation of social impairments as a symptom of schizophrenia (Collo et al., 2020).

Given the central role of D2R in schizophrenia pathology, it is a primary target of antipsychotic medications. While typical antipsychotics primarily antagonize D2R to alleviate positive symptoms, they tend to express side-effects and have limited efficacy against negative symptoms, including social deficits (Correll & Schooler, 2020; Möller, 2005). Atypical, or “second-generation”, antipsychotics, such as amisulpride and clozapine, offer distinct pharmacological profiles that prove to be more effective in addressing symptoms (Huhn et al., 2019). Clozapine is the prototype of second-generation antipsychotics and remains the only medication prescribed in treatment-resistance-schizophrenia (Khokhar et al., 2018). It has a unique wide-ranging affinity profile including histaminergic, cholinergic, and muscarinergic receptors. Prominently, at serotonergic receptors, it works as a serotonin 2 receptor (5-HT2R) antagonist and a 5-HT1R agonist (Marinho, 2024). In addition, it’s antagonizing effect on alpha-adrenergic receptors has been linked to enhanced noradrenaline release (Devoto et al., 2003). In terms of dopamine signaling, it has a remarkably higher affinity for the D4R than D2R, but the entirety of its effect on dopamine are yet to be elucidated (Tauscher et al., 2004).

In contrast, amisulpride exhibits high selectivity as a dopamine D2/D3R antagonist. Although initially believed to act exclusively on dopaminergic targets, it also demonstrates antagonistic activity at serotonergic 5-HT2 and 5-HT7 receptors (Abbas et al., 2009). Notably, amisulpride's pharmacological effects are dose-dependent, engaging distinct mechanisms of action (low dose: < 300mg/day, high dose: < 800mg/day in patients, according to Laux, 2022). At low doses, it preferentially blocks presynaptic D2/D3 autoreceptors in frontal regions, leading to enhanced dopamine release and alleviation of depressive symptoms (Schoemaker et al., 1997). Conversely, at higher doses, it primarily antagonizes postsynaptic D2R in the mesolimbic system, thereby reducing psychotic symptoms in schizophrenia (Perrault et al., 1997; Schoemaker et al., 1997). Thus, the multifaceted mechanisms of atypical antipsychotics highlight the necessity for further research to refine treatment strategies, ensuring a more personalized approach that accounts for differentiated patient subgroups and symptom profiles.

The Disrupted-in-Schizophrenia-1 (DISC1) gene encodes a scaffold protein which orchestrates key cellular pathways involved in neuronal migration, dendritic arborization, and synaptic function (Brandon & Sawa, 2011; Yerabham et al., 2013). Importantly, DISC1 has been closely linked to D2R expression and D2R-mediated signaling (Jaaro-Peled et al., 2013; Onishi et al., 2018; Su et al., 2014). Thus, DISC1-dependent signaling (at the protein level) which is at the crossroads of many behavior-relevant signaling pathways may embody a central role in the pathophysiology of schizophrenia, particularly when dysfunctional, for example due to aggregation or other posttranslational modifications. In line with that, DISC1 aggregates were observed in post-mortem tissue of a subset of patients (Leliveld et al., 2008) as well as in cerebrospinal fluid of first episode patients (Pils et al., 2023). Therefore, we used a transgenic model overexpressing the human non-mutant DISC1 (tgDISC1) to mimic a non-genetic DISC1 protein dysfunctionality and signaling due to DISC1 protein misassembly. In tgDISC1 rats, this leads to an increased proportion of high-affinity D2R, increased intracellular translocation of the dopamine transporter, thus generating an altered dopaminergic state as a key mechanism in their pathophysiology (Trossbach et al., 2016). Hence, tgDISC1 rats represent a face valid animal model for sporadic forms of DISC1 protein-linked behavioral disorders.

Social symptoms in schizophrenia are difficult to classify and challenging to translate into animal modeling for the evaluation of antipsychotic therapy (Nuechterlein et al., 2005). However, the tgDISC1 rat has repeatedly been validated as a model for impaired social

behavior across different settings (Seidisarouei et al., 2022; Uzuneser et al., 2019; Wang et al., 2022). The 3-Chamber task is a widely used paradigm for assessing social behavior, demonstrating strong translational validity in rodents for modelling social impairments observed in neuropsychiatric disorders (Ang et al., 2021). The task allows subjects to freely explore an apparatus with distinct chambers, in which different familiar or unfamiliar conspecific rats are presented across trials. While direct physical contact is restricted, key social interactions such as whisker and snout contact remain possible. By relying on voluntary social preference rather than reactive responses, this assay provides a nuanced assessment of innate sociability and social motivation —domains which are crucial for classifying negative symptoms in schizophrenia. These characteristics make it a valuable tool for investigating the neurobiological underpinnings of social dysfunction in translational models (Ang et al., 2021; Kaidanovich-Beilin et al., 2011).

Here, to investigate whether behavioral impairments in the tgDISC1 model were pharmacologically reversible, we administered two-week continuous treatment with the atypical antipsychotics clozapine and amisulpride. Using sub-cutaneous Alzet osmotic pumps, a continuous drug delivery system, tgDISC1 rats received either clozapine or amisulpride at two dosages, or a vehicle compound. Animals underwent a behavioral test battery to assess social interaction and adaptability, including the 3-Chamber task. We report that amisulpride but not clozapine restores social behavior alterations observed in tgDISC1.

Materials and Methods

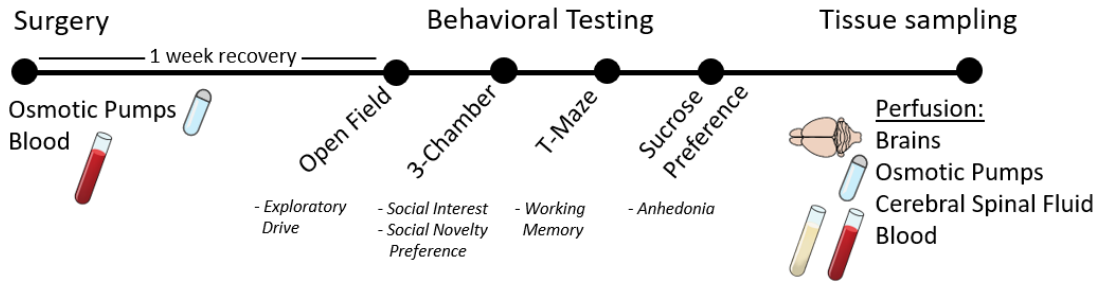

Figure 1: ***Experimental design.***

Animals & Housing

65 male tgDISC1 rats on Sprague Dawley background and 66 of their male wildtype littermates (hereafter "wildtype") were tested. Animals were bred at the ZETT facility (*Zentrale Einrichtung für Tierforschung und wissenschaftliche Tierschutzaufgaben*) at the Heinrich Heine University in Düsseldorf, Germany. Additionally, 24 male aged-matched wildtype Sprague Dawley rats (Janvier Labs, Le Genest-Saint-Isle, France) were used as social demonstrators for the 3-Chamber task. Rats were maintained in Type 4 cages on wood chipped bedding (LASvendi, Soest, Germany). For enrichment, a wooden block and a red PVC tube were added. Food (Ssniff, Soest, Germany) and water were provided ad libitum. The animals were kept at approximately 22± 2ºC and 55± 5% humidity in a reverse 12-hour light-dark rhythm. All animal procedures were approved by the local authority LANUV (*Landesamt für Natur-, Umwelt- und Verbraucherschutz* North Rhine-Westphalia, Germany). The final sample for analysis consisted of 97 rats after applying exclusion criteria (see Supplementary information for detailed description).

Implantation of Osmotic Pumps

After arrival at the lab, the rats were given 1 week to acclimate before the implantation surgery (Fig. 1). Animals were pseudorandomly assigned to either the vehicle group or one of the experimental groups (see below). Alzet® osmotic pumps (model: 2ML4, Durcect, Cupertino, USA) were used to ensure a steady delivery of fluid. Pumps were weighted before filling, after filling and after removal to check for residues and calculate the net injected drug. Detailed descriptions of surgical procedures, recovery, perfusion and post-mortem blood-level analysis can be found in Supplementary information.

<u>Experimental Groups:</u>

Vehicle

The vehicle group received osmotic pumps filled with 2 ml saline and 50% Dimethyl sulfoxide (DMSO; Sigma-Aldrich,St. Louis, USA) as a control solution.

Amisulpride

Animals were pseudorandomly assigned to either a low-dose or a high-dose group. Amisulpride (CBS-FA17868, Biozol, Hamburg, Germany) solutions were prepared in 50% DMSO and saline, with the high-dose concentration adjusted to remain just below the solubility limit of 5.54 µg/µl, ensuring a delivery of 0.8 mg/kg/day based on individual

bodyweights. For the low-dose, the concentration was set to 1.4 µg/µl, which corresponds to a delivery of 0.2 mg/kg/day.

Clozapine

Animals were pseudorandomly assigned to either a low-dose, medium-dose or high-dose group. Osmotic pumps were filled with clozapine hydrochloride (CBS-FC20526-25G, Biozol, Hamburg, Germany) diluted in Saline and 50% DMSO, with the high-dose concentration adjusted to remain just below the solubility limit (39.98 µg/µl), ensuring a delivery of 6 mg/kg/day based on individual bodyweights. For the low-dose, the concentration was adjusted to 8 µg/µl, which corresponds to a delivery of 1.2 mg/kg/day based on individual bodyweights. Note that we encountered problems in dissolving clozapine in the high-dose condition (see exclusion criteria), thus, we decided to include a medium-dose group (med-dose clozapine) with a concentration of 30 µg/µl and a delivery of 4 mg/kg/day.

Behavioral Testing

Before the start of the experiment, the animals were brought into the experimental room for habituation for 30 minutes. Between trials, the experimental set-ups were cleaned with 70% ethanol. Experiments were conducted during the animals' dark phase, over a course of one week. Detailed descriptions of additional control tasks and their respective exclusion criteria are provided in the Supplementary Information.

3-Chamber task

The 3-Chamber task was employed to assess sociability and preference for novel social stimuli (Sukoff Rizzo & Crawley, 2017). The apparatus consisted of a rectangular arena (60 cm × 60 cm × 39 cm, PVC) with two compartments (20 cm × 20 cm x 39 cm) located in the left and right corners (See Fig. 2). These compartments were enclosed by bars, allowing olfactory and limited tactile interaction with conspecifics while preventing full physical contact. The task was conducted in three consecutive trials. During the habituation, the subject rat was placed in the central arena and allowed to freely explore the set-up for 5 minutes before being returned to its home cage. Following a 10-minute inter-trial interval (ITI), the social interest trial was conducted. An unfamiliar demonstrator rat was placed in one of the compartments, and the subject rat was reintroduced to the apparatus. The subject was allowed to explore and interact freely for

5 minutes before both rats were returned to their home cages. After another 10-minute ITI, the initial demonstrator was returned to its designated compartment, and a novel, unfamiliar demonstrator was placed into the remaining chamber. The subject rat was then placed back in the arena for an additional 5-minute exploration period. This is called the social novelty preference trial. All trials were recorded using a video camera (Conrad Electronic SE, Hirschau, Germany). Locomotor parameters were quantified using EthoVision XT 11.5 (Noldus, Wageningen, Netherlands). Social interaction behaviors, defined as direct contact or sniffing towards the demonstrators, were manually scored by a blinded experimenter using Solomon Coder (Solomon Coder beta 19.08.02, András Péter). Social novelty preference was measured as an increased interaction duration with the novel demonstrator compared to the familiar one. Animals were excluded from analysis of the social novelty preference trial if the subject rat did not interact with one or both of the demonstrators. Two animals were excluded from analysis.

Statistical Analysis

Statistical analyses were performed using RStudio (v2023.06.2), with significance set at $p<0.05$. Normality of the data was assessed using the Kolmogorov-Smirnov test. Depending on distribution, group comparisons used unpaired t-tests or Mann-Whitney U test. Pearson or Spearman correlations were applied based on normality. Robust linear-models (RLM) assessed main and interaction effects of multiple independent variables and linear mixed-effect models where used for repeated measures. When post-hoc pairwise comparisons were necessary, the Benjamini-Hochberg false discovery rate (FDR) procedure was applied to adjust for multiple comparisons. Statistical figures were created using GraphPad Prism 9.5.0 (GraphPad Software, Boston, USA).

Results

Behavior

In order to investigate the effects of antipsychotics amisulpride and clozapine on social behavior we conducted the 3-Chamber task. It offers a high translational validity for social impairments in neuropsychiatric disorders and covers multiple social domains (Silverman et al., 2010; Sukoff Rizzo & Crawley, 2017; Yang et al., 2011). First, it covers the dimension of social interest by assessing the willingness to engage in social interaction

with an unfamiliar conspecific. It also measures the level of social adaptability and curiosity by quantifying the social novelty preference when an unfamiliar conspecific is introduced. We also conducted multiple control tasks to ascertain that the drug effects on behavior in the 3-Chamber task could not be explained by differences between genotype and drug conditions in anhedonia, working memory, or preservative behavior, such as rigid exploration patterns. To control for a general deficit in reward-related behaviors, we compared sucrose consumption in all animals but did not find differences (Supplemental Figure S1A).

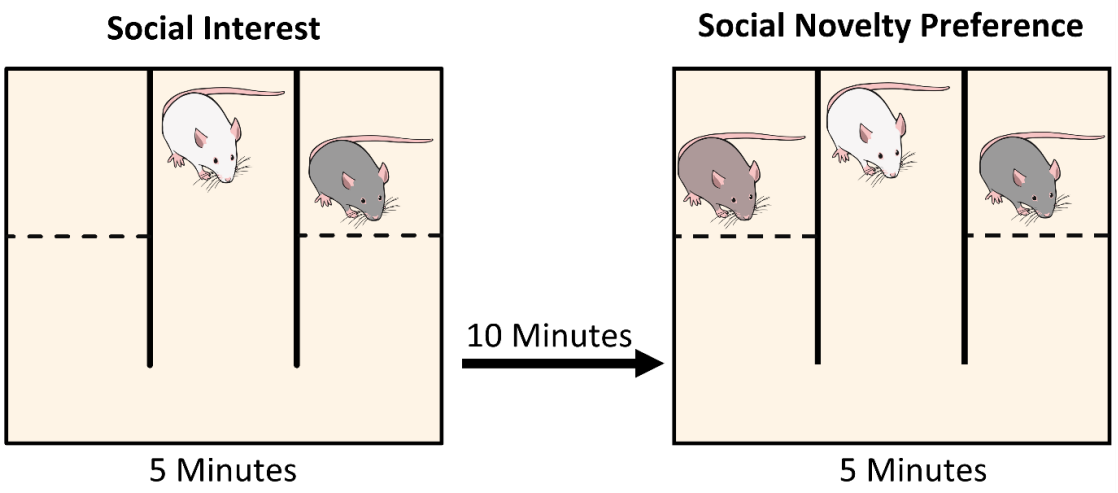

Figure 2 : ***Experimental scheme of the 3-Chamber task and apparatus****. Dashed lines represent the bars which separated the subject animal (white) and demonstrators (grey; brown). Demonstrators were aged- and sex-matched and of the same strain (colors differ for visualization).*

Social Novelty Preference

For amisulpride treatment, we used a linear mixed-effects model to examine the main and interaction effects of novelty (within-subject factor), dose (between-subject factor), and genotype (between-subject factor) on social novelty preference. The analysis revealed a significant 3-way interaction at both doses (novelty * genotype * low-dose: b = -42.84 ± 21.12, t(115) = -2.03, p = 0.045; novelty * genotype * high-dose: b = -54.72 ± 21.27, t(115) = -2.57, p = 0.011). Post-hoc two-sided t-tests revealed that wildtype vehicles had a significant preference for the novel conspecific (adjusted p = 0.018). In contrast, vehicle tgDISC1 rats did not significantly prefer a novel conspecific over the familiar one (adjusted p = 0.431), confirming that tgDISC1 rats have altered social novelty preference. Notably, we found that both the low-dose and high-dose treatment of amisulpride increased social novelty preference in tgDISC1 animals (low-dose: adjusted p = 0.002; high-dose: adjusted p = 0.021, Fig.3). Conversely, we found no significant evidence that

wildtype animals treated with either amisulpride dose preferred the novel conspecific (low-dose: adjusted $p = 0.395$; high-dose: adjusted $p = 0.129$, Fig. 3). This suggests that the rescue-like effect of amisulpride was specific to tgDISC1 animals.

Regarding the total duration of social exploration, an RLM revealed no significant main effects or dose-by-genotype interactions (all $p > 0.263$), suggesting that the effects amisulpride were specific to novelty exploration and not general exploratory social behavior. RLMs for locomotor activity revealed dose-dependent reductions in distance traveled and average velocity, but these effects were not genotype-dependent. Specifically, amisulpride significantly reduced distance traveled at low doses in both genotypes ($b = -355.74 \pm 176.03$, $t(58) = -2.02$, $p = 0.048$; interaction: $b = 220.65 \pm 237.80$, $t(58) = 0.93$, $p = 0.356$). Similarly, velocity was reduced at low doses ($b = -1.33 \pm 0.61$, $t(58) = -2.18$, $p = 0.033$; interaction: $b = 0.97 \pm 0.82$, $t(58) = 1.18$, $p = 0.243$).

These findings highlight a genotype-dependent rescue effect of amisulpride in transgenic animals, as evidenced by increased novelty preference following treatment. This effect was absent (even inverted) in wildtype control animals, supporting the specificity of amisulpride's action in rescuing DISC1-related impairments in social adaption. Importantly, amisulpride-induced reductions in locomotor activity were dose-dependent but not genotype-dependent, suggesting that the rescue effect on social novelty exploration occurred independently of locomotor suppression. Total exploration duration remained unaffected, underscoring the targeted nature of the rescue by amisulpride concerning novelty exploration.

In summary, we found that, compared to wildtype controls, tgDISC1 rats had significantly impaired social novelty preference which was rescued by amisulpride treatment.

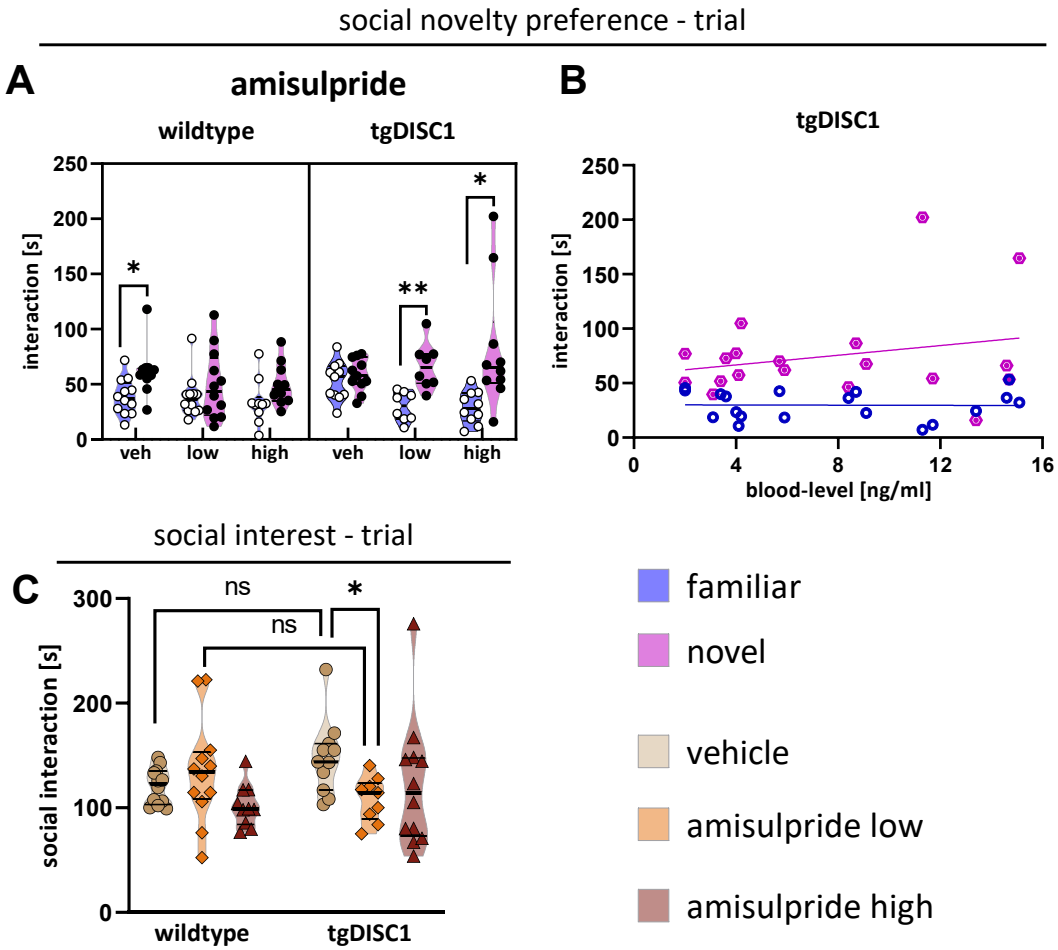

Figure 3 ***Effects of amisulpride treatment on social behavior in the 3-Chamber task.*** *(A) Social novelty preference in tgDISC1 and wildtype rats following amisulpride treatment. Social novelty preference was measured as an increased interaction duration [s] with the novel conspecific compared to a familiar one. A linear mixed-effects model revealed significant 3-way interactions (novelty * genotype* dose). Post-hoc two-sided t-test showed a significant preference for the novel conspecific in wildtype vehicles (adjusted p = 0.018), whereas this preference was absent int vehicle-treated tgDISC1 rats (adjusted p = 0.431), indicating impaired social novelty preference in tgDISC1 animals. Notably, further post-hoc tests revealed intact social novelty preference in tgDISC1 rats after treatment with either dose of amisulpride. veh = vehicle (B) Amisulpride blood-levels did not significantly correlate with social exploration of neither the novel (diamond) nor a familiar (bold circle) conspecific in tgDISC1 rats. (C) Duration of social exploration during the social interest trial in the 3-Chamber task. Results of post-hoc group comparisons are visualized. ns = not significant. Data are presented as median ± quartiles. *p < 0.05, **p < 0.01*

The linear mixed-effects model of clozapine treated animals revealed no significant main or interaction effects on social novelty preference (all p-values > 0.061, Fig. 4). In addition, further analysis of total exploration duration or locomotion yielded no significant results in any of the parameters measured (all p-values > 0.098). Thus, treatment with clozapine did not influence social novelty preference behavior of tgDISC1 (or wildtypes) to a significant extent.

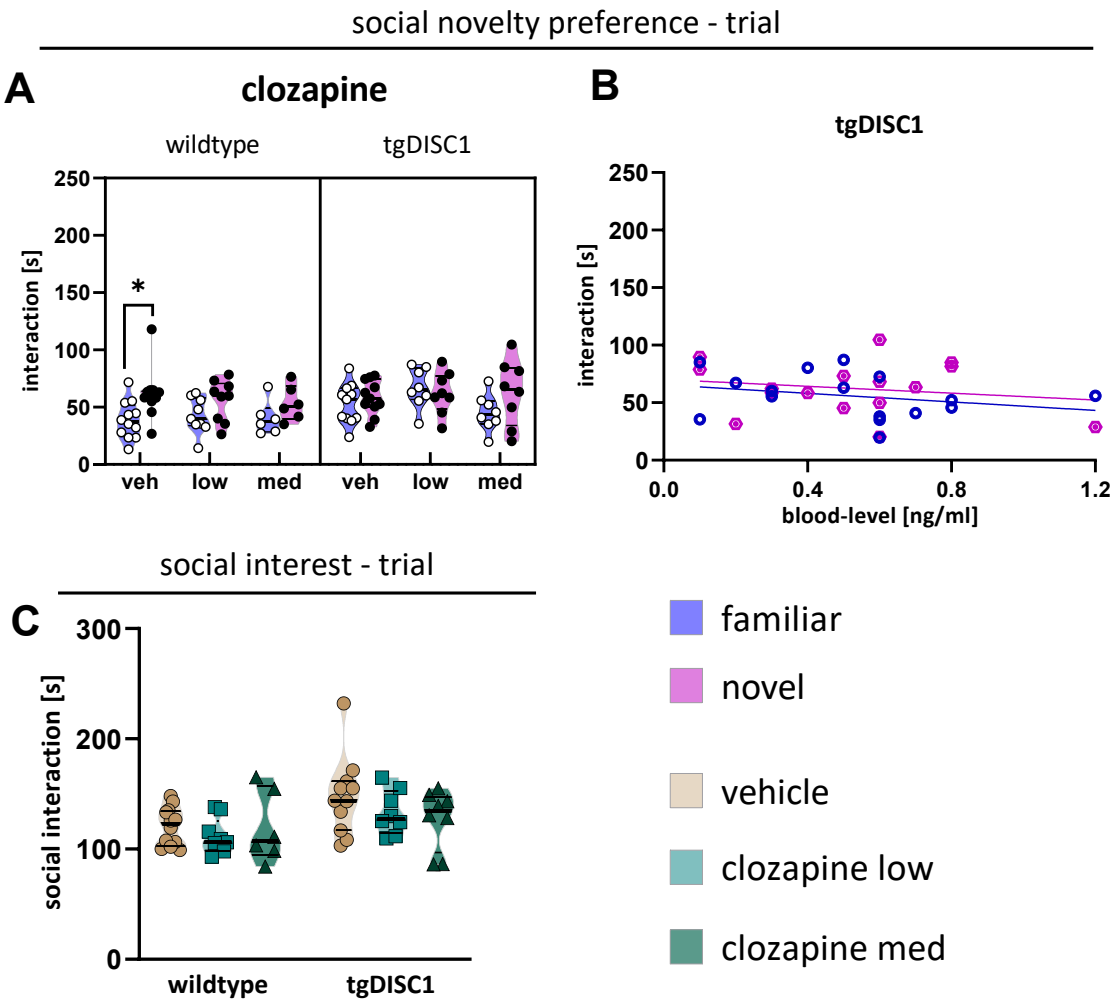

Figure 4 ***Effects of clozapine treatment on social behavior in the 3-Chamber task.*** *(A) Social novelty preference in tgDISC1 and wildtype rats following clozapine treatment. Social novelty preference was measured as an increased interaction duration [s] with the novel conspecific compared to a familiar one. A linear mixed-effects model revealed no significant effects. med = medium; veh = vehicle (B) Clozapine blood-levels did not significantly correlate with social exploration of the novel or familiar conspecific in tgDISC1 rats. (C) Duration of social exploration during the social interest trial in the 3-Chamber task. No significant effects were revealed in the analysis. Data are presented as median ± quartiles.*

Social Interest

In the social interest trial of the 3-Chamber task, RLMs were used to analyze genotype- and dose-dependent effects in the time rats spent in the social chamber, interacting with the unfamiliar conspecific. No significant baseline differences in social contact between vehicle wildtype and tgDISC1 rats were revealed (wildtype vehicle vs. tgDISC1 vehicle, adjusted $p = 0.075$; descriptively, tgDISC1 rats had higher social contact durations than wildtypes).

For treatment with amisulpride, a significant dose-genotype interaction was found for the low-dose ($b = 45.07 \pm 18.57$, $t(60) = 2.43$, $p = 0.018$). Post-hoc comparisons revealed that tgDISC1 rats treated with low-dose amisulpride spent significantly less time in the social chamber than the vehicle tgDISC1 rats (adjusted $p = 0.033$, Fig. 3), while this effect was absent in wildtypes. However, a comparison between genotypes treated with low-dose of amisulpride did not show significant differences (wildtype low-dose vs. tgDISC1 low-dose, adjusted $p = 0.096$, Fig. 3), suggesting no differences in sociability between both genotypes. For high-dose treatment, the RLM did not show a significant dose-genotype interaction effect on time spent in the social chamber ($b = 11.08 \pm 18.29$, $t(60) = 0.61$, $p = 0.544$).

For clozapine-treated animals, we found no significant dose-genotype interaction effects in the social interest task. Neither low-dose nor medium-dose clozapine significantly affected social interaction in the social chamber in any group (all $p > 0.713$). However, medium-dose clozapine was associated with a significant genotype-dependent reduction in wildtypes for distance traveled ($b = -562.84 \pm 239.23$, $t(48) = -2.35$, $p = 0.023$) and velocity ($b = -2.03 \pm 0.89$, $t(48) = -2.28$, $p = 0.027$).

Sucrose Preference

The Sucrose Preference task revealed no baselines differences between the vehicle groups, indicating no anhedonia in tgDISC1 rats. Further, Amisulpride had no significant effect on 10% sucrose consumption in either genotype or at low/high doses (all $p > 0.109$). Similarly, clozapine did not alter sucrose intake across genotypes or doses (all $p > 0.126$).

T-Maze

In the T-maze task, amisulpride had no effect at either dose in either genotype on cognitive performance measures - score, triplets, direct/indirect revisits, and first error (all p-values > 0.085). Likewise, general activity readouts (arm entries, distance traveled, velocity) were unaffected by treatment or genotype (all p-values > 0.161). For clozapine, results were similar, with no dose-dependent or genotype-related effects on any variable (triplets, direct/indirect revisits, score, first error, arm entries, distance and velocity; all p-values > 0.051). Together, these findings indicate that neither amisulpride nor clozapine notably altered cognition and exploratory behavior, spatial learning, or short-term working memory performance.

Open Field

In the Open Field task, amisulpride treatment did not influence behavioral metrics in any of the tested conditions. The RLMs revealed no significant main effects of drug dose or genotype, or their interactions, on locomotor activity, overall distance traveled, individual velocity, or number and duration of visits to the center-zone, as a proxy for exploratory drive (all p-values > 0.531). Likewise, the treatment of clozapine had no significant effects on neither genotype in any of these parameters (all p-values > 0.225).

Blood-levels

As a manipulation check, analysis of the blood-levels of the drugs revealed significant differences in drug concentrations of amisulpride between the low- and high-dose conditions, both in wildtype ($t[20] = 6.62$, $p < 0.0001$) and tgDISC1 rats ($U = 9$, $p = 0.001$, Fig. S2). The same was found in clozapine-treated rats (wildtype: $t[13] = 2.55$, $p = 0.023$; tgDISC1: $U = 0$, $p < 0.001$, Fig. S2). Further, analysis of bodyweights revealed that none of the drugs or their concentrations affected weight gain (all p-values > 0.068).

Lack of correlations of drug plasma levels with behavioral read-outs

We exploratively examined whether the behavioral task read-outs correlated with individual blood-levels of amisulpride or clozapine. Amisulpride concentrations were negatively associated with locomotor activity across genotypes in the T-maze task, as reflected in reduced distance traveled (wildtypes: $r = -0.49$, $p = 0.018$; tgDISC1: $r = -0.46$, $p = 0.032$) and velocity (wildtypes: $r = -0.48$, $p = 0.022$; tgDISC1: $r = -0.46$, $p = 0.034$). In tgDISC1 rats, higher amisulpride levels also correlated with fewer arm entries ($r = -0.51$, $p = 0.017$) and triplets ($\rho = -0.48$, $p = 0.024$). No other behavioral correlations were found for amisulpride. For clozapine, higher blood-levels were linked to reduced social interaction in wildtypes during the 3-Chamber social interest trial ($r = -0.52$, $p = 0.044$).

Discussion

We investigated a distinctive social impairment in male tgDISC1 rats in the 3-Chamber task, specifically their reduced preference for interacting with a novel social conspecific over a familiar one. This deficit in social novelty preference was successfully restored after a two-week treatment with the D2R/D3-receptor antagonist amisulpride. In contrast, treatment with clozapine, acting on a broader receptor profile, did not rescue this social phenotype. These results highlight a critical role of dopaminergic modulation in driving the social-behavioral alteration of tgDISC1 rats**.** This gives important insights into the face validity of tgDISC1 rats, while the rescue-effect of amisulpride allows us to make critical mechanistic and therapeutic distinctions that have direct implications for (a subset of) schizophrenia patients.

Our results suggest that tgDISC1 rats show no generalized anhedonia or cognitive alterations and even retain the interest to engage with social stimuli comparable to wildtypes, a critical distinction from models of severe negative symptoms (Wilson & Koenig, 2013). The social tgDISC1 phenotype was restricted to a lack of social novelty preference. This suggests that our rat model is not characterized by generally diminished social functioning, but rather a context-specific bias toward engaging with familiar individuals. The tgDISC1 rat thus mirrors the challenges faced by individuals with schizophrenia and other psychiatric disorders, where a reluctance to engage in novel social interactions may co-exist with preserved social interest (Morrison et al., 2017; Weittenhiller et al., 2021): if patients place less value on interacting with unfamiliar individuals, this may lead to rigid or maladaptive responses to new group dynamics, which have previously been described as reduced social effort or impaired social skills in individuals with schizophrenia (Fulford et al., 2018).

Various studies reported markedly improvement of social functioning and social adaption in schizophrenia patients treated with amisulpride (Carrière et al., 2000; Juruena et al., 2010; Krause et al., 2018; Mortimer, 2009; Saleem et al., 2002). Social novelty preference is underlying dopaminergic control (Molas et al., 2024). Even more specific, studies in rats revealed a strong regulation of D2R rather than D3R. Several studies selectively injecting antagonists of either D2R or D3R, revealed impairments in social novelty preference for D2R antagonist or no effects for D3R antagonist in this task (Millan et al., 2007; Watson et al., 2011). Here, we extend this line of research by our observation that social novelty preference in wildtype rats is disrupted by antagonizing D2R/D3R with

amisulpride. Notably, by contrast, amisulpride rescued, rather than diminished, social novelty preference in tgDISC1 rats, presumably because D2R/D3R antagonism leads to more efficient regulation of dopamine signaling in the case of D2R overexpression, as seen in tgDISC1 rats (Trossbach et al., 2016).

Our findings are consistent with the observation in human patients that behavioral symptoms and motor side effects do not exhibit a straightforward correlation with plasma concentrations of antipsychotics (Horvitz-Lennon et al., 2017). While exploratory analyses revealed a correlation between blood-levels of amisulpride and reduced locomotion during the T-maze task, this effect was neither genotype-dependent nor sufficiently robust to yield significant differences compared to vehicle-treated groups. Overall, amisulpride demonstrated good tolerability with no persistent side effects, aligning with its established profile of a lower incidence of extrapyramidal symptoms compared to other antipsychotics (Huhn et al., 2019).

The absence of treatment effects of clozapine on the social tgDISC1 phenotype is important as clozapine has a unique receptor profile and remains the only medication for treatment-resistant-schizophrenia (Chakos et al., 2001; Pandey & Kalita, 2022). Still, the results of the presented study need to be interpreted with caution due to the relatively small sample size and measured blood-level concentrations, which were rather low (about 100-fold lower), compared to the concentrations considered therapeutically relevant in psychotic patients. However, an early pharmacokinetic study of clozapine in rats proved pronounced species differences between humans and rats, with much shorter half-life times of clozapine and its active metabolites in rodents, requiring continuous dosing which we addressed in this study by using Alzet pumps (Baldessarini et al., 1993). In addition, a receptor occupancy study in rats showed that continuous clozapine administration is significantly less effective than single injections, requiring up to fivefold higher doses for comparable occupancies (Kapur et al., 2003), and, notably, does not lead to drug accumulation despite chronic treatment – contrasting with typical patterns seen in humans (Baldessarini et al., 1993; Wilk & Stanley, 1978). Here, the highest clozapine dosage used was constrained by the need to maintain continuous solubility over weeks, which remained below 50 mM even in 50% DMSO, consistent with previous findings (Kapur et al., 2003), adding another explanation for the low blood-levels. Of note, previous literature on the usage of low-dose clozapine in rat indicates that dosages even smaller than those used here result in pronounced behavioral effects in rats (Ilg et al.,

2018). In line with that, we were able to discover significant correlations of measured clozapine blood-levels and sucrose consumption (Fig. S1) arguing that behavioral effects were observable despite the relatively low concentrations achieved. Nevertheless, we cannot completely rule out that higher clozapine concentrations would have led to different effects on the social phenotype of tgDISC1 rats. It is our impression that animal experimental reports on clozapine administration are difficult to compare between each other and to humans and further research is needed to standardize experimental approaches of clozapine administration in animals.

The tgDISC1 rat model bridges a gap between subtle alterations in critical signaling pathways and resulting behavioral phenotypes in psychiatric research. By focusing on social novelty preference, tgDISC1 rats may model a critical yet underexplored domain of social adaptability. The ability of amisulpride—but not clozapine— to restore social novelty preference in tgDISC1 rats highlights the centrality of dopaminergic dysregulation in their behavioral phenotype, offering a valuable target for precise therapeutic interventions in patients with DISC1-related alterations, for whom we previously proposed potential biomarkers (Leliveld et al., 2008; Pils et al., 2023). Future studies should explore how sporadic DISC1-alterations disrupt connectivity and plasticity within dopaminergic circuits of novelty processing and clarify the strong effects of amisulpride on social behavior.

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Pharmacological rescue of social deficits in rats featuring Disrupted-in-Schizophrenia-1 (DISC1) protein aggregation

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Supplementary Materials

Supplementary Materials and Methods

Genotyping & Re-Genotyping

The procedure for genotype assessment was following established qPCR protocols (Trossbach et al., 2016). After termination of animals, we performed a re-genotyping to ascertain correct group assignment.

Surgery & Recovery

Prior to surgery, rats received analgesia (5 mg/kg carprofen s.c.). For anesthesia, inhalation was induced with 5% isoflurane until rats lost mobility, and then, isoflurane levels were lowered to 2% to 3% for maintaining anesthesia. Upon reaching surgical state, rats were fixed with their teeth into a stereotactic apparatus (David Kopf Instruments, Los Angeles, USA).

The fur was shaved on pseudorandomly assigned left or right dorsal flank and a ca. 2cm long incision was made for subcutaneous placement of the osmotic pump. The wound was closed with stitches and treated with antiseptic spray. In addition, blood samples were collected. Bodyweights were taken the day of the surgery as well as the first and second day following. Rats had one week of recovery before the start of the behavioral experiments. One rat died during surgery.

Perfusion & Tissue Preparation

Approximately three weeks (21 – 24 days) after receiving the pumps, rats were terminated. At termination, rats were injected with pentobarbital and deeply anesthetized with isoflurane until reaching surgical state. Blood was drawn to check blood-level concentration of drugs. Following, cerebrospinal fluid was collected and half of the rats had their brains removed that got immediately snap frozen in Isopentane.

The other half of the rats was perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were immediately removed (and snap frozen) and stored at -80°C. In addition, rats in the treatment groups had cerebral spinal fluid collected. Osmotic pumps were removed and weighted to check for any residuals of leftover drugs and to calculate the net amount injected over the implanted period.

Post-mortem Blood-level Analysis

Amisulpride and clozapine were quantified by isotope dilution mass spectrometry (IDMS) using an AB Sciex QTrap 5500 (AB Sciex™ DH Tech., Framingham, MA 01701, US) with a Shimadzu prominence HPLC-System (Shimadzu, Duisburg, Germany) as front end. Method was adapted to the method previously published (Kirchherr & Kühn-Velten, 2006). In short, 10 µl of serum was mixed with 40 µl water and 150 µl precipitation solution (70 % methanol, 30 % acetonitrile (v/v))

containing internal standards. Internal standards were fluoxetine D5 (Toronto Research Chemicals Inc. North York, Kanada and amisulpride D5 (Alsachim; Shimadzu Chemistry & Diagnostics, Illkirch Graffenstaden, France). 5 to 10 µl of supernatant (10000*g, 10 minutes) were injected into the LCMS system. Separation was carried out on an Onyx C18 column (100 x 3.0 mm; Phenomenex, Aschaffenburg, Germany) by gradient elution. Starting with 90 % mobile phase A: water purified by Milli-Q® IQ 7000 purification system (Merck Chemicals GmbH Darmstadt, Germany) buffered with 0,1 % acetic acid and 12,5 mM NH_4OAc (both Merck KGaA, Darmstadt, Germany) changing to 100 % mobile phase B: LCMS-grade methanol (Th. Geyer GmbH & Co. KG. Renningen, Germany) buffered equal to mobile phase A. After 5 minutes concentration was set back to 90 % phase A. Total run time was 6.5 minutes. Quantification was performed by peak integration in MRM mode. 3PLUS1® Multilevel Plasma Calibration Set Neuroleptics 1 and 2 (Chromsystems GmbH, München, Germany) were utilized. Mass transition 370.2/242.0 was used to quantify amisulpride and 327.2/192.1 to quantify clozapine. Quantification was controlled by MassCheck® Neuroleptics 1 Plasma Control and MassCheck® Neuroleptics 2 Plasma Control, two levels each (Chromsystems GmbH, München, Germany). With the selected dilution a lower limit of quantification (LOQ) of 0.5 ng/ml for amisulpride and 0.1 ng/ml for clozapine was achieved.

Exclusion Criteria

Despite reports of sufficient clozapine solubility in DMSO (W. Huang et al., 2021) at the highest concentrations used (6 mg/kg/day in 2.2 ml saline and 50% DMSO), clozapine formed visible, insoluble precipitates over the three-week treatment. This resulted in incomplete emptying of the pump (weighed at termination), indicating no diffusion into the rat bodies.

Individuals were excluded from further analysis if their blood-levels of amisulpride or clozapine were below 0.1 ng/ml (i.e. detection limit). Initial checks revealed that all nine animals tested until then that received the highest clozapine dose (6 mg/kg/day) met the exclusion criteria due to precipitates or undetectable blood levels, leading us to discontinue the high-dose treatment. After completing data collection, we found that seven of 24 rats in the low-dose group (1.2 mg/kg/day) and ten of 24 in the medium-dose group (4 mg/kg/day) also met the exclusion criteria and were subsequently removed from analysis. Furthermore, six rats were excluded due to incorrect genotyping (heterozygotes), and one rat was terminated after meeting termination criteria.

Behavioral Testing

Open Field

An Open Field test was conducted to assess potential differences in locomotion and exploration between the groups. Rats were placed in the center of a square arena (50 cm x 50 cm x 45 cm, PVC) and could freely explore it for 10 min while being recorded by a camera (Conrad Electronic SE, Hirschau, Germany) from above.

The tracking software EthoVision XT 11.5 (Noldus, Wageningen, Netherlands) was used for behavioral read-outs. The number of visits to the center zone were used as a measure for exploratory drive and the total distance moved as well as the average velocity of an individual were measured to assess locomotor activity and potential deficits.

T-Maze

To assess short-term working memory and (rigid) pattern exploration, we utilized a T-maze task. The T-shaped apparatus consisted of three arms (57 cm × 16 cm × 37 cm each, PVC) and a center zone (37 cm x 37 cm x 37 cm, PVC). For distinction, each arm of the T-maze had unique visual cues on the walls. The animals were placed in the center zone facing a wall. For a period of five minutes, the animals could explore the maze freely and the order of arm entries were noted. The trials were recorded (Conrad Electronic SE, Hirschau, Germany). Parameters measured were numbers (#) of: total arm entries, triplets, direct re-visits, indirect re-visits, number of the first error entry, as well a performance Score. The Score was calculated as follow:

$$Score = \frac{\#\ triplets}{(\#\ total\ entries\text{-}2)}$$

In addition, EthoVision XT 11.5 (Noldus, Wageningen, Netherlands) was used to measure total distance travelled and average velocity as locomotion readouts.

Sucrose Preference

The Sucrose Preference Task assesses anhedonic phenotypes by measuring the preference for a sucrose solution over water (Scheggi et al., 2018). Animals were single housed the night prior to the test and had free access to water and food by distributing food pellets into the cage. The following morning, a 10% sucrose solution (Roth, Karlsruhe, Germany) was prepared. The bottles containing the sucrose and an additional bottle of water were placed in a random order on the cage lids. The weight of the bottles was measured before presenting them to the animals and after 6 hours. After the 6-hour period,

rats were put back into their home cage. The weight measurements were analyzed. Individuals were excluded from analysis if any of the presented bottles happened to spill. Seven animals were excluded from analysis.

Figure S1 Methods. This task-design is based on a previous publication about the social phenotype in the tgDISC1 rats (Seidisarouei et al., 2022). Here, we made an attempt to adapt a one-shot version of the paradigm, challenging different motivational states by presenting two different reward types at the same time. Thus we were able to compare the time allocation of rats in each reward zone. In brief, during a 10 minute trial, rats had the chance to freely explore a rectangular apparatus (154 cm x 16 cm x 37 cm, PVC). In the far ends, either a bottle containing 10% sucrose solution or a restrainer, holding an unfamiliar conspecific of the same age and sex, were placed. The restrainer was made out of bars, allowing olfactory and limited tactile interaction with the conspecific while preventing full physical contact. The duration of social interaction and time spent drinking the sucrose solution were manually scored. In addition, bottles containing the sucrose solution were weighed before and after the experiments to determine the amount of consumption. Note that rats of each genotype treated with the vehicle compound preferred social contact over sucrose consumption and thus did not differ in their time allocation between the two rewards.

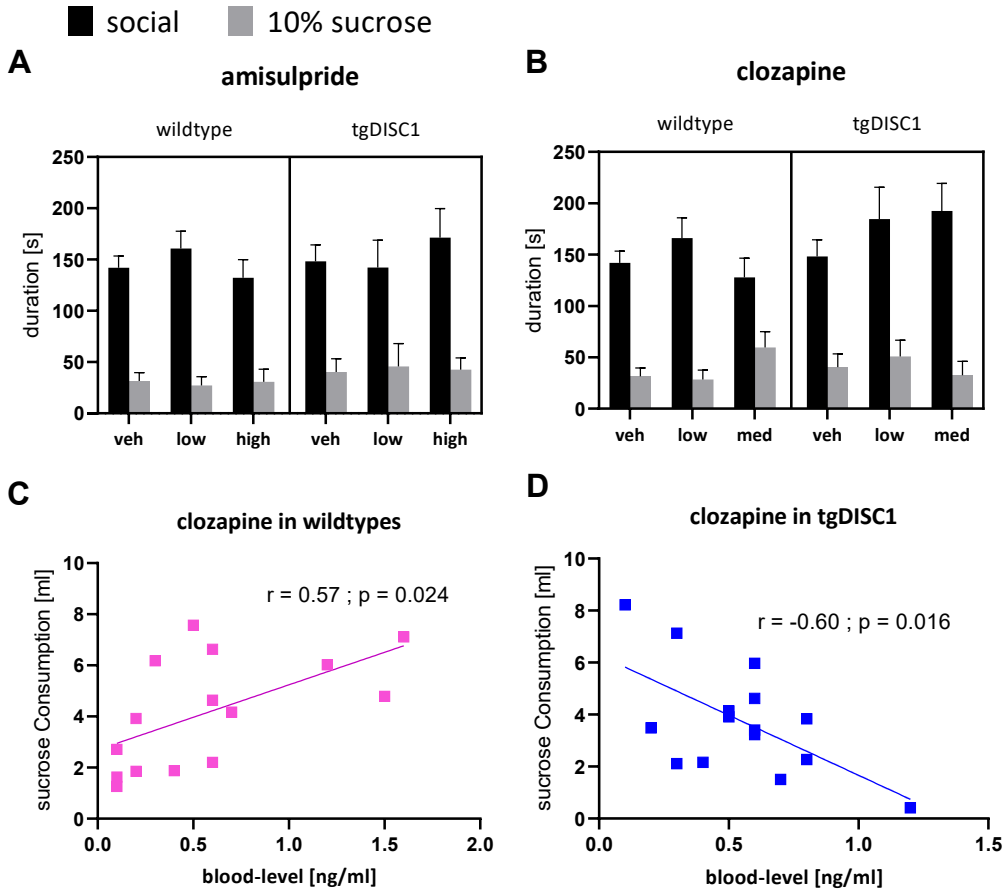

Figure S4: ***Comparison of different reward types in wildtype and tgDISC1 rats****. During the task, rats had the chance to freely explore an apparatus which far ends offered either a bottle containing 10% sucrose solution or the interaction with an unfamiliar conspecific of the same age and sex. Data is show as mean ± standard error of mean (SEM). (A) Duration spent in each reward zones. Amisulpride treatment did not significantly effect behavior of either genotype. (B) Duration spent in each reward zones. Clozapine treatment did not significantly effect behavior of either genotype. (C) Correlation of clozapine blood-levels and sucrose consumption in wildtypes. Higher blood-levels of clozapine were significantly correlated with higher sucrose consumption. (D) Correlation of clozapine blood-levels and sucrose consumption in tgDISC1. Higher blood-levels of clozapine were significantly negatively correlated with sucrose consumption.*

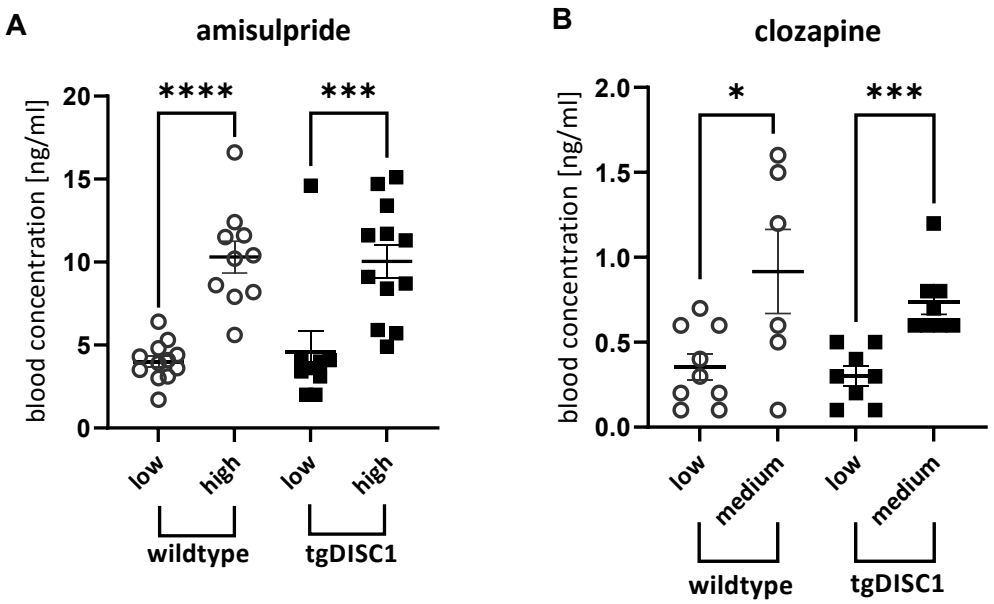

Figure S2: ***Blood-levels of amisulpride and clozapine, in wildtype and tgDISC1 rats.*** *(A) Blood concentration levels (mean ± SEM) of amisulpride in wildtype and tgDISC1 rats following low- and high-dose treatment. The blood concentrations differed significantly between the low- and the high-dose conditions in both genotypes (wildtype: $p < 0.0001$; tgDISC1: $p = 0.001$). (B) Blood concentration levels (mean ± SEM) of clozapine in wildtype and tgDISC1 rats following low- and medium-dose treatment. The blood concentrations differed significantly between the low- and the medium-dose conditions in both genotypes (wildtype: $p = 0.023$; tgDISC1: $p < 0.001$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$*

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Study 2 - Original Paper

Social Reward Learning Deficits and Concordant Brain Alterations in Rats Overexpressing Disrupted-In-Schizophrenia 1 (DISC1)

Dören, J. *§, Kupriyanova, Y. §, Schäble, S., Troßbach, S., McGuire, B., Vernon, A. C., Roden, M., Korth, C., & Kalenscher, T. (2025). Social Reward Learning Deficits and Concordant Brain Alterations in Rats Overexpressing Disrupted-In-Schizophrenia 1 (DISC1). The Journal of Neuroscience, e1067252025.

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Social Reward Learning Deficits and Concordant Brain Alterations in Rats Overexpressing Disrupted-In-Schizophrenia 1 (DISC1)

Abbreviated Title: Social Reward and Brain Alterations in DISC1 Rats

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Conflict of interest statement: MR received fees consulting, lecturing or serving on advisory boards from Astra Zeneca, Boehringer-Ingelheim, Echosens, Eli Lilly, Merck-MSD, Madrigal,

Novo Nordisk, Madrigal, Synergy and Target RWE and has performed investigator-initiated research with support from Boehringer-Ingelheim, Novo Nordisk to the German Diabetes Center (DDZ).

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The AI-based language tools DeepL and ChatGPT3.5 have been used for grammar correction and improving readability. Following their use, the authors thoroughly reviewed and revised the material as necessary, taking full responsibility for the final content of the publication.

Abstract

Social deficits are a hallmark of schizophrenia, often characterized by impairments in processing and integrating socially transmitted information. However, translational models that accurately capture these deficits remain scarce. The Disrupted-in-Schizophrenia 1 gene (*DISC1*), a key susceptibility factor implicated in the etiology of psychiatric disorders, has been shown to cause DISC1-protein aggregation and dysfunctional signaling when modestly overexpressed, ultimately resulting in aberrant dopamine homeostasis. In this study, we employed a transgenic rat model overexpressing human *DISC1* (tgDISC1 rats) to investigate social reward learning and microstructural integrity in the brain. Using a modified Social Transmission of Food Preference (STFP) task, we report that male tgDISC1 rats failed to update reward preferences based on social information, despite intact non-social reward learning—suggesting a specific deficit in social reward learning. Diffusion tensor imaging (DTI) in a behaviorally naïve cohort revealed reduced fractional anisotropy (FA) in key subcortical regions, including the nucleus accumbens, amygdala, and substantia nigra, as well as areas mediating cortical-subcortical communication as the thalamus. Structural alterations in corresponding neuroanatomical areas have also been described in DTI of schizophrenia patients. Our findings link aberrant DISC1 signaling with impaired connectivity in parts of the mesolimbic system, critical for integrating social information into decision-making. This model recapitulates both behavioral and structural endophenotypes of schizophrenia and suggests that social impairments may stem from a fine-grained circuit-selective dysfunction rather than a generalized reward processing deficit. The tgDISC1 rat thus offers a translational platform for probing the neural substrates of social dysfunction in psychiatric disorders.

Significance Statement

Disrupted-in-Schizophrenia-1 (DISC1) is a scaffold-protein regulating various functions related to psychiatric disorders. Its overexpression causes DISC1-protein aggregation and altered signaling, impairing dopamine pathways and behavior. We investigated whether DISC1 overexpression affects social influence on reward valuation using a modified Social Transmission of Food Preference (STFP)-task. Wildtype rats shift preferences after social interaction, favoring an initially non-preferred reward. In contrast, DISC1-overexpressing (tgDISC1) rats did not shift their preference based on social information. In-vivo diffusion-tensor-imaging (DTI) in a behaviorally naïve cohort of tgDISC1 rats revealed structural changes in limbic areas, potentially favoring the deficits in STFP. These findings highlight the importance of DISC1-signaling and related circuits for integrating social cues during decision-making, offering insights into impaired social reward learning in psychiatric disorders.

Introduction

Schizophrenia is a complex psychiatric disorder of heterogenous biological origin marked by a spectrum of symptoms, including pronounced deficits in social behavior. While social withdrawal and anhedonia are well-documented features, patients also show impairments in social learning—specifically, the ability to integrate social cues to guide behavior and decision-making (Bellack et al., 1990; Catalano et al., 2020; Morrison et al., 2017). For instance, individuals with schizophrenia exhibit reduced sensitivity to social rewards (Fett et al., 2019), likely impeding their ability to adapt to social environments and contributing to the broader social dysfunction characteristic of the disorder (van't Wout et al., 2009). Yet, translational models mimicking these deficits remain limited. To address this gap, we employed a modified version of the Social Transmission of Food Preference (STFP; Galef et al., 1984) paradigm, which has recently been adapted as a model for social reward learning (Noguer-Calabús et al., 2022). In this task, observer rats first express a preference between two differently flavored rewards. A demonstrator rat is then fed the observers non-preferred flavor, after which both rats briefly interact. Following this interaction, the observer's preference is reassessed. Typically, observers shift their preference toward the previously non-preferred reward—reflecting integration of social information into their own value representation. This ethologically relevant paradigm thus enables investigation of social reward learning mechanisms and their potential disruption in psychiatric conditions.

Dopaminergic signaling plays a central role in social learning—especially in the encoding of reward value and guiding social decision-making in both humans and animals (Bayer & Glimcher, 2005; Castrellon et al., 2019; Kalenscher & Pennartz, 2008; Soutschek et al., 2017; Terenzi et al., 2022). Impaired sensitivity to social rewards in schizophrenia has been linked to alterations in dopaminergic brain regions (Butler et al., 2020), supporting the relevance of dopamine pathways in the disorder's social deficits (Kapur et al., 2005).

The Disrupted-in-Schizophrenia 1 (DISC1) protein is of particular interest in psychiatric research, given its strong link to dopamine signaling, brain development and cellular

processes, such as synaptic plasticity and spine formation (Brandon & Sawa, 2011; Dahoun et al., 2017).

There is substantial evidence supporting the pathogenic relevance of DISC1 protein dysfunction for schizophrenia and other mental illnesses, as insoluble DISC1 protein aggregates have been found in post-mortem brain tissue and CSF in a subset of patients (Leliveld et al., 2008; Pils et al., 2023). DISC1 aggregation has also been reported in human cell-lines and mouse brains, following proteostasis disruption by influenza A infection (Marreiros et al., 2020). This suggests that aberrant DISC1 protein handling and aggregation are a disease-relevant mechanism, even in the absence of overt gene mutation or widespread overexpression in the general schizophrenia population.

To model the DISC1 related pathology, a transgenic (tgDISC1) rat line was developed in which the human, non-mutant DISC1 protein is modestly overexpressed. Due to the protein's intrinsic propensity to misfold and aggregate (Cukkemane et al., 2025; Leliveld et al., 2008), the model is suitable to mimic cases of DISC1 multimerization observed in patients and investigate mechanistic effects. Supporting this, tgDISC1 rats exhibits dysregulated dopamine homeostasis—evidenced by increased dopamine transporter availability and elevated high-affinity dopamine D2 receptor expression—alongside behavioral phenotypes resembling psychiatric symptoms (Nani et al., 2020; Trossbach et al., 2016; Uzuneser et al., 2019).

Based on this, we hypothesized that DISC1 protein aggregation would disrupt the function of dopaminergic circuits involved in social reward learning, leading to impaired performance of tgDISC1 rats in the STFP paradigm. To further characterize the tgDISC1 model on a neurostructural level, we conducted in vivo diffusion tensor imaging (DTI) in a test-naïve rat cohort. This analysis aimed to identify microstructural alterations associated with disrupted DISC1 signaling. Specifically, we assessed structural integrity across key neuroanatomical regions relevant to the STFP paradigm. This two-sided approach— investigating behavioral assessment and structural imaging— provides a comprehensive characterization of the

139 tgDISC1 rat, including features potentially relevant to schizophrenia-related social dysfunction
140 and/or associated hallmarks of microstructural brain pathophysiology.

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Materials & Methods

Animals & Housing

A total of 96 male Sprague Dawley rats, aged 3 to 6 months, were tested. The animals included transgenic homozygous DISC1 rats, as well as their wildtype littermates matched as siblings of the same parents (hereafter referred to as wildtype). Before testing, wildtype rats were assigned to either serve as controls or social demonstrators. The animals were bred at the ZETT (*Zentrale Einrichtung für Tierforschung und wissenschaftliche Tierschutzaufgaben,* Düsseldorf, Germany) of the Heinrich Heine University in Düsseldorf, Germany. The animals were maintained in Type 4 cages on wood chipped bedding (LASvendi, Soest, Germany) at approximately 22± 2ºC and 55± 5% humidity. Rats were paired-housed unless described differently (see below). For enrichment, a wooden block and a red PVC tube were added. The animals were kept in a reverse 12-hour light-dark rhythm. Rats were supplied with laboratory rodent chow (Ssniff, Soest, Germany) and water ad libitum, unless stated otherwise in the behavioral task descriptions. All animal procedures were conducted in accordance with the German *Tierschutzgesetz* (Animal Welfare Act) and were approved by the local authority LANUV (*Landesamt für Natur-, Umwelt- und Verbraucherschutz* North Rhine-Westphalia, Germany).

Genotyping

The generation and genotyping of the tgDISC1 model has been described to great detail previously (Trossbach et al., 2016). Briefly, for genotyping, small parts of the tail tips were lysed in a buffer (100 mM Tris [pH 8], 5 mM EDTA, 0.2% SDS, 200 mM NaCl, and 100 mg/ml proteinase K). After overnight incubation in 500µl of lysis (50°C, 800rpm), genomic DNA was precipitated (100% isopropanol;70% ethanol), centrifuged for 30 min with 14.000rpm at 4°C and subsequently solubilized in distilled water. For qPCR detection, primers targeting PrP promoter region (forward: 5′-CTGATCTCCAGAAGCCCAAA 3′; reverse: 5′-CAGGCCTATTCCTTGACAGC-3′) and rat β-actin (forward: 5′

GCAACGCGCAGCCACTGTCG-3′; reverse: 5 ′-CCACGCTCCACCCCTCTAC-3′) as a reference gene were utilized. For polymerase chain reaction (PCR; 10 min at 95°C, followed by 40 cycles of 10 s at 95°C, 20s at 60°C, and 30 s at 72°C), DNA samples, either PrP or β-actin primers, SYBR Green I SuperMix (Roche, Mannheim, Germany), FactorQ and distilled water were mixed. PCR products were analysed via gel electrophoresis and LightCycler 480 software (Roche, Mannheim, Germany), with β-actin used for normalization.

Procedure

Rats were tested in a modified variant of the STFP as well as in a number of control tasks. The tasks were conducted in a fixed, chronological order: all observer rats first completed the 3-Chamber task, followed by the Odor Discrimination task, and then the STFP task (see below for task descriptions). The Reward Magnitude Discrimination and Reversal task were performed by a separate batch of rats. In general, all rats were handled for 5 minutes on 3 consecutive days before starting the first experiments. Before the start of the experiments, the animals were brought into the experimental room for habituation. Between trials, the experimental set-ups were cleaned with 70% ethanol. Experiments were conducted during the animals' dark-phase.

Social Transmission of Food Preference Task

The experimental design and analysis were performed as described by Noguer-Calabús et al. (2022) (Fig. 1). Three days prior to the STFP, rats were single-housed in type 4 cages with enrichment (wood block and tube) and acclimatized to the experimental setup. During this period, they were provided with custom-made metal hanging feeders containing two bowls with either 10 grape-flavored or 10 banana-flavored pellets (TestDiet, Richmond, USA).

The STFP protocol was implemented in several stages: Habituation to the experimental procedure (Day 1), Pre-Interaction Preference Testing (Days 2 and 3), Social Interaction (Day 4), and Post-Interaction Preference Testing (Days 4 and 5).

During the entire course of the STFP, rats were subjected to mild food restriction, maintaining them at 85% of their free-feeding body-weight. Standard laboratory chow was removed each morning on test days and returned after the 6-hour preference measurements were completed. Water was available ad libitum.

Pre-Interaction Preference Testing

Each day during the Pre-Interaction Preference Testing, the observer rats were offered two food cups containing two different reward flavors (grape and banana). The rats had unrestricted access to the food cups for 6 hours. Afterward, the cups were removed. Cups were weighed before and after testing.

Consumption was quantified individually for each observer rat by calculating the difference in cup weight before and after the 6-hour testing period. On Day 3, following the 6-hour measurement, individual preferences were determined based on the quantity of each pellet type consumed. The flavor consumed in greater quantity during Pre-Interaction Preference Testing was designated as the individual's preferred flavor (see exclusion criteria below).

After observers' preferences were quantified on Day 3, demonstrator rats were single-housed (with enrichment) and provided with a hanging feeder containing the pellets that were not preferred by their assigned observers. Demonstrators had access to the feeder all night preceding the Social Interaction on Day 4 (see below). Demonstrators were age- and sex-matched, unfamiliar wildtype rats of the same strain.

Social Interaction

On Day 4, it was confirmed that demonstrators had consumed the flavored pellets before interaction by inspecting if any pellets were left in the cups. To enhance the odor that was to be transmitted, crushed pellets were gently rubbed onto the demonstrators' back, snout and genital area. Subsequently, the demonstrator was marked with a black pen on the back for identification purposes. A matched pair of demonstrators and observers were then allowed to interact freely in an open field (50x50x45 cm, PVC, illuminated to 5-15 lux) for 20 minutes.

The interaction was recorded (Conrad Electronic SE, Hirschau, Germany), and an experimenter blinded to the genotypes scored the social initiation behavior of the observer using Solomon Coder (Solomon Coder beta 19.08.02 © András Péter).

Post-Interaction Preference Testing

Immediately after Social Interaction on Day 4, the observer rats were placed back into their individual cages. As in the Pre-Interaction Preference Testing, they were given two separate cups, each filled with one of the two pellet flavors. The cups were removed and weighed after a 6-hour interval. This preference test was repeated the next day. After completion, all animals were returned to their previous group housing conditions.

Analysis

A daily Preferences Index (PI) was calculated as described below (Noguer-Calabús et al., 2022):

$$\text{Preference Index} = \frac{(\text{preferred [g]} - \text{nonpreferred [g]})}{(\text{preferred [g]} + \text{nonpreferred [g]})}$$

with preferred[g] and nonpreferred[g] referring to the amount eaten of the respective preferred and non-preferred reward in grams. Individual indices were used to compare Pre-Interaction and Post-Interaction preference strengths. A PI-value of 1 means exclusive consumption of the originally preferred reward, a PI-value of -1 means exclusive consumption of the originally non-preferred reward, and a PI-value of 0 means indifference (equal consumption of both rewards).

Exclusion Criteria

Observer rats were excluded from analysis if they did not consume any of the flavored pellets during the Habituation and Pre-Interaction Preference Testing. Further, rats with inconsistent Pre-Interaction preferences were also excluded from the analysis. This criterion applied if the reward type preferred on Day 3 was different from the preferred reward on Day 2. The reason

for being strict about the consistency of the observer's food preference across Pre-Interaction days was to make sure that demonstrators were fed with the food that truly contrasted with the observer's original preference. Six rats of each genotype group were excluded from further analysis due to inconsistent preferences, or not consuming any flavored pellets at all.

- Insert Figure 1 here -

Control tasks

We employed a number of control tasks described below. All observer rats were tested in all control tasks, except the Reward Magnitude Discrimination & Reversal task.

3-Chamber task

The 3-Chamber task is a well-established method for examining sociability and general interest in an unfamiliar conspecific (Ku et al., 2016). The apparatus consisted of an open field (60 cm x 60 cm x 39 cm, PVC, 5-10 lux) with two 20 cm x 20 cm compartments located in the left and right corners, separated by bars that allowed snout to snout contact. The task was performed in two trials, both trials were video-recorded (Conrad Electronic SE, Hirschau, Germany). The first trial was a habituation trial during which the observer rat was placed in the starting chamber and was allowed to freely explore the box for 5 minutes before being returned to its home cage. After a 10-minute inter-trial interval (ITI), a second, unfamiliar rat was placed in one of the compartments, and the observer rat was again placed in the starting chamber. This social trial lasted for 5 minutes. We pseudo-randomly counterbalanced across observers into which compartment the second rat was placed. The recorded trials were analyzed using EthoVision XT 9 (Noldus, Wageningen, Netherlands), which measured locomotion, the time the observer spent in the interaction zone with the second rat, and the time spent exploring the empty compartment.

Odor Discrimination

To control for rats' ability to identify and discriminate between specific odors, an Odor Discrimination task was implemented prior to testing the modified STFP. The protocol was adapted from Noguer-Calabús et al. (2022). All trials were video-recorded (Conrad Electronic SE, Hirschau, Germany). Initially, the rats were placed into an open field (50x50x45 cm, PVC, illuminated to 5-15 lux) for 10 minutes to allow habituation to the arena. On the following day, during the sample trial, two customized 3D-printed bowls were placed at randomized corners of the open field. These bowls contained crushed pellets, either grape or banana (TestDiet, Richmond, USA), mixed with water in a 1:3 ratio to a volume of 10 ml. During the sample trial, both bowls contained the same odor; the choice of odor was pseudo-randomized across rats. A 3D-printed grid cover on the bowls prevented the animals from consuming the liquid, allowing only olfactory exploration for 5 minutes before the rats were returned to their home cage. Following a 15-minute ITI, the test trial was conducted. In this trial, two bowls were placed in the same positions as in the sample trial. One bowl contained the familiar odor from the sample trial, while the other contained a novel odor. The location and type of odor were pseudo-randomized across rats. Recorded trials were analyzed using EthoVision XT 11.5 (Noldus, Wageningen, Netherlands). During the habituation phase, exploratory drive was measured by the number of visits to the center zone. In the sample and test trials, olfactory exploration of the bowls was evaluated by the number of nose touches and by comparing the total exploration duration between genotypes.

Reward Magnitude Discrimination and Reversal

The Reward Magnitude Discrimination and Reversal task were used to assess potential differences between genotypes in goal-directed motivation, reward magnitude discrimination, and reversal learning. Rats were food-restricted to 85% of their free-feeding body weight but remained pair-housed throughout the experiment. Because this task involved the consumption of sucrose pellets, which might interact with performance in the STFP, we used rats from a different batch that were not tested in the STFP.

297 A customized T-maze was used (Ugo Basile S.R.L., Gemonio, Italy). The T-maze featured
298 automatic sliding doors that separated each arm, which were equipped with a pellet dispenser
299 (Noldus, Wageningen, Netherlands) and a light signal at the far end. One arm of the T-maze
300 was designated as the "start arm" (consistent for each animal), while the remaining two arms
301 served as choice-arms. The doors were independently operable, allowing access to one arm
302 at a time during forced trials (see below). The entire apparatus was controlled by EthoVision
303 XT 11.5 (Noldus, Wageningen, Netherlands).

304 **Habituation and training**

305 The training procedure followed the protocol previously described and consisted of three
306 stages: Habituation, Shaping 1, and Shaping 2 (Zech et al., 2022).

307 Habituation: During Habituation, rats were allowed to explore the T-maze for 10 minutes.
308 When a rat entered a choice-arm, the associated automatic sliding door closed, and a food
309 reward (sucrose pellet, 20 mg dustless precision pellets; Bio-Serv, Flemington, USA) was
310 delivered by the pellet dispenser, accompanied by a 1-second light flash. After a short delay,
311 the door reopened, allowing the rat to return to the start box to begin a new trial. There was
312 no restriction on the number of pellets delivered during Habituation.

313 Shaping 1: Shaping 1 was conducted over four days, with a maximum session duration of 40
314 minutes per day. Each session allowed a maximum of 16 free trials per rat, where both arms
315 were accessible and provided the same reward (one sucrose pellet). A session ended either
316 when all free trials were completed or when the maximum session duration was reached. The
317 number of completed free trials were compared each day between genotypes.

318 Shaping 2: In the Shaping 2 stage, rats first completed six forced trials where only one arm (in
319 pseudo-random order; three trials allocated to each choice-arm) was accessible, followed by
320 16 free trials where both arms were accessible. The maximum session duration remained 40
321 minutes. The reward in both arms continued to be 1 pellet. The number of completed free trials
322 was compared each day between genotypes. Although Shaping 2 was planned to last for 4

days, technical issues on the final day resulted in the doors not responding adequately. Consequently, data from Day 4 of Shaping 2 were excluded from the analysis. To control for side bias, the number of free trials completed in each choice-arm was compared across genotypes, with data from Day 3 being used for this comparison.

Reward Magnitude Discrimination Task (RMDT)

Upon completing the training phase, rats were subjected to the Reward Magnitude Discrimination Task (RMDT) over the course of three days. In this task, the arms of the T-maze were associated with either a small reward (1 pellet) or a large reward (8 pellets). The assignment of reward amounts to arms was pseudo-randomized between individuals and remained consistent throughout the RMDT. Each session consisted of 6 forced trials followed by 16 free trials, with a maximum session duration of 40 minutes. The percentage of large reward choices was recorded and compared between genotypes daily.

Reversal learning

Following the completion of the RMDT, rats underwent a reversal learning session. In this session, the location of the arm delivering the large reward was swapped for each individual. The number of forced trials, free trials, and the maximum session duration remained unchanged from the previous tasks. The reversal learning was conducted over a period of 3 days. The percentage of large reward selections was compared between genotypes on a daily basis.

Exclusion Criteria

Rats were excluded from the tasks if they failed to complete a minimum of 10 free trials on two consecutive days. One animal had to be excluded from the reversal learning.

Magnetic resonance imaging and diffusion tensor imaging

A total of 34 rats underwent magnetic resonance imaging (MRI) examination. All MRI measurements were performed in a horizontal 11.7 T 16-cm bore magnet (Bruker Biospin,

Bruker, Karlsruhe, Germany) using a transmit-receive 40 mm volume coil. The animals were anesthetized by 1.5-2% isoflurane in pure O_2 delivered via a nose cone during the whole imaging session.

First, a high-resolution T2-weighted rapid acquisition with relaxation enhancement (RARE) anatomical scan was performed with the following parameters: repetition time (TR) / echo time (TE) = 2800/ 30 ms, field of view (FOV) = 22 x 15 mm^2, in-plane resolution 156 µm x 156 µm, slice thickness 1 mm, number of signal averages 4. The images were used as a quality control to check for any volumetric deviations or structural abnormalities.

DTI data acquisition

After performing magnetic field shimming, DTI images were acquired with a spin-echo echo planar imaging sequence with the following parameters: TR / TE = 3200 / 21 ms, 30 diffusion gradient directions, b = 1000 s/mm^2, FOV = 22 x 15 mm^2, in-plane resolution 156 µm x 156 µm, slice thickness 1 mm, 4 averages in order to increase the signal-to-noise ratio. Five additional DTI images with b = 0 s/mm^2 were also obtained.

Volumetric Segmentation

As slight changes in ventricle size has been an established feature of the tgDISC1 rat (Trossbach et al., 2016), we used volumetric analysis to ensure comparability between genotypes in this regard. First, manual segmentation of the right and left lateral ventricles was performed on MR images using ITK-SNAP (Yushkevich et al., 2006). The ventricles were segmented from coronal slices along a 5.88 mm section, from Interaural 11.28 mm / Bregma 2.28 mm to Interaural 5.40 mm / Bregma -3.60mm (Paxinos & Watson, 2013). The start and end points of the segmentation were best marked by the appearance of the corpus callosum and inferior lateral ventricles respectively. Prior to segmentation, MR images were thresholded and binarized to show only the top 1% of voxel intensities, which should correspond to CSF on a T2-weighted MR image. All MRI analysis was carried out by a single operator, but showed

excellent intra-rater consistency with a Dice co-efficient 0.99 ± 0.002 across two independent segmentations using all images available in the dataset.

DTI data processing

DTI data were post-processed using DSI Studio (http://dsi-studio.labsolver.org). Raw Bruker data were imported and corrected for distortions. Next, the quality of the data (number of bad slices indicated by DSI Studio) was checked. Masks were specified in order to eliminate background signals. Further, image orientation was corrected in order to align the measured volume with the rat brain atlas implemented in DSI Studio (Johnson et al., 2021). Generalized Q-Sampling Imaging (GQI) was used in order to reconstruct fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) maps, as measures of microstructural integrity and structural properties of the measured tissue. FA, AD, and RD maps were registered to the implemented atlas and values of FA, AD, and RD were computed in the regions of interest (ROIs, Fig. 2), selected based on their potential implication in social transmission of food preference (see Table S2): nucleus accumbens (NAc), basolateral amygdala (BLA), cortical amygdala (CoA), hippocampus (HPC), infralimbic cortex (IL), lateral septum (LS), diagonal band of broca (DB; as representative of a major cholinergic structure of the basal forebrain, Berger-Sweeney et al., 2000), olfactory areas (OLF), orbital cortex (ORB), piriform cortex (PIR), prelimbic cortex (PL), substantia nigra pars compacta (SNc) and the thalamus (TH).

- Insert Figure 2 here -

Exclusion Criteria

One rat died while under anaesthesia for MRI scan and three rats with visible abnormalities (ventricular enlargements) in the anatomical images were excluded from further DTI measurements. Subsequent volumetric segmentation measurement uncovered substantial ventricular enlargement, in another two animals, which were also excluded from further

analysis (see Figure S1). Importantly, the ventricular enlargement was not restricted to one genotype, but found in both wildtypes and tgDISC1 rats (wildtype n = 3; tgDISC1 n = 2), suggesting it is likely attributable to spontaneous variation within the background strain, as reported by other researchers, too (Mulla et al., 2012; Tu et al., 2014, 2017). Five more rats were excluded due to inability to finish DTI acquisition because of movement and one rat was excluded due to poor quality of the scan, indicated by DSI Studio. Finally, 22 rats (n=11/genotype) were included into the DTI data analysis.

Data analysis

For all parameters, data are presented as means ± standard errors of the mean (SEM). Calculations were performed with RStudio (Version 2023.06.2) and GraphPad Prism 9.5.0 (GraphPad Software, Boston, USA). Graphs were generated with GraphPad Prism 9.5.0 (GraphPad Software, Boston, USA). For statistical analysis, differences in the dependent variables between genotypes were compared with unpaired t-tests, or by non-parametric Mann-Whitney U-tests, dependent on the (lack of) normal distribution, as assessed with Kolmogorov–Smirnov tests. Mixed-Effect models with Restricted Maximum Likelihood estimation were used to compare the influence of multiple fixed factors. If applicable, post-hoc analyses were calculated, corrected with Benjamini–Hochberg False Discovery rate (FDR) for multiple comparisons. The statistical significance level was set to $\alpha = 0.05$.

Results

Behavior

tgDISC1 rats fail to update reward values after social contact with a demonstrator

We calculated an individual Preference Index before and after Social Interaction, indicating the strength of preference for one reward flavor over the other in each respective task phase (Noguer-Calabús et al., 2022). We computed a mixed-effect model of the PI, with contact (Pre-Interaction vs. Post-Interaction) as within-subject factor and genotype (wildtype vs. tgDISC1) as between-subject factor. The analysis revealed a main effect of contact as well as an interaction effect of contact and genotype (contact: $F[1, 26] = 15.62$, $p = .0005$; genotype: $F[1, 26] = 1.93$, $p = .1769$; contact*genotype: $F[1, 26] = 8.89$, $p = .0062$, Fig. 3). Post-hoc tests demonstrated a difference in PI for wildtype rats depending on social contact ($p < .0001$), indicating that these rats shifted their food preferences following Social Interaction. This result supports the occurrence of social transmission of food preferences in wildtype rats. Conversely, tgDISC1 rats showed no difference in PI before and after interaction ($p = .4967$), suggesting that tgDISC1 rats failed to show socially transmitted food revaluation.

We additionally assessed total pellet consumption, i.e., the sum of both pellet types, to test for potential differences in hunger or satiation between genotypes. We found that total consumption of flavored pellets did not differ before or after the Social Interaction or between genotypes, as revealed by a mixed effect model (contact: $F[1, 26] = 2.63$, $p = .1168$; genotype: $F[1, 26] = 0.53$, $p = .37$; contact*genotype interaction: $F[1, 26] = 0.43$, $p = .5181$). This suggests that the genotype-dependent differences in the propensity to show social transmission cannot be explained by differences in general appetite, satiation, or food consumption (Fig. 3).

We further analyzed the average amount consumed of the originally preferred and non-preferred flavors separately, using mixed-effects models with contact as the within-subject factor and genotype as the between-subject factor. For the originally preferred reward flavor, there was a main effect of contact ($F[1, 26] = 7.41$, $p = .0114$) and a contact*genotype interaction ($F[1, 26] = 4.65$, $p = .0405$). Post-hoc comparisons showed a decrease in preferred reward consumption in wildtype rats after interaction ($p = .0039$), but no change in tgDISC1 rats ($p = .6924$).

For the non-preferred rewards, the mixed-effects model also revealed a main effect of contact ($F[1, 26] = 19.25$, $p = .0002$) and a contact*genotype interaction ($F[1, 26] = 7.48$, $p = .0111$). Wildtype rats increased their consumption of the non-preferred reward after Social Interaction ($p < .0001$), whereas tgDISC1 rats showed no change ($p = .2530$). Thus, following Social Interaction, wild-type rats increased their intake of the previously non-preferred reward and reduced their consumption of the initially preferred one. In contrast, tgDISC1 rats showed no change in their reward preferences.

- Insert Figure 3 here –

An overview of the conducted test battery of the control tasks and control variables, and respective parameters is listed in Supplementary Table S1. None of the comparisons revealed any significant differences in any of the variables between genotypes.

tgDISC1 rats show intact social interest and motivation compared to wildtype controls

To investigate potential social behavior impairments in tgDISC1 rats, we manually scored several aspects of social behavior initiated by the observer during the STFP task, including snout to snout contact, partner exploration, allogrooming, social play, following, and genital

exploration. Comparisons between tgDISC1 and wildtype rats revealed no significant differences in any of these behaviors (Fig. 4; statistics for the group comparisons are summarized in Table S1). Stereotypical behaviors, such as repetitive self-grooming and rearing, were also compared as indicators of arousal. Again, no significant differences were observed between genotypes (Fig. 4 and Table S1).

Prior to the STFP task, the 3-Chamber task was conducted to assess whether general social interest in an unfamiliar conspecific differed between genotypes. During the habituation phase, we recorded the observers' locomotion, measured by total distance traveled, and their average velocity, with no significant differences between genotypes (Table S1). In the social interest phase, a mixed-effects model with genotype as the between-subject factor and chamber (conspecific vs. empty) as the within-subject factor showed a main effect of chamber on exploration duration ($F[1, 76] = 58.46$, $p < .0001$), but no main effect of genotype ($F[1, 76] < 0.01$, $p = .9934$) nor a interaction effect ($F[1, 76] = 2.95$, $p = .0898$). These results suggest that we have no evidence to assume that tgDISC1 rats have impaired social interest in the 3-Chamber task.

- Insert Figure 4 here –

Olfactory capacity and odor discrimination are not altered in tgDISC1 rats

To control for potential olfactory impairments that could influence the transmission of reward preference, we used an Odor Discrimination task to assess the olfactory capacity of tgDISC1 rats. During habituation in the open field, the number of visits to the center zone and general locomotion were measured, with no significant differences between genotypes (Table S1).

In the sample trial, two bowls containing the same odor were presented, and a mixed-effects model with genotype as the between-subject factor and bowl as the within-subject factor was used to compare the number of nose touches. No differences were found between genotypes

(genotype: F[1, 38] = 0.95, p = .34; bowl: F[1, 38] = 0.44, p = .51; bowl*genotype interaction: F[1, 38] = 1.29, p = .26). We also found no significant difference in total exploration time between genotypes (Table S1).

In the test trial, which introduced a novel odor alongside a familiar one, a mixed-effects model with genotype as the between-subject factor and novelty as the within-subject factor revealed a main effect of novelty on number of nose touches (F[1, 38] = 6.99, p = .0118), but no main effect of genotype (F[1, 38] = 0.54, p = .465) nor an interaction effect (F[1, 38] = 0.52, p = .474). These results indicate that tgDISC1 rats show functional olfactory behavior and are capable of odor discrimination, suggesting that olfactory processing is not impaired in these animals (Fig. 5).

- Insert Figure 5 here –

Goal-directed motivation and reward magnitude discrimination are not different between tgDISC1 and wildtype rats

We assessed goal-directed motivation and reward magnitude discrimination in tgDISC1 rats using the Reward Magnitude Discrimination Task (RMDT) in a T-maze setup. We found no significant difference between genotypes in the number of free trials performed during the two Shaping phases (Table S1), suggesting no evidence for a difference in learning speed and ability.

On Day 3 of the second Shaping phase, a Wilcoxon matched-pairs signed rank test was conducted for each genotype to determine if there were potential side biases toward one arm of the T-maze. No side biases were found in neither wildtype (p = .500) nor tgDISC1 rats (p = .187).

In the RMDT, we analyzed the daily percentages of choices of the arm containing the larger reward. No significant differences in large reward choices were observed between genotypes on any of the three days of testing (Fig. 5, Table S1).

No difference between tgDISC1 and wildtype rats in reversal learning

Following the RMDT, we evaluated cognitive flexibility with a reversal learning task. Over the course of three days, we compared, between genotypes, the daily percentage of large reward choices after reversing the magnitude-to-arm contingencies. No significant differences between genotypes were detected on any of the three days, indicating that tgDISC1 rats exhibit similar learning strategies and cognitive flexibility as wildtype rats (Fig. 5, Table S1).

Magnetic resonance imaging

tgDISC1 rats display impaired organization of tissue in multiple limbic areas

To investigate differences in brain (micro)structures between wildtype and tgDISC1 rats, we performed in vivo DTI in a behaviorally naïve cohort of rats. FA, AD, and RD, reflecting tissue structural properties, were compared on group-level between tgDISC1 and wildtype rats. tgDISC1 rats had significantly lower FA values in regions of (or closely related to) the limbic system, including the NAc, amygdala (BLA and CoA), LS, DB, OLF, SNc and TH (Fig. 6; Table 1).

– Insert Figure 6 here –

There were no significant differences in AD and RD after correcting for multiple comparisons (Table 1). The observed reductions in FA, in the absence of changes in AD or RD, suggest subtle disruptions in microstructural organization rather than gross abnormalities in tissue diffusion. These results indicate that tgIDSC1 rats exhibited compromised tissue organization

543 in key regions, potentially associated with social reward, rather than widespread structural
544 impairments.

545

546 - Insert Table 1 here –

Discussion

This study aimed to characterize behavioral and structural consequences of *DISC1* overexpression, leading to DISC1 protein aggregation, in a rat model of schizophrenia, with a particular focus on social reward learning and brain microstructure integrity. Using a modified version of the Social Transmission of Food Preference (STFP) paradigm, we examined whether tgDISC1 rats could update subjective reward values based on social information. In line with our hypothesis, tgDISC1 rats failed to change their initial reward preference after interacting with a demonstrator rat fed with the observers' non-preferred food, indicating a selective impairment in socially mediated reward value updating. Notably, performance in a non-social reward learning task was unimpaired, suggesting that the deficit was specific to the social domain rather than reflecting general learning or motivational dysfunction. This behavioral phenotype mirrors findings in schizophrenia patients, who show reduced sensitivity to social, but not non-social, rewards (Catalano et al., 2018; Lee et al., 2019), and difficulties integrating cognitive and affective information during decision-making (Heerey et al., 2008).

To further characterize the tgDISC1 model on a neural level, we conducted in vivo DTI in a separate cohort of behaviorally naïve animals. This design choice allowed us to assess baseline alterations caused by disrupted DISC1 signaling without the confounding effects of behavioral testing, which has been shown to rapidly modulate DTI readouts within 1-hour past testing (Blumenfeld-Katzir et al., 2011; Ding et al., 2013). ROIs were selected based on their previously established involvement in social learning in an STFP task (Table S2). Our analysis revealed significant structural changes in tgDISC1 rats, evident by decreases in FA values in key limbic structures, including the NAc, amygdala (BLA; CoA), LS, and SNc. We observed additional alterations in nodes controlling cortical-subcortical communication, such as the TH and the basal forebrain (Cruz et al., 2022; Gielow & Zaborszky, 2017). These changes in FA values conform with the known biological roles of DISC1, which is critically involved in synaptic trafficking, dendritic arborization, and neurodevelopment (Brandon & Sawa, 2011; Lipina &

573 Roder, 2014), and support the interpretation that DISC1 protein aggregation may lead to
574 altered microstructural organization in these ROIs. Importantly, the current results extend and
575 replicate prior neuropathological findings in tgDISC1 rats, including divergent dopaminergic
576 cell counts in the substantia nigra (Hamburg et al., 2016). Further, the absence of significant
577 differences in other DTI measures suggests that the observed FA reductions are unlikely to
578 stem from myelin or axonal deficits but rather reflect alterations in neurite organization within
579 these subcortical regions. Although speculative, this aligns with the idea that FA in grey matter
580 is more sensitive to dendritic complexity and synaptic architecture rather than traditional white
581 matter integrity markers (Müller et al., 2019). Together, these data suggest that tgDISC1 rats
582 display a network-level disruption in subcortical nodes which likely is the result from a subtle
583 impairment of brain development (Brandon & Sawa, 2011; Kamiya et al., 2005).

584 Social information processing critically depends on the coordinated interaction of distributed
585 neural circuits (Huang et al., 2020; Kalenscher et al., 2025; Kietzman et al., 2022; Menon et
586 al., 2021; O'Connell & Hofmann, 2012; Poggi et al., 2024; Wang et al., 2021). A well-
587 characterized BLA–PL–NAc circuit, for instance, is critical for integrating socially acquired
588 information into reward-based decisions in mice (Kietzman et al., 2022), a process closely
589 mirrored in our STFP paradigm. The critical involvement of BLA-PL-NAc is in line with work
590 demonstrating that the NAc is essential for STFP, as male rats with exocytotic lesions of the
591 NAc Shell were unable to revalue the originally non-preferred reward (Noguer-Calabús et al.,
592 2022). Importantly, neither the disruption of the BLA-PL-NAc circuit nor the NAc Shell lesion
593 affected odor discrimination or general social interest, paralleling the presented phenotype of
594 tgDISC1 rats. Similarly, previous studies stressed the importance of the amygdala and its
595 subregions for the social transmission, as lesioning the BLA prevented associating social with
596 olfactory cues (Wang et al., 2006). In addition, the CoA plays a unique role in integrating social
597 and olfactory information, as it was engaged during STFP but not when social or olfactory
598 stimuli were presented in isolation (Liu et al., 2024). In our model, FA reductions in these same
599 regions—many of which are downstream targets of mesolimbic dopamine—may reflect the

underlying vulnerability of this circuitry to disturbed DISC1 signaling. Indeed, aberrant DISC1 signaling via modest DISC1 protein aggregation has been shown to impair dopamine homeostasis (Trossbach et al., 2016) and monoamine levels in post-mortem NAc and amygdala tissue in tgDISC1 rats (Uzuneser et al., 2019; Wang et al., 2017). In summary, since both, animal and human studies, have demonstrated a central role for dopamine in social reward processing, revaluation, and decision-making (Burke et al., 2017; Castrellon et al., 2019; Dang et al., 2018), it is plausible that the impaired social reward learning observed in tgDISC1 rats results from dysregulated mesolimbic dopaminergic signaling.

In studies involving human patients, several of the regions showing reduced FA in our rat model have also been implicated in the pathophysiology of schizophrenia across multiple MRI modalities. DTI studies previously reported reduced FA values in the amygdala, TH and NAc (Cuesta et al., 2021; Hashimoto et al., 2009; Kalus et al., 2005; Spoletini et al., 2011). Importantly, these findings have been interpreted as impaired modulation of dopaminergic relay stations (Kalus et al., 2005) and disturbed information flow between limbic and cortical systems (Spoletini et al., 2011). Further, reduced FA along the NAc-TH pathway, regions also found altered in our model, has been observed in individuals at high risk for psychosis, suggesting an early involvement of these tracts in schizophrenia pathophysiology (Chen et al., 2025). Beyond structural abnormalities, consistent evidence from patient fMRI studies revealed altered functional connectivity in the same regions, including the amygdala (Kim et al., 2020), the TH (Avram et al., 2018), the SNc and ventral striatum (White et al., 2015). Further, Martino et al. (2018) identified decreased connectivity within subcortical circuits overlapping with areas included in our results, strongly supporting the idea of broader functional network disruptions in schizophrenia (Metzner et al., 2024). Importantly, the aforementioned study also emphasizes the importance of dopamine dysregulation in regard to changed connectivity (Martino et al., 2018). Supporting this, a combined PET-fMRI study revealed a causal link between dopaminergic receptor binding potential, along with abnormal dopamine release, and altered connectivity patterns in subcortical-cortical regions in

627 schizophrenia (Horga et al., 2016). Hence, empirical evidence from patient data suggests
628 strong parallels with the altered brain regions and aberrant dopamine signaling observed in
629 our tgDISC1 rats, even across a methodological variety, which further supports the clinical
630 relevance of our findings.

631 Previous studies in healthy individuals have uncovered DISC1-dependent differences in the
632 volume of brain regions closely related to our findings (Mühle et al., 2017), corroborating our
633 conclusion that disruptions in DISC1 signaling influence regional brain structure and function.
634 Interestingly, these changes were found to be sex-dependent. Other research has proposed
635 that estradiol may exert a beneficial effect on altered DISC1 function (Erli et al., 2020). Thus,
636 it would be worthwhile to investigate this further in female tgDISC1 rats. While current literature
637 reports no sex differences in social or memory behavior in this model (Uzuneser et al., 2019),
638 it has not yet examined more nuanced interactions, such as those involving our adapted STFP
639 paradigm or microstructural integrity.

640 Finally, the specificity of the social deficit in tgDISC1 rats' contributes to an ongoing discussion
641 about whether social impairments in schizophrenia reflect a general reward processing deficit
642 or a more selective dysfunction in integrating social information (Butler et al., 2020; Fett et al.,
643 2019; Hanssen et al., 2020; Lee et al., 2019). Our data support the latter view, suggesting that
644 while basic reward processing may remain intact, the ability to flexibly integrate social cues in
645 decision-making is compromised (Catalano et al., 2020; Lee et al., 2019) - a challenge that
646 may arise from impaired communication within circuits to integrating emotional, cognitive, and
647 social information to guide behavior (Heerey et al., 2008).

648 In conclusion, this study shows that DISC1 overexpression leading to DISC1 protein
649 aggregation and altered DISC1 signaling impairs social, but not general, reward learning and
650 is linked to specific microstructural alterations in a fine-grained network of subcortical regions
651 critical for social reward learning. Future research should try to establish a mechanistic link
652 with a focus on region- and circuit-specific interventions, as well as cellular analyses, to test

(regional) causal links between DISC1 protein dysfunction and impaired social value computation. Given that current clinical assessments of social deficits in patients rely heavily on subjective self-report, animal models may provide an outset for quantifiable behavioral markers that link hallmarks of subcortical pathology to functionally relevant endophenotypes. The tgDISC1 model thus provides translational value for understanding circuit-level vulnerabilities that may underlie social dysfunction in psychiatric disorders like schizophrenia.

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Figure Legends

Figure 1 Study Design**.** Illustration of the experimental adaption of the Social Transmission of Food Preferences-Paradigm by Galef et al. (1989) to assess the social influence on revaluation of food rewards (Noguer-Calabús et al., 2022). In the example, the observer rat prefers flavor A over B. **Habituation & Pre-Interaction Preference Testing:** During the Habituation & Pre-Interaction Testing phase, observer rats were presented with two weighed cups on three consecutive days, each containing a different type of flavored pellets (A or B). The testing lasted for 6 hours each day. After completing testing on Day 3, individual preferences of the observer were quantified by weighing the amount consumed of each respective reward. On Day 3, demonstrators were single housed and provided with a hanging feeder overnight containing the pellets that were not preferred by their assigned observers. Demonstrators were age- and sex-matched, unfamiliar wildtype rats of the same strain (for visualization purposes, colors differ). **Social Interaction:** On Day 4, each matched pair of demonstrators and observers were allowed to interact freely for 20 minutes. **Post-Interaction Preference Testing:** Immediately after the Social Interaction, observer rats were returned to their individual cages and provided with two cups, each containing one of the two pellet types. As in the Pre-Interaction Testing, the cups were removed after 6 hours to assess observers' preferences. This procedure was repeated the next day. Habit. = Habituation. Illustrations were sourced from SciDraw and adapted by the author.

Figure 2 Representative weighted color maps of Fractional Anisotropy (FA). **A** FA weighted color maps from slices displaying regions of interest (ROIs). The ROIs were bilaterally selected from the atlas implemented in DSI-Studio (based on Johnson et al., 2021). Nucleus Accumbens (NAc), Basolateral Amygdala (BLA), Cortical Amygdala (CoA), Hippocampus (HPC), Infralimbic Cortex (IL), Lateral Septum (LS), Diagonal Band of Broca (DB), Olfactory Areas (OLF), Orbital Cortex (ORB), Piriform Cortex (PIR), Prelimbic Cortex (PL), Substantia Nigra pars compacta (SNc) and the Thalamus (TH). **B** Exemplary 3D illustration of ROIs across the brain. Note that olfactory areas and piriform cortex are excluded for simplified visualization, as they cover the majority of the ventral areas. **C** Individual streamlines of a weighted color map. The color represents the direction of the structural organization in which red is medial-lateral, green is anterior–posterior, and blue is dorsal-ventral direction.

Figure 3 tgDISC1 rats show no revaluation of reward values after social contact with a demonstrator. **A** Preference index (PI). The PI indicating the strength of preference for one reward over the other, for both genotypes and before (pre) vs. after (post) Social Interaction. While wildtype rats decreased their preference for the originally preferred reward, thus showing social transmission of food preference, the PI did not change in tgDISC1 rats. **B** Consumption of originally preferred food: wildtype, but not tgDISC1 rats decreased their mean consumption of the originally preferred food type (in grams) from pre- to post-interaction. **C** Consumption of the originally non-preferred food: Wildtype, but not tgDISC1 rats, increased the consumption of the originally non-preferred food type (in grams) from pre- to post-interaction. **D** Total pellet consumption over the course of the STFP. No change in the total consumption of flavored pellets, regardless of the flavor (in grams) from pre- to post-interaction for both genotypes. Data are means ± SEM. *p < 0.05 and **p < 0.01 for contact*genotype interaction.

Figure 4 Behavior during the Social Interaction in the STFP. tgDISC1 rats do not significantly differ from wildtype rats in any of the measured social (**A**-**F**) or stereotypical behaviors (grooming and rearing; **G**-**H**) during STFP interaction. All data for social initiation by the observer in seconds. **A** Duration of snout to snout sniffing. **B** Duration of unspecific partner exploration by sniffing. **C** Duration of allogrooming. **D** Duration of social play. **E** Duration of following. **F** Duration of genital exploration. **G** Duration of self-grooming. **H** Duration of rearing. All data are means ± standard error of the mean.

Figure 5 No impaired social interest, odor discrimination, motivation or cognitive flexibility in tgDISC1 rats. **A** Social interest to approach an unknown conspecific in the 3-Chamber task. The duration of exploration in the apparatus shows a significant main effect of chamber (empty vs. conspecific), but there was no significant difference in exploration of the conspecific between genotypes. **B** Odor discrimination between a novel and a familiar odor. We found a significant effect of novelty on the number of nose touches at both odors, but no difference between genotypes. **C** The ability to distinguish large and small food rewards and the motivation to obtain them was tested in the Reward Magnitude Discrimination Task (RMDT). Percentages to choose the large food rewards in 16 free trials did not significantly differ between genotypes (cf. Table 1). Red line indicates chance-level of 50%. **D** Flexible adaptation to changed reward contingencies during a reversal phase. Percentages to choose the large food rewards in 16 free trials did not significantly differ between genotypes (cf. Table 1). Red line indicates chance-level of 50%. *p < 0.05, **** p < 0.0001.

Figure 6 Changes in Fractional Anisotropy (FA) observed in tgDISC1 rats compared to wildtypes. Abbreviations: Nucleus Accumbens (NAc), Basolateral Amygdala (BLA), Cortical Amygdala (CoA), Hippocampus (HPC), Infralimbic Cortex (IL), Lateral Septum (LS), Basal Forebrain (BF), Olfactory Areas (OLF), Orbital Cortex (ORB), Piriform Cortex (PIR), Prelimbic Cortex (PL), Substantia Nigra pars compacta (SNc), Thalamus (TH). Data are means ± standard error of the mean; ns = non-significant; *p < 0.05

Table Legends

Table 1 Summary of results of group-level comparisons in Fractional Anisotropy (FA), Axial Diffusivity (AD) and Radial Diffusivity (RD) values of brain regions implicated for Social transmission of Food Preference (STFP) performance. SEM = Standard error of the mean. Significant adjusted values are indicated in bold.

	Brain Region	wildtype Mean ± SEM	tgDISC1 Mean ± SEM	p-value	Adjusted p-value
FA					
	Nucleus Accumbens	0.30 ± 0.01	0.27 ± 0.01	0.017	**0.041**
	Diagonal Band of Broca	0.34 ± 0.01	0.31 ± 0.01	0.013	**0.041**
	Basolateral Amygdala	0.30 ± 0.01	0.26 ± 0.01	0.019	**0.041**
	Cortical Amygdala	0.36 ± 0.01	0.34 ± 0.00	0.013	**0.041**
	Hippocampus	0.30 ± 0.01	0.26 ± 0.01	0.057	0.082
	Infralimbic Cortex	0.29 ± 0.01	0.29 ± 0.01	0.572	0.62
	Lateral Septum	0.31 ± 0.01	0.28 ± 0.01	0.03	**0.049**
	Olfactory Areas	0.35 ± 0.01	0.30 ± 0.01	0.003	**0.02**
	Orbital Cortex	0.30 ± 0.01	0.27 ± 0.01	0.117	0.138
	Piriform Cortex	0.31 ± 0.01	0.30 ± 0.01	0.089	0.116
	Prelimbic Cortex	0.29 ± 0.01	0.29 ± 0.01	0.997	0.997
	Thalamus	0.32 ± 0.01	0.28 ± 0.01	0.03	**0.049**
	Substantia Nigra	0.36 ± 0.01	0.31 ± 0.01	0.001	**0.013**
AD					
	Nucleus Accumbens	0.98 ± 0.02	0.94 ± 0.01	0.176	0.656
	Diagonal Band of Broca	1.04 ± 0.02	1.02 ± 0.01	0.307	0.656
	Basolateral Amygdala	1.03 ± 0.04	0.98 ± 0.02	0.268	0.656
	Cortical Amygdala	1.15 ± 0.04	1.05 ± 0.02	0.034	0.358
	Hippocampus	1.12 ± 0.04	1.10 ± 0.03	0.724	0.798
	Infralimbic Cortex	0.96 ± 0.02	0.97 ± 0.03	0.796	0.798
	Lateral Septum	1.12 ± 0.03	1.09 ± 0.01	0.353	0.656
	Olfactory Areas	1.23 ± 0.04	1.50 ± 0.12	0.055	0.358
	Orbital Cortex	0.98 ± 0.02	0.96 ± 0.02	0.607	0.798
	Piriform Cortex	1.06 ± 0.02	1.06 ± 0.02	0.798	0.798
	Prelimbic Cortex	1.07 ± 0.03	1.05 ± 0.03	0.792	0.798
	Thalamus	1.13 ± 0.05	1.07 ± 0.02	0.235	0.656
	Substantia Nigra	1.09 ± 0.03	1.06 ± 0.02	0.49	0.796
RD					

	Nucleus Accumbens	0.63 ± 0.01	0.63 ± 0.01	0.951	0.951
	Diagonal Band of Broca	0.62 ± 0.01	0.63 ± 0.01	0.932	0.951
	Basolateral Amygdala	0.66 ± 0.02	0.68 ± 0.01	0.486	0.94
	Cortical Amygdala	0.67 ± 0.02	0.63 ± 0.01	0.099	0.358
	Hippocampus	0.71 ± 0.01	0.74 ± 0.01	0.11	0.358
	Infralimbic Cortex	0.64 ± 0.01	0.63 ± 0.01	0.738	0.951
	Lateral Septum	0.71 ± 0.02	0.73 ± 0.01	0.506	0.94
	Olfactory Areas	0.70 ± 0.03	1.04 ± 0.13	0.025	0.325
	Orbital Cortex	0.63 ± 0.01	0.64 ± 0.01	0.468	0.94
	Piriform Cortex	0.67 ± 0.01	0.67 ± 0.01	0.7	0.951
	Prelimbic Cortex	0.68 ± 0.02	0.68 ± 0.02	0.908	0.951
	Thalamus	0.70 ± 0.02	0.71 ± 0.01	0.705	0.951
	Substantia Nigra	0.65 ± 0.01	0.68 ± 0.01	0.066	0.358

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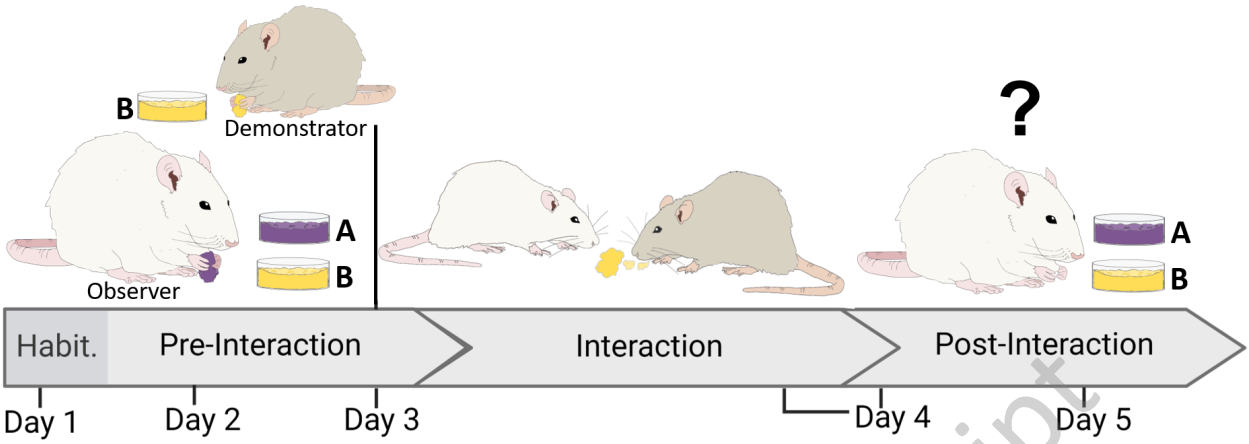

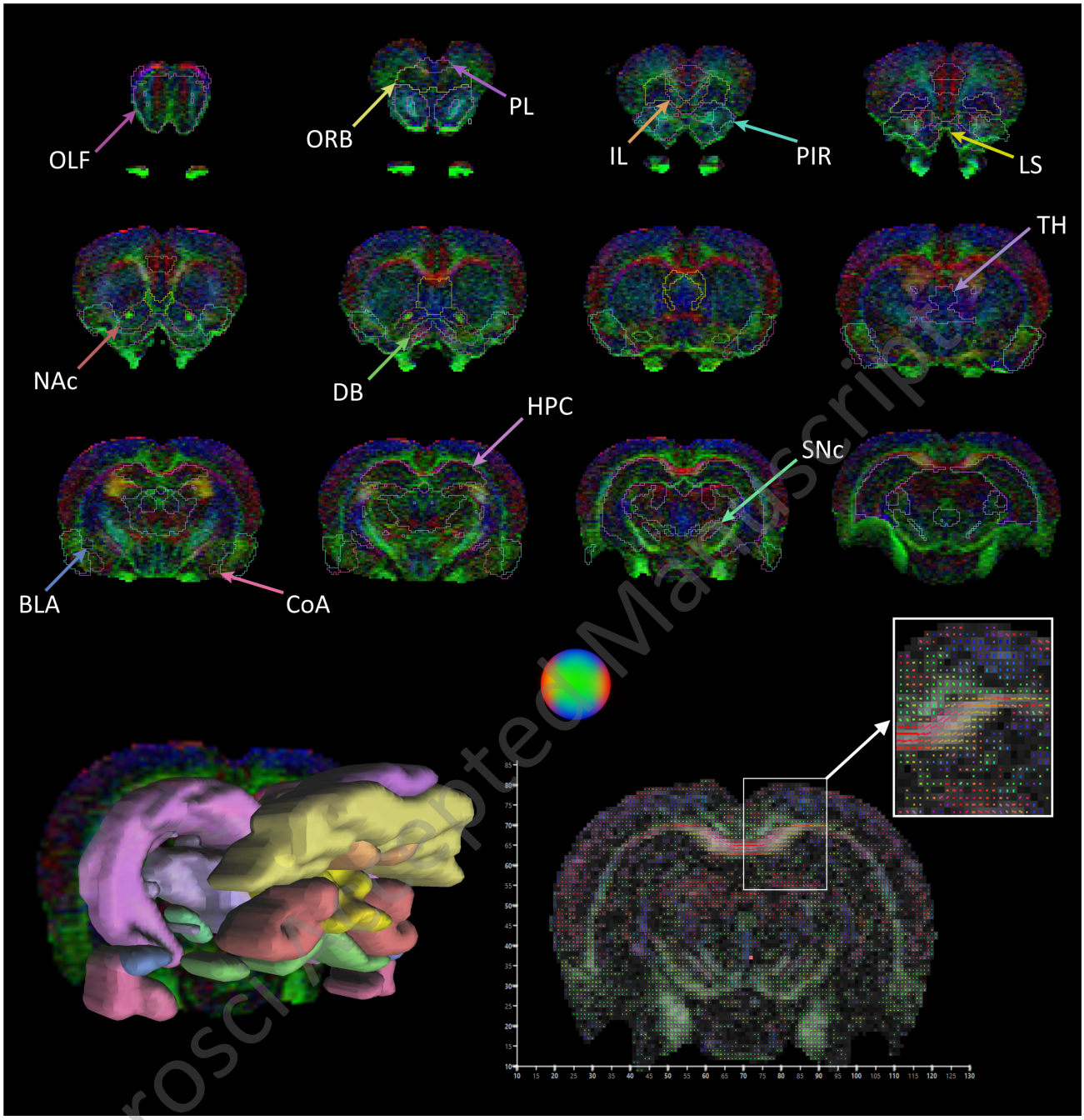

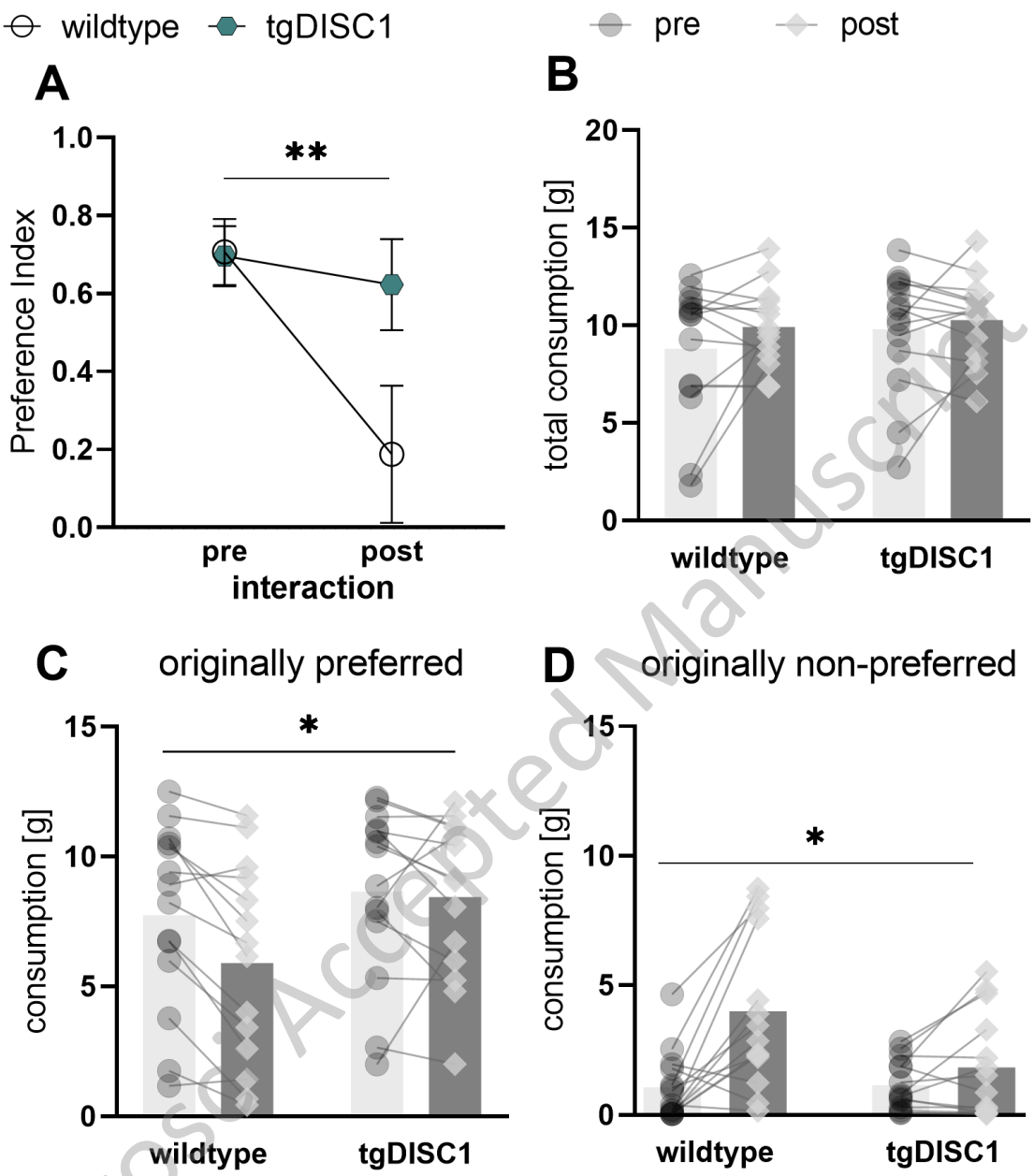

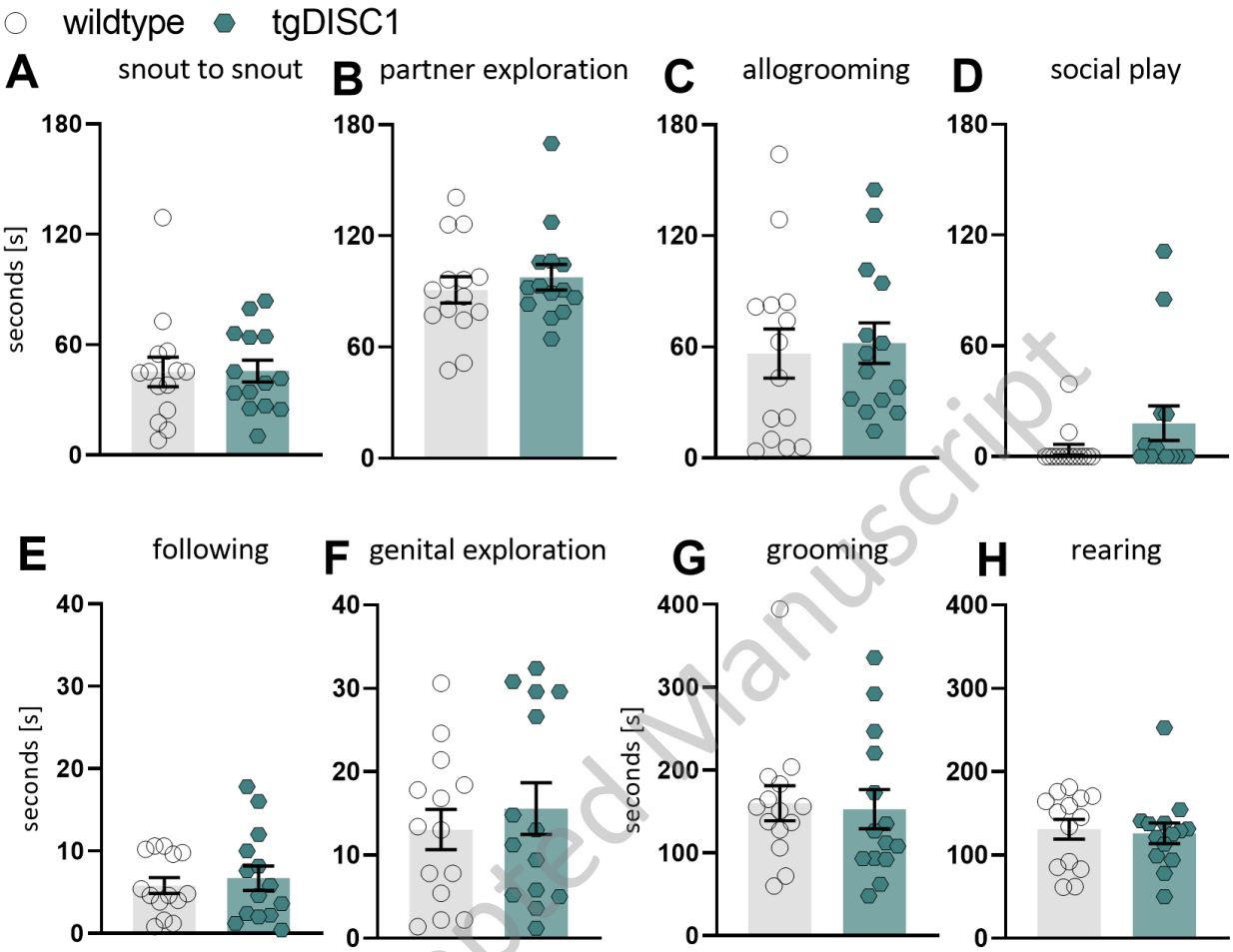

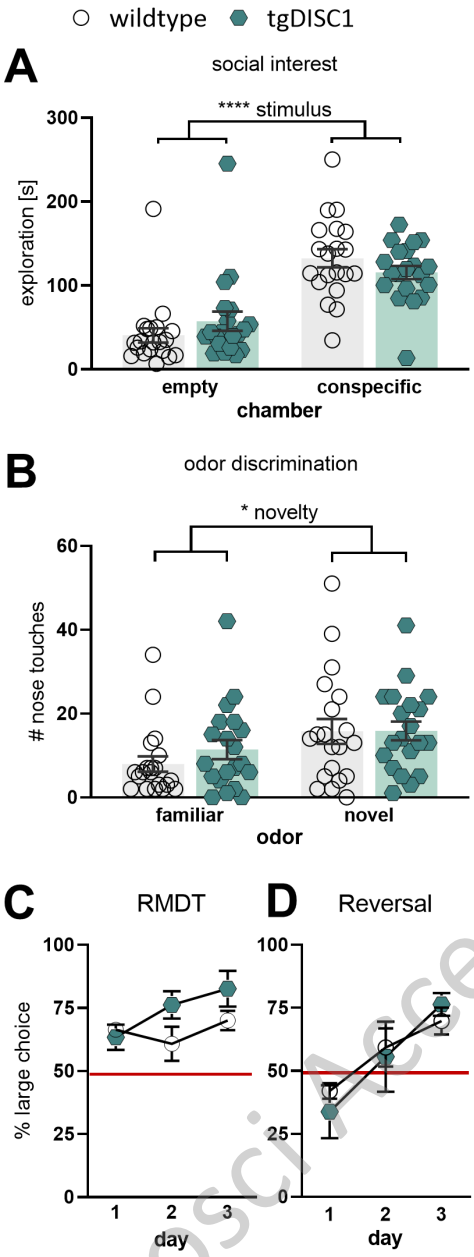

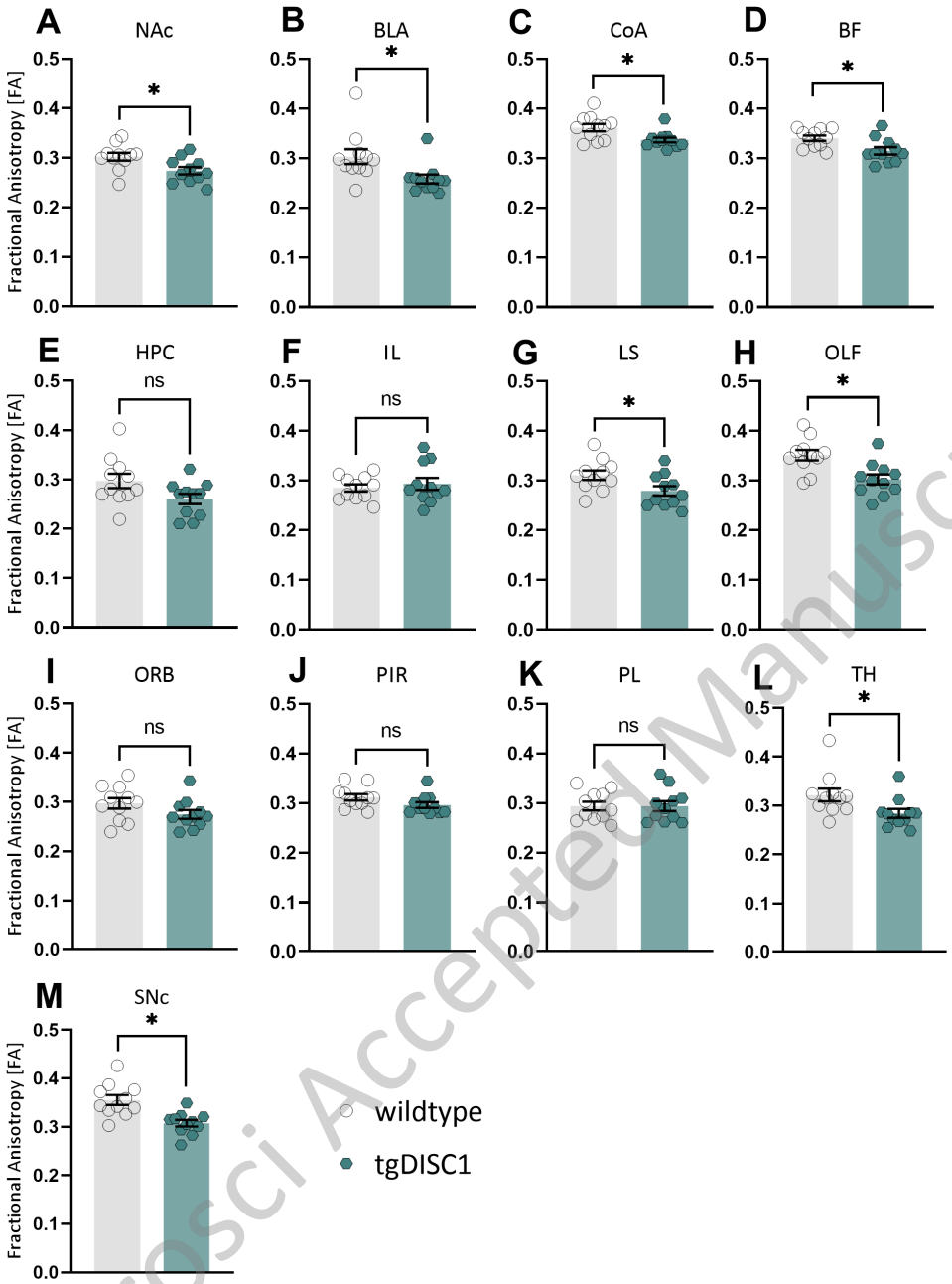

Study 3 - Original Paper

Oxytocin effects on socially transmitted food preferences are moderated by familiarity between rats

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Tobias Kalenscher: Conceptualization, Methodology, Resources, Writing - Review & Editing, Supervision, Funding acquisition.

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ORIGINAL INVESTIGATION

Oxytocin effects on socially transmitted food preferences are moderated by familiarity between rats

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Abstract

Rationale In the socially transmitted food preference (STFP) paradigm, rats change their preference for food rewards after socially interacting with a conspecific who has been fed with the originally non-preferred food. Here, we asked if oxytocin (OXT), a neuropeptide known for its role in social affiliation and social behavior, plays a role in STFP. Since OXT's influences on social behavior can be familiarity-dependent, we further asked if OXT effects on STFP are moderated by the familiarity between rats.

Objectives Does OXT modulate rats' socially transmitted food choices in a familiarity-dependent way.

Methods We systemically injected either vehicle, low-dose (0.25 mg/kg) of OXT, or large-dose (1.0 mg/kg) of OXT before social interaction with either a familiar cagemate (in-group) or an unfamiliar conspecific from a different cage (out-group).

Results We found an intergroup bias in STFP: vehicle-treated rats showed larger socially transmitted changes in food preference in the out-group than the in-group condition. OXT modulated STFP in a familiarity-dependent way: OXT prevented the increase in the consumption of the non-preferred food in the out-group, and decreased the consumption of the preferred food in the in-group. These effects were dose-dependent and observed under acute OXT action, but also on the subsequent day when acute OXT effects dissipated, suggesting long-lasting social learning effects of OXT. Additional analyses suggest that the familiarity and dose-dependent effects of OXT on STFP cannot be attributed to OXT's anorexic actions or differences in the duration of the social interactions.

Conclusions OXT modulates STFP in a familiarity-dependent way.

Keywords Familiarity · Food preference · Group bias · Oxytocin · Reward revaluation · Social behavior.

Introduction

What we eat is a daily decision that is influenced by our knowledge of the available resources and our dietary preferences. To make these decisions, we gather relevant information either from our own experience or through social learning. Relying on social information to choose food has proven to be an adaptive foraging strategy in many situations and in several species (Kendal et al. 2005). To operationalize social food learning in animals in a laboratory setup, Galef and Wigmore (1983) established the socially transmitted food preference (STFP) paradigm where one rat (the observer) reveals a preference for a flavored food after interacting with a demonstrator who recently ate it. Years of research using the STFP paradigm have provided solid evidence for socially transmitted food preferences, which occur independent of the observer's energy state (food-deprived or fed ad-libitum) or the demonstrator's characteristics, such as health (poisoned, anesthetized or controls) or age (Galef et al. 1983, 1984; Galef and Wigmore 1983; Galef and Whiskin 2004, 2008a). Aligning food preferences to those of conspecifics is a phenomenon found in many mammals including humans (Nook and Zaki 2015).

Here, we asked what the psychopharmacological mechanism of socially transmitted food preference is. One strong neuromodulator candidate is oxytocin (OXT). OXT is a neuropeptide primarily synthesized in the paraventricular hypothalamic nucleus and the supraoptic nucleus of the hypothalamus that modulates neural activity in many parts

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of the brain (Ferris et al. 2015; Salvi et al. 2018; Liu et al. 2021). It is prominently involved in social behavior, such as reproduction, social recognition and memory, pair bonding, and prosociality, as well as the regulation of fear, anxiety and food consumption (Jurek and Neumann 2018; Sakamoto et al. 2019; but see Berendzen et al. 2023). OXT can modulate social cognition at different levels. Enhanced OXT release in olfactory circuits increases social exploration and social recognition without interfering with other olfactory-dependent behaviors (Oettl et al. 2016). However, the modulation of social recognition by OXT subcutaneous injections follows an inverted U-shaped dose-response curve. Intermediate doses facilitate social recognition to a greater extent than low or high doses (Popik et al. 1992). In non-human primates, OXT boosts own- and other-regarding preferences (Chang et al. 2012), and in humans, OXT has been shown to promote social cognition and prosocial behavior, too (Jurek and Neumann 2018; Marsh et al. 2021). OXT in mice is also implicated in social learning (Dölen et al. 2013; Choe et al. 2015). For instance, systemic administration of OXT and vasopressin prolonged the memory recall of socially transmitted changes in drink preference (Popik and Van Ree 1993), suggesting OXT is indeed important for at least some cognitive aspects of STFP. However, direct evidence for the effects of OXT on STFP is, so far, elusive (Lindeyer et al. 2013; but see Popik and Van Ree 1993).

In humans, OXT effects on social behavior have been shown to be subject to intergroup-biases: OXT promotes empathy, cooperation, trust and conformity with members of the same social group, but it fosters defensive behaviors and social distancing against members of a competing social group (De Dreu et al. 2010; Scheele et al. 2012; De Dreu and Kret 2016; Strang et al. 2017). Interestingly, in rodents, group affiliation seems to matter for social behavior, too. For instance, rats exhibit intergroup biases in prosociality (Ben-Ami Bartal et al. 2021), and there is evidence, although weak and inconclusive, that STFP also depends on the familiarity, i.e., group affiliation in a wider sense, between the observer and the demonstrator rat (Galef et al. 1984; Galef and Whiskin 2008a; Agee et al. 2019). It is therefore plausible to assume that any putative OXT effect on STFP might depend on the familiarity between demonstrator and observer.

In the current study, we therefore hypothesized that STFP in rats is modulated by OXT action, and that the predicted OXT effects on STFP are dependent on the familiarity between observer and demonstrator rats.

We trained rats in an adapted within-subject variant of the STFP paradigm (Galef and Whiskin 2008b; Jolles et al. 2011; Noguer-Calabús et al. 2022) that allowed us to quantify the individual magnitude in the change of socially transmitted food preference after relative to before social interaction. Briefly, observer rats reveal their original food preferences by choosing between two appetitive, differently flavored food rewards. Subsequently, they interact with a demonstrator rat who has been fed the food that was revealed non-preferred by the observer. After social interaction, we measure the observer rats' food preferences again. Observers typically increase the consumption of the originally non-preferred pellets and/or decrease the consumption of the originally preferred pellets (Galef and Whiskin 2008b; Noguer-Calabús et al. 2022).

We manipulated familiarity, as a proxy of group affiliation, between observers and demonstrators (Ben-Ami Bartal et al. 2014; Agee et al. 2019), as follows: during the social interaction phase of the STFP task, observers were either paired with a familiar cagemate demonstrator (in-group) or with an unfamiliar demonstrator from a different cage (out-group). To evaluate OXT effects on STFP, observers in the in-group and the out-group conditions received one of three treatments: vehicle injections, low-dose OXT, or large-dose OXT, systemically injected prior to social interaction. We measured the observers' revealed food preferences before and immediately after social interaction, hence during acute OXT action, as well as one day later, when the exogenous OXT effects on the brain can be assumed to have faded. The second day of post-interaction preference testing allowed us to test whether OXT facilitates, or hampers, long-term social learning, and to rule out alternative explanations of putative changes in STFP.

Materials and methods

Subjects

We trained and tested 239 observer and 140 demonstrator Long-Evans male rats (Charles River, Germany) for this study, about 9–10 weeks old at arrival and weighing 410 ± 50 g on the injection day. 28 observers met the exclusion criteria (see below) and had to be removed from the analysis, leaving a final sample size of $n = 211$ observers. The temperature in the housing room was maintained at 22ºC ± 2ºC, with humidity set at 55% ± 2%. Subjects were kept under an inverted 12:12 light-dark cycle. Rats were supplied with laboratory rodent food (Sniff, Germany) and water ad libitum except for the STFP testing period when rats were food-restricted to 85% of their free-feeding body weight and fed daily after finishing the experimental procedure. All rats were handled for 5 min/day for 3 days before starting the experiment. All animal procedures were conducted in accordance with the German Welfare Act and were approved by the local authority LANUV (*Landesamt*

für Natur-, *Umwelt- und Verbraucherschutz* North Rhine-Westphalia, Germany).

Socially transmitted food preference task

Housing and habituation

Three days before the start of the STFP task, all rats underwent a 10-minute habituation session in an open field (50 × 50 × 45 cm, PVC, illumination to 5–15 lx). To this end, cagemates were placed together in the open fields. Upon habituation to the open field, all subjects were henceforth housed individually and were food-restricted. To habituate rats to the feeder setup, for three days, all rats were provided with hanging feeders in their home cages containing 10 grape-flavored and 10 banana-flavored pellets (TestDiet, USA). Then, rats were tested in the STFP task. The STFP protocol involved three stages: individual preference testing (days 1, 2, 3), social interaction (day 4), and post-interaction preference testing (days 4 and 5).

Individual preference testing

On testing day one, observer rats were provided with two weighed cups, each of them containing a different pellet type (grape and banana). These cups were positioned in hanging feeders (pictured in Fig. 1), and observers had unrestricted access for 6 h. Subsequently, the cups were removed and weighed. This process was replicated over the next two days. The observers' consumption was quantified individually and daily as the difference in cup weight before and after the 6-hour testing period. Upon concluding the pre-interaction testing, original individual preferences were determined by how much of each pellet type was consumed on day 3 (see exclusion criteria below).

Social interaction

On the fourth day of the STFP task, both observers and demonstrators were relocated to a room adjacent to the social interaction room. Demonstrators were fed with those pellets that were not revealed preferred on day 3 by their assigned observers. To enhance the corresponding odor, crushed pellets were spread to the demonstrator's back, snout, and anal area. Then, demonstrators and observers were allowed to freely interact in the open field for 15 min. The interaction between the observer and demonstrator was recorded and an evaluator analyzed the time spent by the observer exploring the demonstrator using Solomon Coder (Solomon Coder beta 19.08.02 © András Péter).

Post-interaction preference testing

Following the interaction, observer rats were promptly returned to their individual cages and provided with two cups, each containing one of the two banana- and grape-flavored food types. Similar to the pre-interaction testing, the cups were taken out and weighed after a 6-hour interval. The same preference test was repeated the next day. Subsequently, all animals were reintegrated into prior group housing.

Exclusion criteria

If a rat revealed preferred a particular pellet type on day 3 that was different from the pellet type revealed preferred on days 1 *and* 2, we assumed that this rat's preferences were inconsistent since it was not evidently clear what the truly preferred reward was on day 3. Rats with inconsistent preferences were excluded from further analysis. For example, if a rat preferred grape pellets on days 1 *and* 2, but banana

Fig. 1 Photo example of the individual cage with the metal hanging feeder and two cups containing grape and banana pellets

pellets on day 3, it would be excluded from analysis since we could not tell with certainty if this rat truly preferred banana, or grape. The reason for this exclusion criterion is to make sure that demonstrators were fed with the truly non-preferred food, and to avoid accidentally feeding the demonstrator with actually preferred food.

Familiarity group assignment

We operationalized group affiliation as familiarity between observers and demonstrators (Ben-Ami Bartal et al. 2014). Therefore, there were two familiarity groups: the in-group and the out-group. In the in-group condition, pairs of observers and demonstrators ($n = 100$) were housed together in one cage upon arrival at the animal housing. In the out-group condition, pairs of observers were housed together, but in separate cages from the demonstrators (three demonstrators per cage) to prevent contact before the STFP interaction. The out-group consisted of 111 observers and 40 demonstrators. In general, rats were housed according to this group assignment protocol for 2–3 weeks upon arrival in the animal facility; at the start of the experiment, they were housed individually (see below).

Oxytocin treatment

Within each familiarity group, observers were randomly assigned to one of three treatment groups: the control group (vehicle = saline), the group treated with low-dose OXT (0.25 mg OXT/ml), and the large-dose OXT group (1.0 mg OXT/ml), with an injection volume of 1 ml/kg. All observers received a single intraperitoneal injection immediately before the social interaction phase during the STFP.

Data analysis

We used a mixed analysis of variance (ANOVA; SPSS 27.0.1, IBM, USA; R 4.0.2; R Core Team, 2020, special usage of the ggbreak package for plotting (Xu et al. 2021) with the dependent variable *pellet consumption* (grams eaten), and the within-subject factors *pellet preference* (originally preferred vs. non-preferred pellets), *day* (pre-interaction day 3 vs. post-interaction day 4 vs. post-interaction day 5), and the between-subject factors *familiarity* (in-group vs. out-group) and *treatment* (vehicle vs. low-dose OXT vs. large-dose OXT). Post hoc analyses were performed with two-sided t-tests. Benjamini–Hochberg correction was applied to correct for multiple comparisons.

Occasionally, rats exhibited very strong STFP, resulting in a full preference reversal post- vs. pre-interaction. Preference reversals were defined as higher consumption of the originally non-preferred food than the originally preferred food after the social interaction on day 4. We compared the frequency of full preference reversals between conditions with a Fisher's exact test.

Finally, we measured the time the observer spent socially exploring the demonstrator during the social interaction phase of the STFP. We examined observer behavior exclusively because existing literature indicates minimal effects of the demonstrator's behavior on the observers' STFP performance (Galef and Wigmore 1983; Galef and Whiskin 2008a). To detect differences in social interaction times between groups and conditions, we employed a mixed ANOVA and its corresponding post-hoc two-sided t-tests and corrections for multiple comparisons.

Results

Familiarity modulates STFP in vehicle rats

To evaluate how familiarity modulates STFP in general, i.e., in the absence of OXT effects, we compared the amount of pellets eaten by vehicle observers between days 3 and 4, i.e., before vs. immediately after social interaction, as a function of familiarity (in- vs. out-group) and pellet preference (originally preferred vs. non-preferred pellets; Fig. 2). The mixed ANOVA showed a simple main effect of pellet preference on amount consumed ($F_{[1, 67]} = 136.816$, $p = .000$) and a simple main effect of day ($F_{[1, 67]} = 23.969$, $p = .000$), as well as an interaction effect between pellet preference and day ($F_{[1, 67]} = 21.837$, $p = .000$), suggesting that rats showed STFP. Importantly, we also found a significant interaction effect between pellet preference and familiarity ($F_{[1, 67]} = 8.405$, $p = .005$). The post-hoc tests (all post-hoc tests were corrected for multiple comparisons) indicated that both familiarity groups increased their consumption of the originally non-preferred pellets on day 4 compared to day 3 (in-group: $t_{[30]} = -3.16$, $p = .005$; out-group: $t_{[37]} = -5.53$, $p = .000$), suggesting that STFP was found in both familiarity groups. However, a between-group comparison showed that consumption of the originally non-preferred pellets was higher in the out-group than the in-group on day 4 (in- vs. out-groups: $t_{[66.2]} = -2.19$, $p = .032$), implying stronger STFP in the out-group than the in-group. Consistent with this conclusion, only the out-group decreased the consumption of their originally preferred pellets on day 4 compared to day 3 (out-group: $t_{[37]} = 3.14$, $p = .005$; in-group: $t_{[37]} = 0.48$, $p = .635$) and compared to the in-group (day 4 in- vs. out-groups: $t_{[65.7]} = 3$, $p = .004$). Accordingly, the change in consumption of the originally preferred pellets, but not non-preferred pellets, from day 3 to 4 differed between familiarity groups (difference in originally preferred pellets: $t_{[66.9]} = -2.05$, $p = .044$; originally

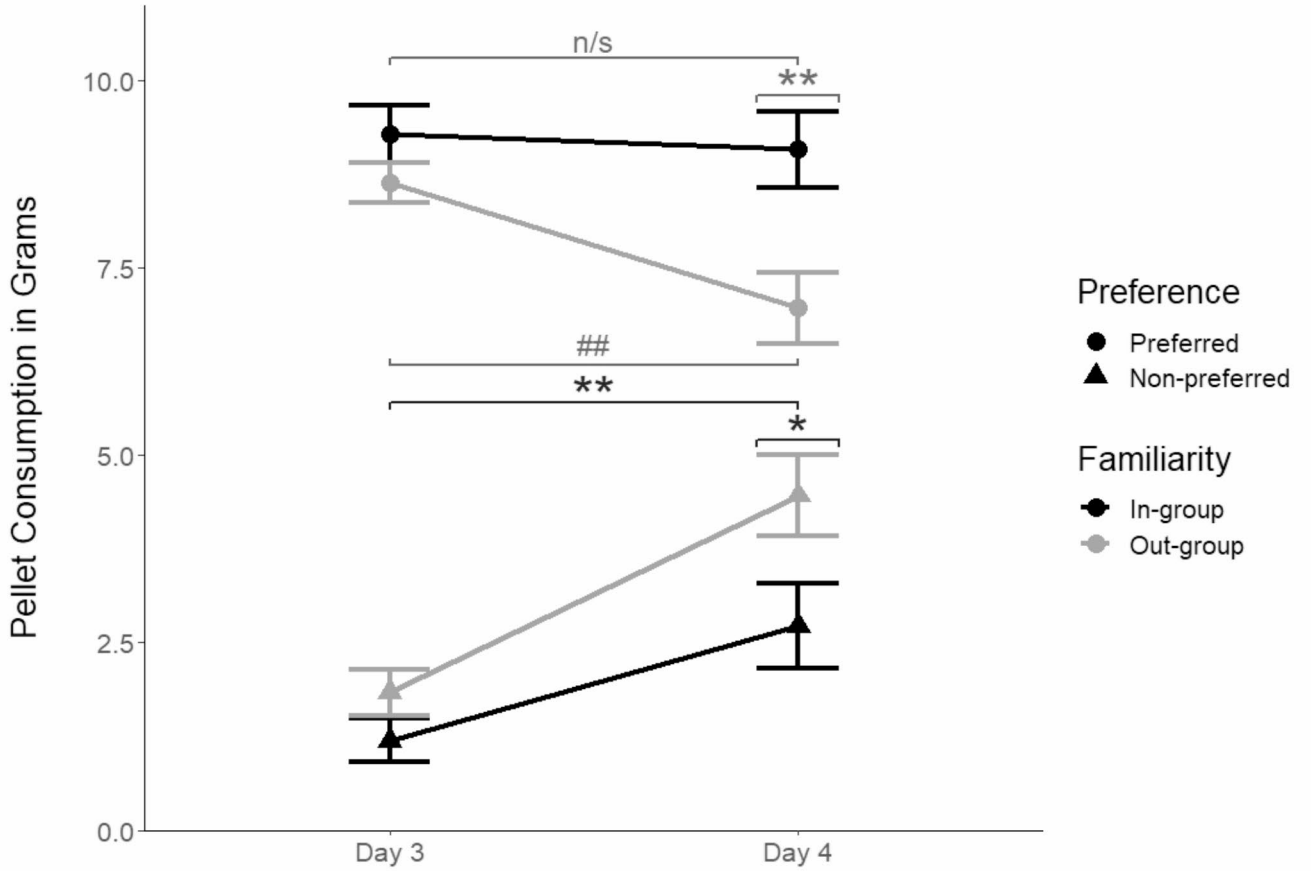

Fig. 2 Vehicle-treated observers' socially transmitted food preferences are modulated by familiarity. Mean (±standard error of the mean; SEM) of the pellets (originally preferred, circle; originally non-preferred, triangle) consumed on days 3 (pre-social interaction) and day 4 (post-social interaction) by observers who interacted with a familiar demonstrator (in-group ($n=31$), black) or an unfamiliar one (out-group ($n=40$), light gray). The change in consumption of the originally non-preferred pellets pre- vs. post-interaction was stronger in the out-group than the in-group, and a change in consumption of the originally preferred pellets was only found in the out-group. * $p<.05$; ** $p<.01$; ## out-group $p<.01$, n/s in-group $p>.05$

non-preferred pellets: $t_{[65.7]}=1.56$, $p=.124$). Hence, both familiarity groups exhibited socially transmitted food preferences, but the effect was significantly more pronounced in the out-group than the in-group (Fig. 2).

Full preference reversal

Rats occasionally exhibited very strong STFP, resulting in a full preference reversal on day 4 vs. day 3. We computed the proportion of vehicle-treated observers who fully reversed their pellet preferences, and compared the proportion of pellet preference reversals between familiarity groups (Fig. 3). In the in-group, only 10% of rats (3/31) fully reversed their pellet preferences, in contrast to the out-group, where 39% of rats (15/38) did so. Hence, consistent with the conclusion of the previous paragraph, these data suggest stronger social transmission of food preferences in the out-group than the in-group condition (Fisher's exact test; $p=.006$, two-sided).

Further analyses are available in the supplemental materials, Fig. 1.

Oxytocin effects on social transmission of food preference are modulated by familiarity

To find out if the OXT treatment had an effect on STFP, possibly in a familiarity-dependent way, we ran a four-way mixed ANOVA with pellet preference (originally preferred vs. non-preferred), familiarity (in- vs. out-group), treatment (vehicle vs. low-dose OXT vs. large-dose OXT), and day (days 3 vs. 4 vs. 5) as independent variables on pellet consumption. We found a significant simple main effect of pellet preference ($F_{[1,\ 202]}=440.333$, $p=.000$), a significant simple main effect of treatment ($F_{[2,\ 202]}=9.079$, $p=.000$), and a significant simple main effect of day ($F_{[2,\ 404]}=16.129$, $p=.000$), and a significant four-way interaction between pellet preference, familiarity, treatment and day ($F_{[3.51,\ 354.66]}=3.029$, $p=.023$).

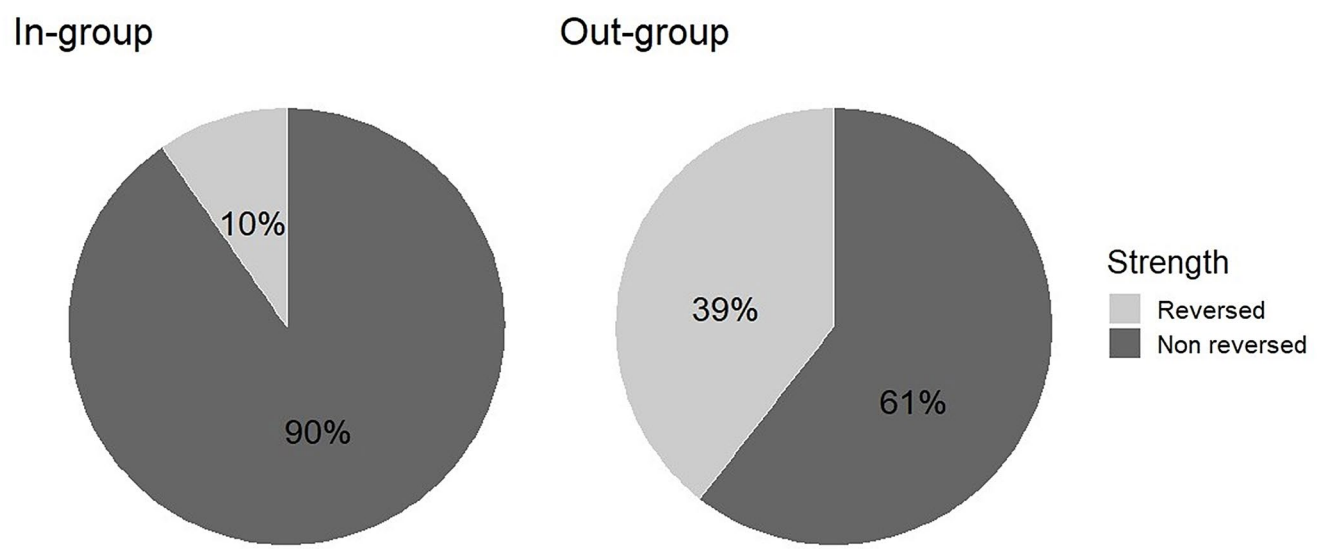

Fig. 3 Frequency of full preference reversals, in percent, after social interaction (day 4 vs. day 3). The frequency of full preference reversals was significantly higher in the out-group than in the in-group

To unpack this complex interaction effect, we ran a suite of post-hoc tests (again, all post-hoc tests were corrected for multiple comparisons). To understand the acute effects of OXT on STFP, we, first, zoomed in on what happened on day 3 vs. day 4 (Fig. 4; individual data plots in Fig. 2 in the supplemental materials). In the in-group (panel A of Fig. 4), we found a significant decrease in consumption of the originally preferred pellets on day 3 vs. day 4 in both OXT groups (low-dose OXT: $t_{[32]}=5.69$, $p=.000$; large-dose OXT: $t_{[35]}=6.69$, $p=.000$), but not in the vehicle group ($t_{[30]}=0.48$, $p=.714$). There was a significant increase in consumption of the originally non-preferred pellets from day 3 to day 4 in all treatment groups (vehicle: $t_{[30]}$ = -3.16, $p=.01$; low-dose OXT: $t_{[31]}$ = -2.93, $p=.013$; large-dose OXT: $t_{[35]}$ = -3.4, $p=.007$), and we found no significant difference in their consumption over days 3 and 4 between treatment groups (vehicle vs. low-dose OXT: $t_{[59.4]}$ = -0.476, $p=.636$; vehicle vs. large-dose OXT: $t_{[40.4]}$ = -1.61, $p=.232$; low-dose OXT vs. large-dose OXT: $t_{[45]}$ = -1.16, $p=.38$). This analysis suggests that, in the in-group, OXT administration led to a stronger decrease in consumption of the originally preferred pellets relative to vehicle administration, but had no marked effect on the consumption of the originally non-preferred pellets.

The picture was different in the out-group (panel B of Fig. 4). Here, we found a significant decrease in consumption of the originally preferred pellets on day 3 vs. day 4 in all treatment groups, including the vehicle group (vehicle: $t_{[37]}=3.14$, $p=.006$; low-dose OXT: $t_{[33]}=3.82$, $p=.002$; large-dose OXT: $t_{[36]}=6.14$, $p=.000$). There was no significant difference in the change in consumption of the originally preferred pellets between any of the treatment groups (vehicle vs. low-dose OXT: $t_{[69.3]}$ = -0.087, $p=.931$; vehicle vs. large-dose OXT: $t_{[66.2]}$ = -0.97, $p=.504$; low-dose OXT vs. large-dose OXT: $t_{[65.5]}$ = -0.969, $p=.504$). By contrast, we found a significant and steep increase in consumption of the originally non-preferred pellets from day 3 to day 4 in the vehicle group ($t_{[37]}$ = -5.53, $p=.000$), but no significant increase in either OXT group (low-dose OXT: $t_{[33]}$ = -2.12, $p=.061$; large-dose OXT: $t_{[36]}$ = -1.7, $p=.136$). Accordingly, vehicle observers in the out-group condition consumed significantly more of the originally non-preferred pellets than the OXT-treated observers (vehicle vs. low-dose OXT: $t_{[63.3]}=3.15$, $p=.024$; vehicle vs. large-dose OXT: $t_{[48.4]}=4.77$, $p=.000$; low-dose OXT vs. large-dose OXT: $t_{[54.3]}=1.74$, $p=.226$). This analysis suggests that in the out-group, OXT had different effects on STFP than in the in-group. In the out-group condition, relative to vehicle administration, OXT dampened the increase in consumption of the originally non-preferred pellets, but it had no marked effect on the consumption of the originally preferred pellets.

Oxytocin has long-term effects on social transmission of food preferences

So far, we presented the results of day 3 (before social interaction) vs. day 4 (immediately after social interaction and immediately after OXT injection, i.e., with acute OXT effects on the rats' system). To understand if OXT had long-term effects on STFP (Fig. 5; individual data plots in Fig. 3 in the supplemental materials), beyond its acute action, we extended our post-hoc analysis to day 5, i.e., one day after OXT or vehicle injection. In the in-group (panel A of Fig. 5), there was no significant difference in originally preferred pellets consumption between day 4 and day 5 in any of the treatment groups (vehicle: $t_{[30]}$ = -0.222, $p=.826$;

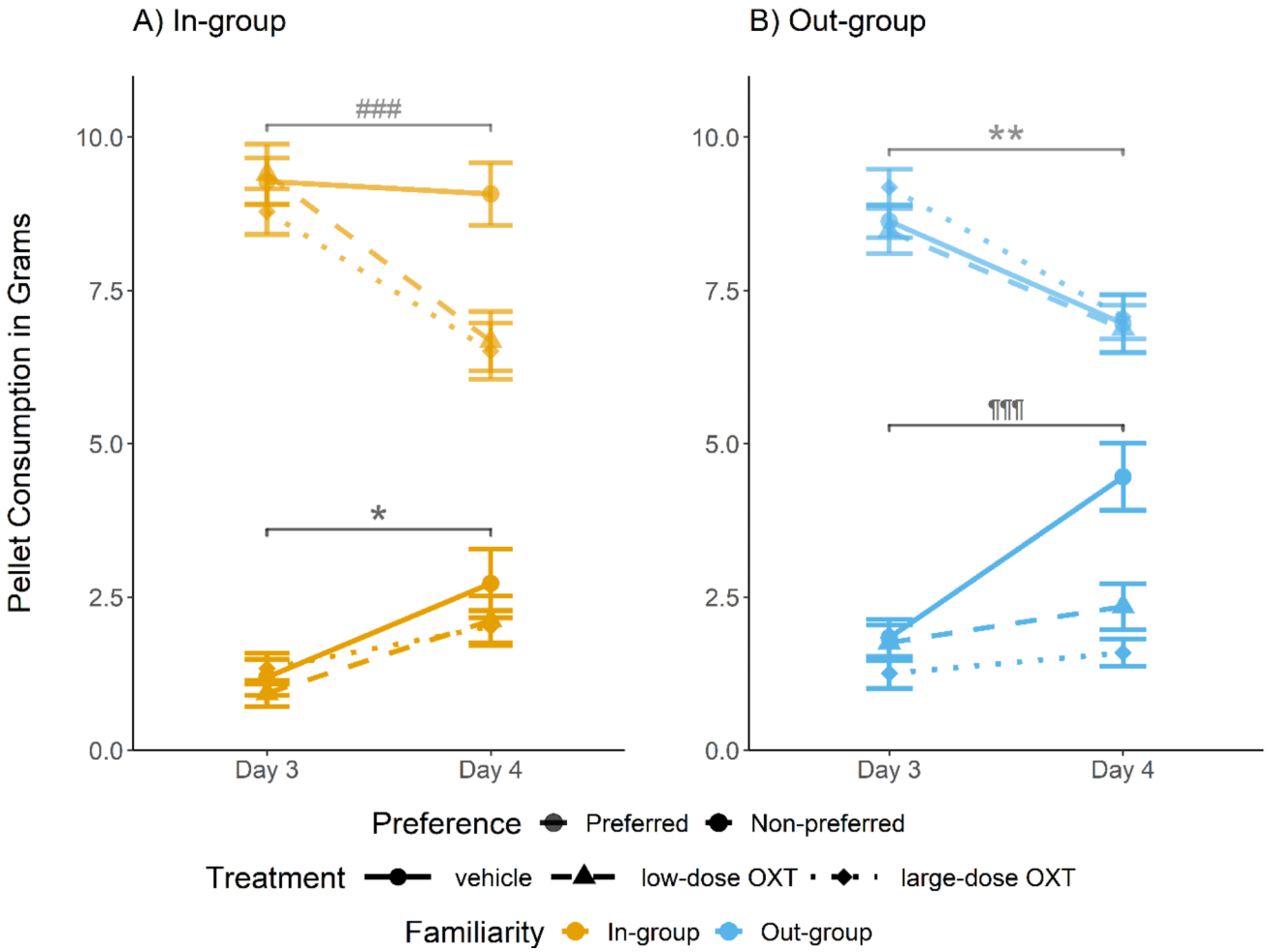

Fig. 4 Acute oxytocin (OXT) and intergroup effects on socially transmitted food preference (STFP). STFP in the in-group (panel A), and the out-group (panel B). In both panels, the pellet consumption (mean ± SEM) of the vehicle group is represented by the solid line and circle symbols, the low-dose OXT group by the dashed line and triangles, and the large-dose OXT group by the dotted line and squared symbols. The originally preferred pellets (upper lines) are indicated in a slightly transparent hue, and the originally non-preferred pellets (lower lines) are in an opaque hue. In the in-group (panel A), rats in all treatment conditions increased their consumption of the originally non-preferred pellets after social interaction on day 4, thus exhibiting STFP. Unlike rats in the vehicle group, rats that received OXT injections prior to social interaction decreased the consumption of the originally preferred pellets. In the out-group (panel B), OXT administration prevented the increased consumption of the originally non-preferred pellets observed in the vehicle group, thus blocking STFP. However, there were no differences between treatment conditions in the consumption of the originally preferred pellets, which decreased between days 3 and 4. * All treatments $p < .05$; ** all treatments $p < .01$; ### OXT-treated groups $p < .001$; ¶¶¶ vehicle group $p < .001$

low-dose OXT: $t_{[32]}$ = -1.9, $p = .091$; large-dose OXT: $t_{[35]}$ = -1.22, $p = .292$). By contrast, both OXT groups, but not the vehicle group, showed a continued increase in consumption of the originally non-preferred pellets from day 4 to day 5 (vehicle: $t_{[30]} = 1.19$, $p = .292$; low-dose OXT: $t_{[32]}$ = -2.38, $p = .043$; large-dose OXT: $t_{[35]}$ = -2.26, $p = .045$), even though the amount of originally non-preferred pellets consumed on day 5 did not differ between OXT and vehicle groups (vehicle vs. low-dose OXT: $t_{[57]}$ = -1.28, $p = .635$; vehicle vs. large-dose OXT: $t_{[65]}$ = -1.02, $p = .635$; low-dose OXT vs. large-dose OXT: $t_{[61.1]} = 0.404$, $p = .843$). Hence, in the in-group, the pattern of effects on STFP observed under acute OXT effects (day 4) persisted, or even increased, on day 5, when the acute OXT effects on the organism can be assumed to have waned.

In the out-group (panel B of Fig. 5), we found a significant increase in consumption of the originally preferred pellets in the large-dose OXT group from day 4 to day 5, but not in the low-dose OXT or vehicle groups (vehicle: $t_{[37]} = 0.944$, $p = .395$; low-dose OXT: $t_{[33]} = 0.366$, $p = .717$; large-dose OXT: $t_{[36]}$ = -3.35, $p = .004$). Although we had found significant OXT effects on the consumption of the originally non-preferred pellets on day 4 (see above), this difference disappeared on day 5 for the low-dose OXT (vehicle vs. low-dose OXT: $t_{[70.7]} = 0.565$, $p = .861$) and only remained significant for the large-dose OXT (vehicle vs. large-dose

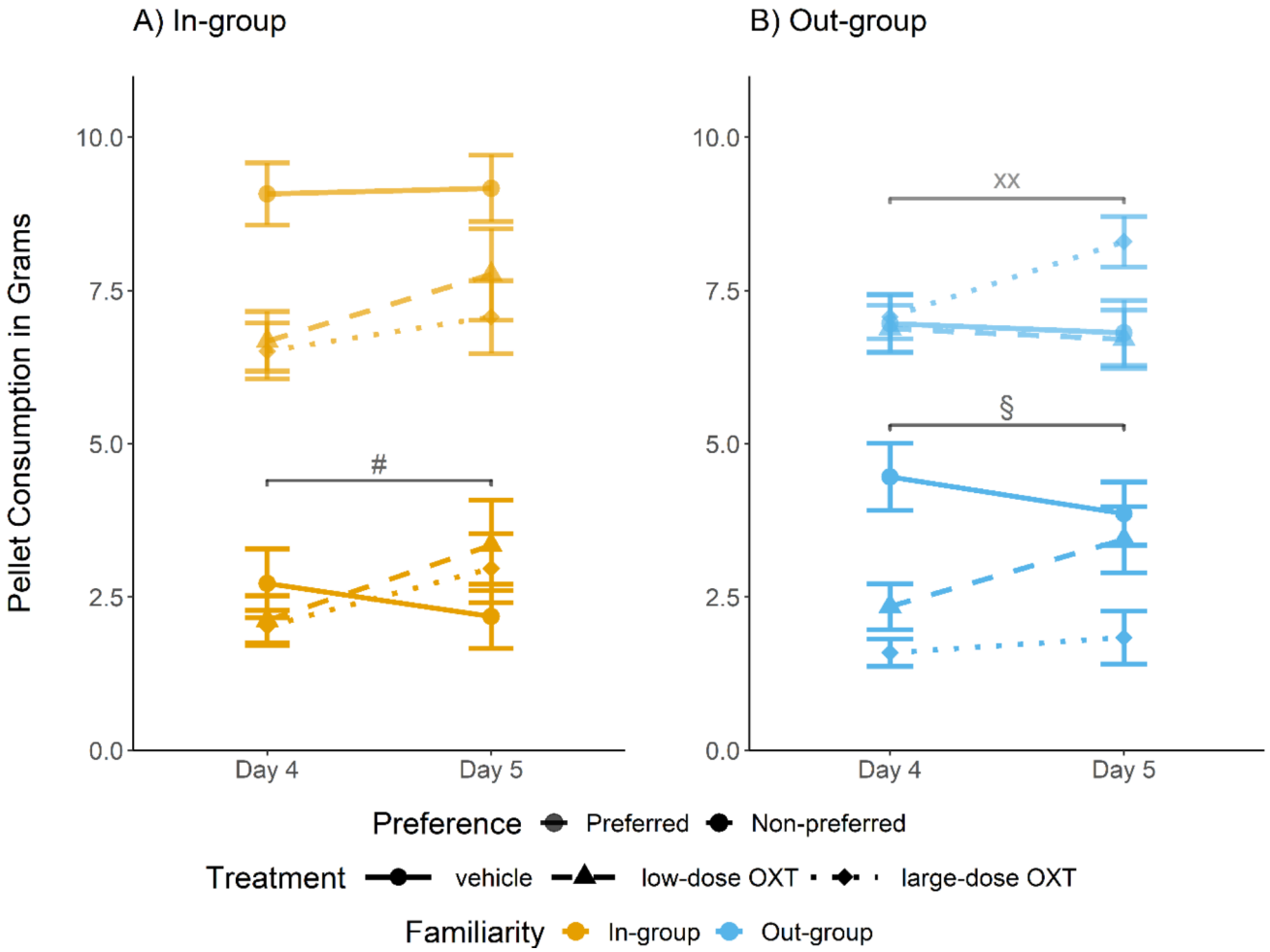

Fig. 5 Long-term oxytocin (OXT) and familiarity effects on socially transmitted food preference (STFP). Line and panel representations are the same as Fig. 4. In the in-group (panel A), rats treated with OXT on day 4 (immediately after social interaction and OXT injection) increased the consumption of the originally non-preferred pellets on day 5 (one day after social interaction and OXT injection) following the previous tendency (from day 3 to day 4). By contrast, the consumption of the vehicle group was relatively constant across days. The consumption of the originally preferred pellets was constant for all treatment conditions. In the out-group (panel B), only the low-dose OXT group increased the consumption of the originally non-preferred pellets from day 4 to day 5. By contrast, the OXT effects on the large-dose OXT group were long-lasting, suggesting that the OXT-related blocking of STFP was stable over time. Regarding the originally preferred pellets, only the large-dose OXT group increased their consumption once acute OXT effects dissipated on day 5; the other treatment conditions remained unchanged. # OXT-treated groups $p < .05$; § low-dose OXT group $p < .05$; XX large-dose OXT group $p < .05$

OXT: $t_{[73.6]} = 3.01$, $p = .024$; low-dose OXT vs. large-dose OXT: $t_{[64.3]} = 2.31$, $p = .086$). In line with this observation, the low-dose OXT group showed an increase in consumption of the originally non-preferred pellets from day 4 to day 5 ($t_{[33]} = -2.45$, $p = .033$), but, the large-dose OXT group continued to show no significant change in consumption of the originally non-preferred pellets from day 4 to 5 ($t_{[36]} = -0.608$, $p = .579$), suggesting that they never acquired STFP. In sum, also in the out-group, we found a complex pattern of results suggestive of the fact that the effects of OXT on STFP outlasted its acute action. Hence, overall, our results suggest that OXT effects on STFP were dependent on familiarity with the demonstrator and reflect long-lasting changes in social learning.

Familiarity-modulated OXT effects on STFP cannot be explained by anorexic effects or social exploration time

Acute OXT action has anorexic effects, especially on palatable food (Olszewski et al. 2010; Herisson et al. 2014). It is therefore possible that the complex pattern of OXT effects on STFP reported here can simply be explained by its anorexic effects. Indeed, we found that OXT injections decreased total pellet consumption (originally preferred and non-preferred pellet types combined) on the day of injections (mixed ANOVA with the factors familiarity, treatment and day; main effect of treatment, $F_{[2, 202]} = 9.079$, $p = .000$; significant simple main effect of day, $F_{[2, 404]} = 16.129$,

$p = .000$, and a significant interaction effect between treatment and day, $F_{[4, 404]} = 21.241$, $p = .000$, Fig. 4 supplemental material). However, these anorexic effects were restricted to day 4, i.e., the day of OXT injection, and did not extend to day 5 (post-hoc test: day 3 vs. day 5; in- low-dose OXT: $t_{[31]} = -1.6$, $p = .165$; in- large-dose OXT: $t_{[35]} = 0.276$, $p = .802$; out- low-dose OXT: $t_{[33]} = 0.252$, $p = .802$; out- large-dose OXT: $t_{[36]} = 1.25$, $p = .284$). In addition, even though we found group-dependent OXT effects on STFP (see analysis above), OXT effects on total pellet consumption did not differ between in-group and out-group ($F_{[1, 202]} = 0.352$, $p = .554$). Our analysis presented above showed that OXT effects on STFP were group-dependent and long-lasting, but OXT effects on total pellet consumption were neither group-dependent, nor long-lasting, suggesting that the reported OXT effects on STFP cannot be straightforwardly explained by its anorexic effects (Table 1 supplemental material; see discussion for further elaboration).

In addition to OXT anorexic effects, OXT and/or familiarity may have modulated the time observers spent interacting with, or socially exploring, the demonstrators. A mixed ANOVA revealed a significant simple main effect of OXT treatment, but not familiarity, on social exploration time (treatment: $F_{[2, 224]} = 7.247$, $p = .000$; familiarity: $F_{[1, 224]} = 1.364$, $p = .244$): rats treated with the large-dose of OXT explored the demonstrators less than the other treatment groups (vehicle vs. low-dose OXT: $t_{[149]} = 0.763$, $p = .447$; vehicle vs. large-dose OXT: $t_{[145]} = 3.55$, $p = .000$; low-dose OXT vs. large-dose OXT: $t_{[148]} = 2.7$, $p = .012$; Fig. 5 supplemental material). Even though the observation that the demonstrator's novelty in the out-group, relative to the in-group, did not lead to a significantly longer duration of partner exploration is somewhat surprising (Oettl et al. 2016), the lack of evidence for a difference in social exploration time suggests that exploration time unlikely explains the familiarity effects on STFP reported above. Likewise, although we did find OXT effects on exploration time, we did not find a significant interaction between OXT and familiarity, suggesting that the complex interaction of OXT and familiarity on STFP cannot be explained by social exploration.

Discussion

In this study, we measured the effects of systemic injections of OXT and the familiarity between observer and demonstrator on STFP. First, our results showed that vehicle rats revealed stronger changes in food preference when encountering an unfamiliar than a familiar demonstrator. Second, we found that systemic OXT administration influenced STFP dependent on whether the demonstrator was familiar or not: when the demonstrator was familiar (in-group), OXT led to a decreased consumption of the originally preferred pellets after social interaction with the demonstrator, but had no effect on the consumption of the originally non-preferred pellets. By contrast, we found opposite effects of OXT on STFP when the demonstrator was unfamiliar (out-group): OXT, relative to vehicle, did not change the consumption of the originally preferred pellets, but, notably, prevented the increase in consumption of the originally non-preferred pellets. These familiarity-dependent OXT effects on STFP could still be found one day later, at least after large OXT doses, when the acute effects of OXT on the organism most likely had waned, suggesting that OXT action during social interaction has long-term effects on STFP. Our results uncover a new mechanism how OXT modulates familiarity-dependent socially transmitted preferences and social reward revaluation.

Previous literature identified an acute anorexic effect after OXT administration in male rats, resulting in less food consumption (Arletti et al. 1989, 1990; Benelli et al. 1991). Our results also show a decrease in total pellet consumption (originally preferred + non-preferred) by the OXT groups. Although anorexic effects might explain our pattern of results, we believe this is not the case. First, if OXT's anorexic effects were the only mechanism, it should reduce consumption of both preferred and non-preferred pellets equally, but we did not find this to be the case (see results above). Second, OXT effects depended on the demonstrator's familiarity – an observation that is also difficult to reconcile with the anorexia hypothesis. Third, and perhaps most importantly, we found that OXT effects on STFP outlasted the acute OXT effects on total pellet consumption, suggesting that OXT action had long-lasting effects on STFP beyond its acute anorexic effects. We, hence, conclude that the results reflect group-dependent OXT effects on social learning, and not merely an OXT-related reduction in hunger or appetite.

Can the observation that vehicle rats showed stronger STFP with unfamiliar than familiar demonstrators be explained by differences in social exploration times? A feasible explanation of this phenomenon in rats is their preference for social novelty. Rats typically interact longer with an unfamiliar individual, which could enhance the chance of olfactory transmission of the demonstrator's food preference via its breath (Galef et al. 1988; Galef and Whiskin 2008a). However, a more recent study could not find support for this explanation, as a more detailed analysis showed that observers spent equal time sniffing the face of their demonstrator or in direct nose contact regardless of familiarity (Agee et al. 2019). In agreement with that, our vehicle rats in both in- and out-group conditions spent equal time sniffing their demonstrator, suggesting that other mechanisms

than merely olfactory recognition or social interaction time accounted for STFP.

So, how can we explain the familiarity- and OXT-dependent changes in consumption of the originally preferred and originally non-preferred pellets? One possibility is that OXT affected the decision weight the observers' placed on the specific kind of social information transmitted by the demonstrator in a familiary-dependent way: in the out-group condition, unlike the control observers, OXT-treated observers simply ignored the food information that was socially transmitted by the demonstrator, and, hence, continued to consume their originally preferred pellets the same way as they did before the social interaction. By contrast, in the in-group condition, OXT-treated observers began to dislike the pellets that were not eaten by the demonstrator, and, consequently, reduced the consumption of those pellets.

However, there are alternative explanations for the complex familiarity- and OXT-dependent effects on STFP that seem equally plausible. For example, one could argue that the information that is transmitted by the demonstrator in STFP would be the palatability of the originally non-preferred reward, but there would be no information transmitted about the originally preferred reward; after all, observer rats smell the scent of the originally non-preferred reward in the demonstrators' breath (Galef et al. 1988), but do not have any social information on the originally preferred pellets. Hence, STFP would mainly manifest as an increase in consumption of the originally non-preferred reward. Since, in vehicle rats, total pellet intake (preferred + non-preferred pellets) usually remains constant after social interaction, the decrease in consumption of the originally preferred reward in STFP would just be the logical, secondary consequence of the increased consumption of the originally non-preferred rewards: if rats eat more of food B after social interaction, they necessarily have to eat less of food A, unless they change their total food intake. According to this view, the difference in consumption of the originally preferred pellets between OXT and vehicle rats in the in-group might just reflect a secondary satiation effect: as mentioned, OXT led to a decreased total amount of pellets eaten on day 4, after the social interaction (see results and supplemental material). OXT-treated rats in the in-group showed STFP much like the vehicle rats, and accordingly ramped up their consumption of the originally non-preferred pellets (Fig. 4), while, at the same time, reducing their overall pellet consumption due to OXT's anorexic action. Hence, the OXT-related decrease in consumption of the originally preferred pellets on day 4 (Fig. 4) may simply reflect satiation effects: [reduced total consumption] minus [increased non-preferred consumption] = [reduced preferred consumption]. Note that this explanation may account for the pattern of results found in the in-group results, but cannot account for our out-group results. Future research needs to disentangle whether the familiarity- and OXT-dependent changes in pellet consumption reported here reflect familiarity-dependent differences in the decision weights attached to social information about the preferred and the non-preferred rewards, or differential satiation effects.

OXT's role in diverse modes of social information processing has become a focus of emerging research, making it a strong candidate for regulating social transmission of food value (Popik and Van Ree 1993; Choleris et al. 2009; but see Lindeyer et al. 2013). A study demonstrated the pivotal role of centrally released OXT in social cue processing, which integrates both odor extraction and social recognition. OXT affected genuine social aspects of social cue processing, as evidenced by the fact that inhibiting OXT signaling in the anterior olfactory nucleus (AON) resulted in compromised social recognition, while object and non-social odor recognition abilities remained unaffected (Oettl et al. 2016). In agreement with the notion that OXT facilitates the olfactory detection of information transmitted by a conspecific, further studies elaborated on that topic. It was shown that OXT signalling in the olfactory sensory cortex is crucial for the association between neutral odors and socially meaningful cues (Choe et al. 2015). Even more strikingly, meeting a conspecific differing in either age or sex activated discrete patterns of OXT neurons in the lateral septum and/or medial amygdala in male rats, hinting at independent subcircuits for certain social modalities (Lukas et al. 2013). While these findings do not explicitly address the different familiarity-dependent OXT effects on STFP in the in- and out-group conditions reported here, it may be reasonable to assume that demonstrators' familiarity, too, activates specialized OXT subcircuits, explaining our observed intergroup differences in flexible social preference revaluation. The differences in STFP between the in-group and out-group conditions might also be suggestive of familiarity effects on the recollection success of social reward revaluation. This familiarity-moderated recollection of reward value might involve hippocampal circuits as they are necessary for STFP (Alvarez et al. 2001; Winocur et al. 2001; Clark et al. 2002; but see Burton et al. 2000; Thapa et al. 2014) though selective OXT effects on GABA action in hippocampus (Maniezzi et al. 2019).

In conclusion, the current study provides evidence that STFP is modulated by OXT in a familiarity and dose-dependent manner. While the socially transmitted changes in food preference were stronger when interacting with strangers, large OXT dosage blocked the integration of social information during reward revaluation. The presented study is in line with the current understanding that OXT can modulate sensitivity to socially significant cues. The interpretation of these cues is affected by contextual elements, particularly

the familiarity of the demonstrator, suggesting that OXT has social effects beyond facilitating prosocial behavior (Anacker and Beery 2013; Olff et al. 2013; Love 2014; Piva and Chang 2018). These results add a layer of complexity to our knowledge of the influence of OXT in social learning. Exploring responsible neuronal areas and their specific dependency requires further investigation.

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Data availability Raw data supporting the findings presented in the study is openly available in OSF at https://osf.io/sfg3x/.

Declarations

Conflict of interest The authors declare no competing interests.

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