The Relationship Between Social Cognition, Bodily Movement and Dopamine

by

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Abstract

A wide range of clinical conditions, such as autism spectrum disorders, Parkinson's disease, Huntington's disease or schizophrenia (amongst others), show co-occurring socio-cognitive and motor symptoms. In addition, all of these populations have been associated with a dopamine-system dysfunction. However, it is currently unclear whether co-occurring symptoms across socio-cognitive and motor domains in these populations relate to the same underlying mechanism (e.g., dysfunctional dopamine signaling) or originate from distinct root causes that lead to seemingly related symptoms. Across four empirical chapters, this thesis explores the link between motor- and social-cognitive function in healthy individuals and in pharmacological models of neuropathology.

The first chapter provides a general introduction into the existing literature on the relationship between social and motor function in healthy and clinical populations. The second chapter addresses the relationship between motor function and mental state attribution. Because existing tasks for the assessment of mental state attribution do not allow the comparison of stimulus and participant movements, first the development of an adaptation of a classic mentalizing task, which is suitable to track both observer and animator kinematics, is outlined. The chapter then explores the role of stimulus kinematics and observer-animator kinematic similarity, alongside other important stimulus characteristics, in successful mental state attribution in this task in healthy adults.

The third chapter examines potential contributions of atypical dopamine signaling to mental state attribution differences in clinical disorders by pharmacological dopamine depletion in healthy adults. Furthermore, this chapter discusses why dopamine imbalances may impact mental state attribution independently of motor function.

The fourth chapter gives insights into the route via which dopaminergic dysfunctions may affect emotion recognition in conditions like Parkinson's disease by pharmacological manipulation of dopamine in healthy participants. Independent effects of dopamine depletion on locomotion and emotion recognition from PLW stimuli, as well as correlations between these effects are discussed.

Chapter five comprises a series of studies which explore the contributions of one's own gait kinematics to emotion recognition from others' gait, using smartphone accelerometers to measure participants' gait kinematics and point-light-walker (PLW) stimuli to assess individuals' emotion perception from whole-body motion information. The chapter further addresses a current shortcoming of the existing literature, which is the lack of knowledge about expression and perception of genuinely felt (as opposed to acted) whole-body motion.

The last chapter integrates all findings presented in this thesis with a specific focus on the role of dopamine as a potential mediator in the relationship between motor function and social cognition. Finally, implications for disorders with dopamine dysfunctions and future research are discussed.

List of publications

This thesis incorporates the following papers, which correspond to two out of the four empirical chapters:

1. **Schuster, B.A.**, Fraser, D.S., van den Bosch, J.J.F., Sowden, S., Gordon, A.S., Huh, D., & Cook, J.L. (2021). Kinematics and Observer-Animator Kinematic Similarity Predict Mental State Attribution from Heider-Simmel Style Animations. *Scientific Reports*. (Chapter two)

2. **Schuster, B.A.**, Sowden, S., Rybicki, A.J., Fraser, D.S., Press, C., & Cook, J.L. Dopaminergic modulation of dynamic emotion perception. Manuscript submitted for publication. (Chapter four)

In addition, chapter five of this thesis presents work published as part of the following two publications:

1. **Schuster, B.A.**, Sowden, S.L., Abdlkarim, D., Wing, A.M. and Cook, J.L. (2019). *Acting is not the same as feeling: Emotion expression in gait is different for posed and induced emotions*. Conference Abstract: 4th International Conference on Educational Neuroscience. doi: 10.3389/conf.fnhum.2019.229.00010

2. Sowden, S., **Schuster, B.A.**, Keating, C.T., Fraser, D.S., Cook, J.L. (2021). The role of movement kinematics in facial emotion expression production and recognition. *Emotion*. Advance online publication. http://dx.doi.org/10.1037/emo00008

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Figures in publication 1:

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List of abbreviations

Amplitude frequency spectral density (AFSD)
Autism spectrum disorder (ASD)
Blood oxygen level dependent (BOLD)
Dopamine replacement therapy (DRT)
Electroencephalogram (EEG)
Fast Fourier Transform (FFT)
Fluorine-18-labelled fluorodopa (FDOPA)
Functional magnetic resonance imaging (fMRI)
Gamma-Aminobutyric Acid (GABA)
Globus pallidus external (GPe)
Globus pallidus internal (GPi)
Goal-Directed (G-D)
Haloperidol (HAL)
Huntington's disease (HD)
Magnetoencephalogram (MEG)
Medial prefrontal cortex (mPFC)
Medium spiny neurons (MSNs)
Mirror neuron system (MNS)
Motor evoked potentials (MEPs)
Movie for the Assessment of Social Cognition (MASC)
Parkinson's disease (PD)
Pedunculopontine tegmentum (PPTg)
Placebo (PLA)
Point-light walker (PLW)
Positron emission tomography (PET)
Posterior superior temporal sulcus (pSTS)
Prefrontal cortex (PFC)
Reading the mind in the eyes test (RMET)
Resting state cerebral blood flow (rCBF)
Scalable vector graphics (SVG)

Substantia nigra pars compacta (SNc)

Substantia nigra pars reticularis (SNr)

Superior temporal sulcus (STS)

Theory of mind (ToM)

Tourette's syndrome (TS)

Transcranial magnetic stimulation (TMS)

Ventral pallidum (VP)

Ventral tegmental area (VTA)

Ventromedial prefrontal cortex (vmPFC)

Working memory (WM)

Chapter 1: Introduction

1.1. General Introduction

Our everyday movements carry a wealth of information about our internal states, including emotions and mental states. Our peers' facial expressions, gestures or body postures can effectively reveal to us their current state of mind without the need for verbal communication. A slumped posture combined with slow, effortful movements, for example, may indicate to us that our counterpart is feeling sad. Researchers dating back to Darwin in 1872[7] assigned a specific role to patterns of body movement and posture in communicating emotional states. Since then, a growing body of empirical work has shown that bodily movements convey important cues about an actor's underlying emotions[8-12], intentions[13,14], and other subjective cognitive states (e.g., confidence[15,16]) and that humans use these cues to effectively infer information about others' internal states[13,15,17,18]. Whilst the literature on body expressions is lagging behind facial expression research[19], an increasing number of studies suggest that body movement comprises cues for emotion recognition that are just as rich in information as facial expressions: Evidence indicates comparable recognition performance for facial and bodily stimuli[19], furthermore, motion recognition from facial expressions is significantly affected by emotional body language[20]. Moreover, humans refer to bodily cues in situations where facial emotion information is not accessible, for instance when judging emotions from a distance[21], or when facial emotion expressions are ambiguous[22,23]. Finally, there is evidence that suggests that some internal states may be better communicated by body, rather than face movement[24,25].

In 1992, a pioneering single-cell recording study[26] discovered that in the macaque, passively viewing an action activates the same motor neurons as performing that same action.

In the subsequent three decades, research involving humans has provided ample evidence for the notion that our perceptions of others' actions are closely linked to our own actions (discussed in more detail in section 1.2.2). Functional magnetic resonance imaging (fMRI) studies in humans showed, similar to what was found in Macaques, overlapping activity during action execution and observation in a network of various brain regions typically referred to as the Mirror Neuron System[27-29]. In the following years, these results were widely interpreted as evidence for a role of motor production areas in action understanding[26,29-31].

Support for a reciprocal relationship between action perception and production is provided by behavioral studies: For example, observing another human performing sinusoidal (e.g., horizontal) arm movements while simultaneously producing incongruous arm movements (e.g., vertical) significantly interfered with participants' own movements as measured by increased variance[32]. This "interference effect" has been attributed to the finding that action observation elicits subtle imitations of the perceived movement as measured by increased motor-evoked potentials in the extremities the observer themselves would use to execute the same movement[33]. Likewise, our experiences with our own movements can shape our judgements about others' actions. For instance, walking, but not standing, while judging the gait speed of point-light displays (coordinated moving dots representing only the joint movements of an agent) significantly interfered with participants' perceptual performance[34]. In short, our own movements impact on the way we perceive and infer information from others' movements.

If our understanding of others' movements is influenced by the way we move ourselves, it is conceivable that compromised motor function may lead to inadequate communication and social understanding. Indeed, a number of disorders primarily classified by clinicians as 'movement disorders'[35], present with deficits in tasks of Theory of Mind (ToM; i.e., the ability

to reflect on the contents of one's own and others' minds[36]) and emotion recognition. For instance, patients with Huntington's disease (HD), an inherited autosomal-dominant progressive neurodegenerative disorder leading to selective atrophy of striatal neurons[37], experience motor symptoms such as chorea (dance-like involuntary movements) and dystonia (uncontrollable muscle spasms)[38] alongside socio-cognitive difficulties. Socio-cognitive impairments in this condition comprise consistent deficits in emotion recognition (from both facial expressions[39] and voices[40]) and various measures of ToM ability[41] (e.g., Frith-Happé Animations task[42], Faux Pas test[43] or Reading the Mind in the Eyes test [RMET][44], though note the debate about whether the RMET is a true measure of ToM[45]).

Unlike HD patients, who have been shown to exhibit a reduced tendency to infer intentions from animations of interacting triangles[46], patients with Tourette's syndrome (TS) tend to *over*attribute intentions and mental states to the same kind of animations[47]. TS is a neurodevelopmental disorder characterized by involuntary repetitive movements and vocalizations (tics). In addition to exhibiting a bias towards hyper-mentalizing[48], TS patients display difficulties in various other tasks of emotion recognition and ToM[49] and show greater interference effects on their own movements while observing others' actions. Together, the socio-cognitive impairments in TS may be suggestive of a hyper-responsiveness to social information conveyed by visuo-motor cues[50].

Two further examples of conditions exhibiting shared motor and socio-cognitive symptoms are elaborated in more detail in section 1.3. of the introduction: The case of autism spectrum disorder (ASD) and the case of Parkinson's disease (PD). Altogether, a noteworthy number of clinical populations exhibit co-occuring socio-cognitive and motor symptoms. Yet, while this co-occurrence is intriguing, little is currently known about the causality of this relationship between social and motor impairments. It may be the case, as stated above, that

motor abnormalities cause difficulties in understanding others' actions. However, the opposite direction of causality may be true: socio-cognitive difficulties could result in atypical motor development. Finally, co-occurrences of social and motor atypicalities may not be related at all, but rather independently arise from the same, or entirely different, underlying mechanisms.

Strikingly, the previously mentioned conditions do not only share motor and socio-cognitive symptoms: An additional commonality of these disorders is that they have all been linked to disruptions in the dopamine system. The dopamine system is one of the brain's largest neuromodulatory systems and is, via discrete projections to several different brain regions, implicated in motor control, cognition, and emotion. Dopamine system dysfunction is associated with a number of neurodegenerative and psychiatric disorders, among them PD[51], HD[52], TS[53], ASD[54], but also schizophrenia[55] or depression[3]. In PD, for example, pathological changes in dopamine neurotransmission are well studied: Degeneration of dopamine producing neurons in the substantia nigra pars compacta (SNc) leads to dopamine loss in the striatum and is thought to be responsible for motor symptoms such as bradykinesia (slowness of movement), rigidity and resting tremor.

There are several ways in which dopamine system disruptions may be responsible for shared deficits in social and motor function in these clinical populations. It is possible that dopamine affects socio-cognitive and motor abilities independently, via distinctly separate pathways. Equally conceivable, however, is that dopamine primarily affects patients' motor function, and that difficulties in social understanding arise as a consequence of altered movement patterns or motor simulation processes. Evidence in support of and against these hypotheses is further elucidated in section 1.4 of the introduction. Yet, it is important to consider that there are other possible mechanisms which may be responsible for socio-cognitive impairments among movement disorder populations. Psychosocial changes accompanying

diagnoses could over time lead to altered social responses. For example, a common symptom of PD, hypomimia (reduction in voluntary and spontaneous facial expression), can lead to patients being perceived as disinterested, awkward and less likeable, and ultimately lead to bidirectional interaction problems[56].

This thesis addresses two primary questions: First, how do our own bodily actions and the similarity to others' actions influence our perception of others' affective and mental states? Second, what is the role of the neurotransmitter dopamine in the co-occurrence of socio-cognitive and motor deficits in various clinical populations? I attempt to answer these questions with a series of empirical studies that appraise the link between motor and social function first in healthy participants and subsequently in a pharmacological model of neuropathology. My overall goal is to gain insight into the relationship between social, motor and dopamine system function in the general population so that future work may make clear and testable predictions about the likely effects that dopaminergic disruption should have on social and motor function in clinical conditions. Correspondingly, in the General Discussion (Chapter six) I reflect upon the implications of my findings across various clinical populations.

The remainder of the introduction first provides an overview of the way in which movement kinematics convey information related to one's internal states and on how one's own movement kinematics affect the perception of others' internal states. On the basis of two examples (ASD and PD), the introduction further outlines evidence concerning the relationship between impairments in social and motor function in clinical populations. Finally, I evaluate how disruptions of the dopamine system in these conditions may contribute to deficits in social understanding and communication, highlight the questions presently unanswered by the literature, and discuss how this thesis addresses these gaps.

1.2. The relationship between motor function and social cognition in healthy individuals

1.2.1. What are 'internal states'?

Throughout different fields of human and life sciences, different conceptualizations of what constitutes a mental state have been adopted. Oosterwijk et al.[57] for example, argue that neuroscientific evidence speaks for a broad, constructionist conception of mental states as comprising emotions, cognitions and (bodily) perceptions, arising from a combination of multiple domain-general psychological processes. They refer, for instance, to the 'default mode network', a large-scale brain network including the medial prefrontal cortex, medial temporal lobe and posterior cingulate cortex, which is recruited during emotion processing[58] as well as mental state attribution[59] (amongst a multiplicity of other cognitive processes). In line with this, Salzman and Fusi[60] describe mental states as behavioral dispositions comprising "thoughts, feelings, beliefs, intentions, active memories, and perceptions" and refer to functional interactions between brain areas traditionally associated with emotion processing (e.g., amygdala) and cognitive processes (e.g., prefrontal cortex).

In contrast, although there is no generally accepted definition of what constitutes a 'mental state', social cognitive psychologists commonly describe mental states as beliefs, desires, and intentions, but usually exclude emotions from this definition. This is evidenced by the observation that socio-cognitive research typically clearly distinguishes between emotion recognition and 'mentalizing'[1]/ToM, with distinctly different tasks used to assess either ability (e.g., whereas emotion recognition studies classically employ stimuli of either all or a subset of

[1] In the relevant literature, the term 'mentalizing' is predominantly used equivalently to ToM and can be defined as 'the process of attributing mental states to others, where mental states refer to another person's thoughts or cognitive states' (e.g., see 61 Blakemore, S.-J. The Developing Social Brain: Implications for Education. *Neuron* **65**, 744-747, doi:10.1016/j.neuron.2010.03.004 (2010).).

the six basic[62] emotions, traditional ToM tasks test a person's ability to infer (false) beliefs[63] or reason about another person's intentions[64]).

The principle of 'intentionality' views a person's subjective states as having an 'intentional' relationship with the outer world[65]. Intentionality hereby encompasses all the ways in which the mind can be directed at or related to states of affairs in the world (e.g., one believes X, one desires X). Thus, intentionality refers to the understanding that others' actions are goal directed and arise from unique beliefs and desires. In his recent book, Whiting[66] takes up the view proposed by 19th century philosopher David Hume that emotions are bodily feelings lacking intentional or representational qualities (i.e., they make no references to external objects). In his 'feeling theory of emotion', although Whiting classifies emotions under the umbrella term 'mental states', he argues they stand in contrast to 'representational mental states', such as beliefs or desires, which are always object (including other persons) related. In other words, Whiting views emotions as states which are distinguished by how they feel to an individual, whereas representational mental states are individuated based on how they represent a particular object as being.

The more recently adopted distinction of ToM into the two sub-components affective and cognitive ToM further supports a conceptual separation of emotions and mental states, as it implies the idea that dissociable processes are involved in representing and reasoning about another person's emotions and in representing their intentions, beliefs or desires. Indeed, a series of imaging and lesion studies suggest that cognitive and affective ToM at least in part rely on distinguishable neural substrates[67-70]. These studies have identified the ventromedial prefrontal cortex (vmPFC) as a region which is specifically recruited during tasks requiring affective, but not cognitive ToM.

Throughout this thesis I will honor the distinction between emotions (affective states) and representational mental states and refer to the broader term 'internal states' as all internal states of mind which can be experienced by an individual (i.e., including both emotions and mental states). In two separate empirical studies, I go on to explore the concepts of mental state attribution and emotion recognition (and how they are expressed in and perceived from body movement).

1.2.2. The role of movement kinematics in the expression of internal states

For decades, the question of how we read others' minds has occupied philosophers and psychologists alike. The 'Unobservability Principle'[71] relates to the general idea that another person's internal states are 'hidden', i.e., perceptually inaccessible and therefore can only be inferred. Accepting this notion as true brings to question *how* individuals infer these hidden states from what is accessible to their senses. As Whiten elaborated:

> *[…] mind-reading is not telepathy. So, the recognition of another's state of mind must somehow rest on observation of certain components within the complex of others' behaviour patterns together with their environmental context: that's all we can see - we can't see their minds in the direct way suggested by the idea of telepathy* (Whiten, 1996, p. 277[72])

Accordingly, we use an entity's behaviors in combination with contextual cues to draw inferences about their internal worlds. Amongst other behavioral signals such as facial expressions and vocalizations, bodily movements provide valuable cues about affective and mental states. Early research on emotional body expressions used trained or untrained observers

to rate dynamic stimuli of gait, dance, or isolated limb movements, typically displayed by actors, according to how well they matched pre-defined emotion categories[8,18,73], demonstrating that humans can successfully identify intended expressions of emotions from bodily movement cues. More recently, machine learning techniques have been employed to extract the bodily expressions that best discriminate emotional states[74,75]. The range of bodily cues that have been identified as reliably differentiating emotional states as rated by human observers or machine recognition algorithms include postural and spatial configuration, as well as temporal characteristics, of dynamic arm-, head and whole-body movements[8,9,73,76]. Among these cues, accumulating evidence points to a specific role of movement kinematics, which were shown to be at least sufficient for the accurate classification of internal states[77]. For example, Pollick et al.[9] observed that their participants could adequately detect affective states from point-light displays of instrumental arm movements with minimal configural information. More specifically, they found their emotion categories to be clustered within a two-dimensional psychological space. Within this space, the arms' movement kinematics (velocity, acceleration, and jerkiness) were highly correlated with the 'activation' dimension: While fast and jerky movements were associated with emotions of high activation such as anger or happiness, slow and smooth arm movements tended to be rated as internal states with low activation (e.g., sadness). This relationship between arm movement kinematics and the activation dimension of emotions was preserved even when the point-light displays were altered so they did not resemble an arm anymore (i.e., when only kinematic, and no form information was available). Further tightening the link between kinematics and emotion, several other studies found similar associations between high-speed movements and happiness / anger and decreased movement velocity and sadness[75,78-82]. What is more, movement kinematics have been shown to not only encode emotions, but also intentions (e.g., kinematics discriminate between the intention to

cooperate or compete[83]), and other cognitive states, such as confidence[15]. The study conducted by Pollick and colleagues, however, was unique in that it illustrated that in order to perceive emotional states in others, humans do not need faces, whole bodies, or contextual cues; they can effectively perceive internal states from impoverished stimuli depicting merely the joints of isolated body parts.

In fact, humans do not need bodily expressions at all in order to infer internal states: Motion cues alone are sufficient to cause us to attribute agency, intentionality, and more specific mental states to animated objects. Heider and Simmel[84] demonstrated 1944 in a seminal study that humans readily attribute animacy to and infer mental states from simple animations of two interacting triangles. Their paradigm was subsequently adapted by several research groups[42,85,86], and rapidly gained in popularity amongst psychologists for its suitability to test individual differences in mentalizing abilities. In particular, the Frith-Happé animations[42] have been used extensively to investigate mental state attribution in ASD[42], HD[46], TS[49], and schizophrenia[87] and reliably show performance differences between patients and controls.

At present, however, little is known about why a range of clinical populations show these differences in mental state attribution. One recent study[1] which evaluated the ability to attribute mental states to Heider-Simmel style animations in autistic and non-autistic individuals provides some preliminary clues as to possible underlying reasons for performance differences in this task. In this study, autistic and non-autistic participants were first asked to create their own animations by using magnetic levers to move two cardboard triangles around a horizontally positioned whiteboard (see Fig. 1.1). Whilst participants created animations for four mental state words (coaxing, mocking, surprising and seducing; words were adopted from Abell et al.[42]), a film camera positioned above the whiteboard recorded their stories. Subsequently, both groups were shown a range of animations created by autistic and non-

autistic subjects and asked to rate the extent to which each animation depicted either of the four target mental state words. Their results showed that typical participants were less accurate in labelling the animations when these had been created by autistic participants, relative to animations generated by their own group. In contrast, autistic participants showed no such in-group bias. Crucially, animations created by autistic participants were characterized by increased kinematic jerk. The authors surmised that reduced movement similarity between the groups (i.e., differences in jerk), may have been responsible for difficulties in interpreting animations created by the respective other group.

It is possible that this lack in similarity in the way individuals with and without motor dysfunctions perform certain movements may lead to misunderstandings between populations in real-world communicative situations. Support for this is lent by a study[88] showing that autistic children are less efficient than non-autistic children in reading social intentions from whole-body movements, although stimuli were based on non-autistic actors, thus providing no insights into whether these inference difficulties were bi-directional. Moreover, currently there is no direct evidence linking specific motion characteristics of movement to (impaired)

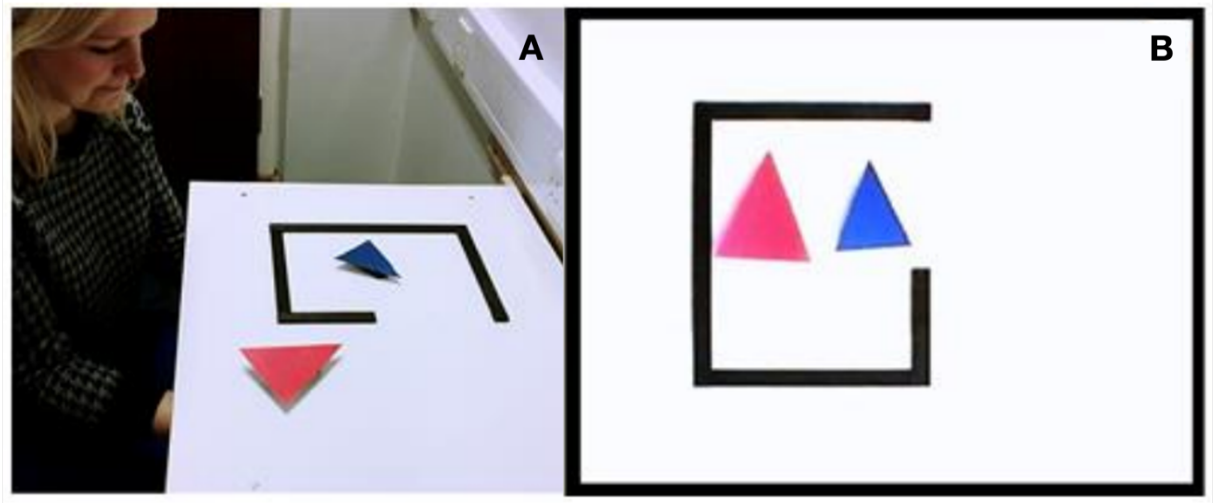

Figure 1.1. Animations task procedure in Edey et al.[1]. (A) Participants were asked to move two cardboard triangles around a white board by moving magnetic levers attached to the triangles. (B) Still of an example animations stimulus created by filming the triangle movements from above. Image from Edey et al.

inference of internal states. In Chapter two I present empirical evidence on which motion cues are relevant for successful mental state attribution using the Heider-Simmel paradigm. In Chapter two, I further demonstrate that movement similarity between agent and observer indeed facilitates the interpretation of those cues.

One issue with investigating bodily and/or motion cues that are associated with successful social interaction is that most of what we know about internal state expression in body movements depends on acted, rather than genuinely felt affective / mental states. In the majority of studies on the subject, either actors or the experimenters themselves created the stimulus material. It is likely that this material is richer in expressive cues than real world affective expressions, as it was purposefully designed to communicate affective states or mentalistic interactions[25]. Chapter two presents a study which uses population-derived animations of interacting triangles to assess mental state attribution and discuss possible differences to existing tasks which use experimenter designed stimuli. Furthermore, chapter five examines the current literature on the spontaneous expression of emotions in body movement and provide some empirical evidence for why researchers need to be careful when drawing conclusions from an evidence base which mainly depends on posed expressions.

1.2.3. The reciprocal relationship between action and perception

Neuroscientific evidence for a 'Mirror Neuron System'

Early indirect evidence for the existence of a brain mechanism that closely couples action perception and production in humans was provided in 1954 by Gastaut and Bert[89] and Cohen-Seat et al.[90]: The research groups showed that the desynchronization of a centrally derived EEG rhythm, the so-called mu rhythm, was present both when their participants observed others' actions, and when they were performing actions themselves. This observation

was subsequently replicated by several other studies using EEG[91-94] and magnetoencephalogram (MEG)[95,96] recordings. More direct evidence for a so-called mirror neuron system (MNS) comes from studies using transcranial magnetic stimulation (TMS) of the motor cortex. Motor evoked potentials (MEPs) are electrical signals recorded from the contralateral extremities following motor cortex stimulation with TMS. These MEPs have been shown to be stronger whilst participants observe another person performing actions compared to a visual control condition, thus illustrating a facilitatory effect of action observation on action execution[33,97,98]. Further insight into the anatomical organization of the MNS is provided by a range of fMRI studies showing overlapping activity during action observation and action execution in a complex network of brain regions: The MNS is thought to comprise as key areas the posterior inferior frontal gyrus[99,100], rostral inferior parietal lobes[100] and ventral and dorsal premotor regions[27]. In addition, the superior temporal sulcus (STS), although it does not involve classical mirror neurons, is often mentioned alongside the MNS for its role in action understanding[101]. Early research on mirror neurons focused on understanding action recognition devoid of inferences about internal motivations of the action, also referred to as the 'what' of an action (i.e., *what* is a person doing?). More recent studies, however, give rise to the idea that human mirror neurons are also involved in processing the 'why' of an action, that is, the underlying intention of an action (i.e., *why* are they performing this action?)[102]. For instance, Iacoboni and colleagues[103] observed increased blood oxygen level dependent (BOLD) signal upon the viewing of actions embedded in informative contexts, relative to videos of actions without contexts, in the right inferior frontal cortex. This suggests that regions of the MNS, which were previously believed to be involved in simple action recognition only, process contextual information related to the intention of an action. Moreover, the human MNS has been shown to be involved in the processing of emotions. For instance, viewing facial

expressions of disgust activated the same parts of the anterior insula as the experience of disgust after exposure of a non-pleasant odorant[104]. Yet, it should be noted that whilst these previous results indicate that the MNS may process cues that can elicit the attribution of specific intentions or emotions to an action, a greater, more complex network of neurons including mirror neurons is presumably involved in enabling action understanding[105]. Altogether, neuroimaging studies provide substantial evidence for a biologically based link between perception and action. Given this evidence, it is plausible that our movements influence the way we perceive others' actions and vice versa.

Behavioral evidence for a functional link between action and perception

Behavioral evidence for an overlapping neural mechanism underlying action perception and production suggests strong reciprocal relationships between a person's own actions and how they perceive others' actions. On the one hand, perceiving someone else's actions can influence the observer's own action production. For example, Kilner et al.[32] found that observing another human performing sinusoidal (e.g., horizontal) arm movements while simultaneously producing incongruous arm movements (e.g., vertical) themselves significantly interfered with participants' own movements as measured by increased variance. More intriguingly, a follow-up study[106] showed that this interference effect only occurred when the observed movements followed a biological (minimum-jerk) movement profile. Their results suggest that the interference effect was not induced by attentional demands or increased task complexity. Rather, they indicate that the interference was caused by the incongruent human arm motion and suggest that the human MNS may respond selectively to biological motion.

On the other hand, our own movements can have direct, on-line effects on how we perceive others' actions. For instance, lifting a heavyweight box whilst simultaneously being

asked to judge the weight lifted by an actor caused participants to underestimate the weight lifted by the other person (and vice versa when the subject was lifting a lightweight box). Similarly, as pointed out earlier, Jacobs and Shiffrar[34] observed a selective interference of subjects' walking speed on their perception of other walkers' speeds: This was evidenced by a reduced ability to discriminate two point-light walkers' (PLWs) speeds whilst walking as opposed to when cycling or standing. The selectivity of this effect for walking relative to cycling movements suggests that currently active motor representations of our own movements may interfere with our observations of others' movements. The more similar an observed movement is to the one we are carrying out in the very same moment, the more difficult it may be for us to represent the observed movement.

Intriguingly, when the subjects in Jacobs and Shiffrar's study were asked to judge the PLWs' speed in relation to their own pace, simultaneous walking on a treadmill did not interfere with their perceptual judgements when their own walking speed was manipulated to be closest to the human average walking speed (which was assumed to be the speed the participants would have chosen themselves, i.e., their preferred walking speed). What is more, when observers' speeds were manipulated, their egocentric judgements of others' speeds were biased towards their own speeds: Increases in walking speed resulted in participants overestimating observed speeds, and vice versa for decreased own speeds. These observations led the authors to conclude that, to facilitate self-relative judgements of others' actions, we draw on visuo-motor experience of our own actions. Together, the previous experiments demonstrate that, amongst other cues, humans use representations of their own actions to make perceptual judgements about other humans' movements. Moreover, the findings indicate that increased similarity between one's own and observed movements can facilitate action understanding.

How do we understand others' actions?

Currently, there are diverging views on precisely *how* our internal action representations shape our perceptions and subsequential inferences about an action's underlying intention. According to the 'direct matching hypothesis'[31] we understand others' actions based on our own prior experience with the very same actions. This account postulates a stimulus-driven feed-forward process, where low-level (e.g., kinematic) representations of observed actions are directly mapped onto the observer's own visual and motor plans, which then activates higher-level goals / intentions which the observer themselves associates with the represented action. In other words, people interpret others' actions by implicit matching of the kinematics of a perceived movement with their own individual action templates and inferring the goal, intention, or emotion they themselves would associate with the observed movement. Crucially, these action templates are presumed to be built from early childhood through associative learning of the sensorimotor consequences of one's own and others' actions[107,108] and can comprise both purely visual representations of movements, as well as visuo-motor representations gathered from simultaneous proprioceptive (i.e., sensorimotor perceptions of body position and movement relative to space) and visual experience with our own actions. Thus, while others' internal states can be interpreted based on mere visual experience from observing actions and their associated outcomes, it has been proposed that observing movements oneself has experience with performing (i.e., motor expertise) additionally activates internal *motor representation*s of that action, reflected by increased activation in regions of the mirror neuron system relative to observing actions one is visually, but not motorically familiar with[109]. In the remainder of this thesis, I refer to representations which are based on visual *and* motor expertise with observed actions, including the internal states associated with these representations, as *'internal action models'*.

In line with this, Edey and colleagues[2] were able to show that subjects make affective judgements about others' actions based on their own internal action models. When comparing participants' preferred walking speeds with their intensity ratings of emotional PLWs, Edey et al. found that individuals whose own preferred walking speed was slower than average were more likely to rate a slow point-light walker as being in a neutral state of mind. In contrast, they perceived a PLW at average velocity as being mildly angry. Equally, those average velocity stimuli were more likely to be rated as mildly sad by participants whose own preferred walking speed was faster than average (see Fig. 1.2).

Thus, we are prone to judge walks with a similar speed to our own neutral walk as reflecting a neutral affective state, whereas walks with distinctly different speeds to our own appear as emotionally intense. Consequently, the labelling of internal states from others' movements could be simply a result of referencing the observed movement against

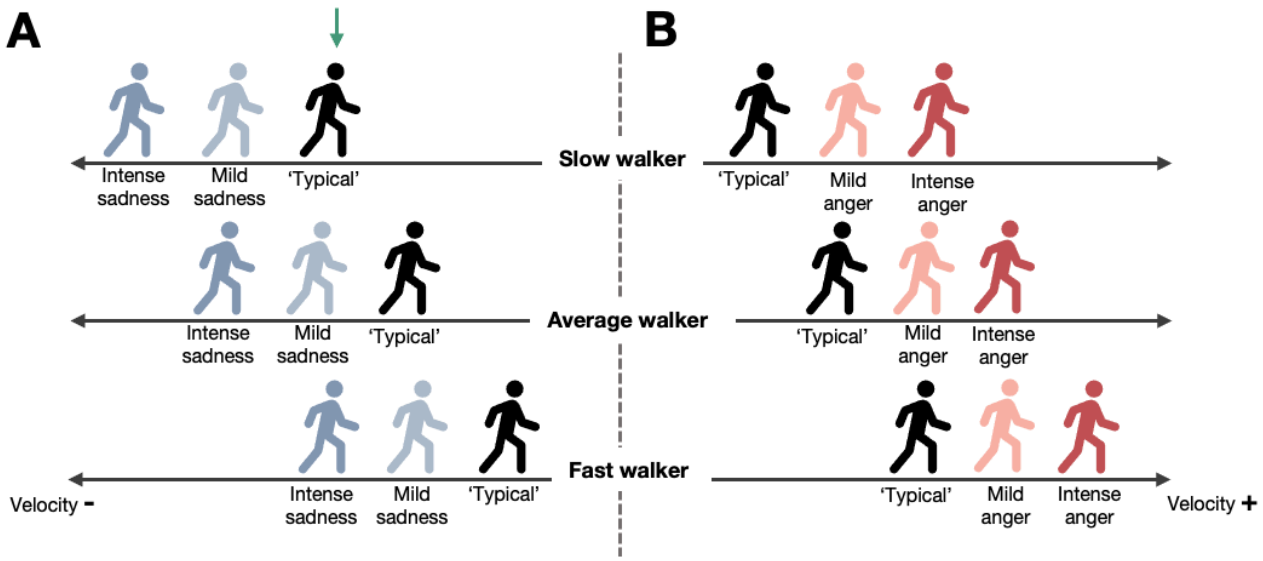

Figure 1.2. Schematic diagram of hypothesis tested in Edey et al.[2]. (A) Hypothetical kinematics of *sad* slow, typical and fast walkers. At the velocity level indicated by the green arrow, a slow walker is in a neutral state, whereas a fast walker would be feeling intensely sad. (B) Hypothetical kinematics of *angry* slow, typical and fast walkers. Image reproduced from Edey et al.

representations stemming from a lifetime of somatosensory and proprioceptive experiences with our own affective kinematics.

It follows that based on individual action idiosyncrasies, people may draw different inferences from others' movements, hence individuals who move in a similar way may understand each other better than people who move very differently. Edey et al. discovered in a subsequent study[110] that internal state attributions of four different age groups (early adolescents, middle adolescents, late adolescents, adults) varied according to their participants' preferred walking speed, which covaried with age. The authors hypothesized that cross-generational conflicts, such as typically observed conflicts between adolescents and adults, might be at least in part attributable to different action models within these generational groups.

'Predictive coding/processing accounts'[111] may be seen as an extension to the direct matching hypothesis. According to these accounts, visual action information is processed via both feed-forward and feed-back loops between the pSTS and the MNS regions. Following initial visual processing of an action, estimations are made, based on a priori internal models[2] of the goals or intentions associated with the observed action, about the visual consequences of that action. This prediction is then compared to the actual visual outcome and a prediction error produced. Depending on the magnitude of the prediction error, an observer's internal model of the underlying cause (i.e., an agent's underlying intention) of the action is continuously revised until the prediction error is sufficiently minimized, or in other words, the observed action consequence fits the predicted action consequence. In addition to the observer's personal visual and visuo-motor experiences with the observed action and linked internal states, contextual cues serve as informative priors that increase the efficiency of ongoing predictions.

[2] Note that here the term 'internal models' refers to statistical estimates an individual holds about hidden states of the world (e.g., an action's underlying intentions) according to predictive coding or Bayesian inference accounts.

Predictive processing accounts extend Bayesian inference theories by positing specific assumptions about the neural structures involved in the prediction process, thereby creating hypotheses that are testable by neuroimaging methods. In the same way that dopamine neurons show increased firing patterns upon receipt of an unpredicted reward, predictive coding theories assume that there is a group of neurons specifically dedicated to reporting more general sensory prediction errors (i.e., 'error neurons'). Within and across many levels of the cortical hierarchy[112,113], these error neurons are believed to be in constant interactions with so-called 'predictor neurons', which encode the representations of predictions[114]. In this relationship, error neurons are thought to compare incoming sensory information with top-down predictions encoded by predictor neurons, and are expected to show increased firing rates upon a mismatch between top-down and bottom-up information. In vision studies, average responses across large populations of neurons have followed activity patterns in line with predictive processing accounts, with attenuated activity for repeated stimuli (e.g., [115,116]). Furthermore, reduced neural responses in brain areas thought to be part of the 'mentalizing system'[117] (pSTS, TPJ, mPFC) have been observed for expected compared to unpredicted actions and intentions[114].

Predictive processing accounts serve a different perspective on the putative underlying causes of co-occuring social and motor symptoms in clinical conditions. For instance, in autistic[3] individuals, atypically highly weighted sensory information – at the expense of information based on priors - is hypothesized to underly a number of behavioral characteristics of the condition[118,119]. This atypicality in predictive processing has been associated with both abnormalities in motor function (such as problems with movement planning and

[3] Disability-first' terminology is used throughout in line with the majority preference expressed in a survey of the autistic community (Kenny, L., Hattersley, C., Molins, B., Buckley, C., Povey, C., and Pellicano, E. (2016). Which terms should be used to describe autism? Perspectives from the UK autism community. Autism Int. J. Res. Pract. 20, 442–462.)

initiation[120,121]), as well as socio-cognitive impairments in ASD[122]. Moreover, besides ASD, other clinical conditions such as PD[123] and schizophrenia[124] have been linked to predictive processing deficits. Thus, in a number of clinical conditions, the very same processes that are hypothesized to underlie atypical motor function may independently be responsible for aberrant internal state attribution from action information. In section 6.2.3 of the discussion, I elucidate how aberrant dopamine signaling may be causally implicated in socio-cognitive deficits by atypical representation of prediction processes.

This section outlined the reciprocal relationship between action and perception and highlighted two prominent theories about how individuals may draw on their own motor experience to understand other peoples' movements. Whilst deciding between these two accounts of action understanding is beyond the scope of this thesis, the present work goes on to discuss both accounts as possible mechanistic pathways via which aberrant dopaminergic signaling may contribute to co-occurrences of socio-cognitive and motor deficits in clinical populations.

Co-morbidities of social and motor dysfunctions are particularly prevalent among conditions which have been linked to a dysfunction in the dopamine system[50], suggesting that aberrant dopamine signaling may contribute to these co-occurrences. Consequently, in the following I first outline the various ways in which the dopamine system is involved in cognition and behavior. I then discuss two examples of conditions involving atypical motor experiences, and how those different experiences may shape individuals' social perception and interactions, before going on to elucidate how dopamine may be a common denominator in observed relationships between motor and social function in these conditions. Finally, in two empirical chapters, I use a pharmacological model to test whether, and if so, *how* altered dopaminergic

states may affect both socio-cognitive and motor processes across a variety of clinical populations.

1.3. Dopamine

1.3.1. Dopamine neurons: Two different activity states

Dopamine is a neurotransmitter which, alongside epinephrine and norepinephrine, belongs to the group of catecholamines. Dopamine neurons are primarily located in the midbrain (ventral tegmental area [VTA] and SNc) and form anatomically distinct subclasses of populations with discrete projections to specific brain regions[3]. Dopaminergic neurons are known to exist in various activity states. While a proportion of dopamine neurons is in an inhibited, non-firing state, another proportion is in an active state, spontaneously firing in a slow, irregular pattern. The proportion of neurons firing in this pattern determines the level of *tonic* dopamine release into the extrasynaptic space, and has been proposed to reflect individual baseline responsivity of the dopamine system[125].

Upon exposure to a salient, behaviorally relevant event, only the active population of dopamine neurons responds with firing of *phasic* bursts, leading to high amplitude, highly transient dopamine release into the synapse (see Fig. 1.3)[3]. This phasic spiking dopamine

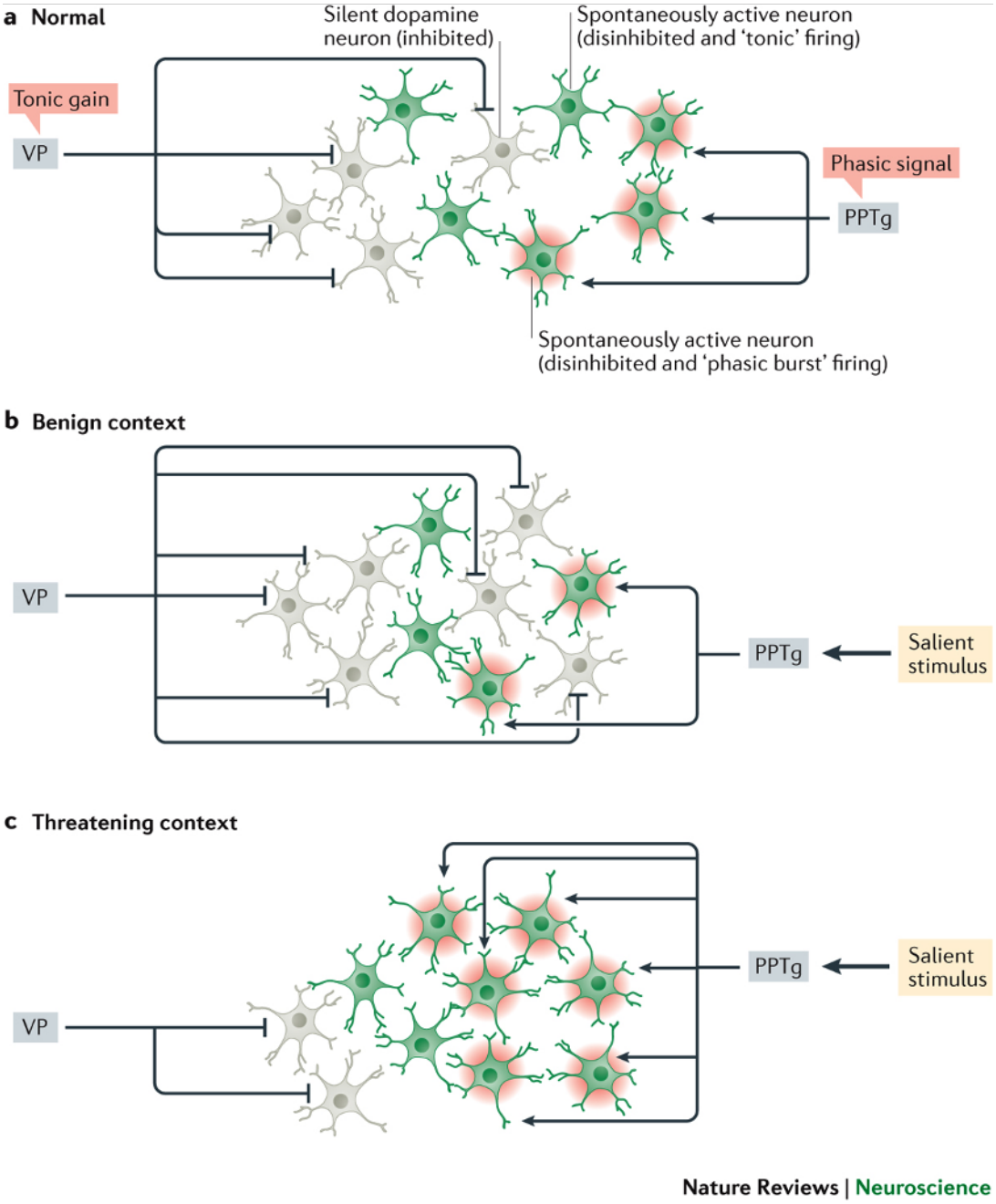

Figure 1.3. Tonic and phasic dopamine neuron regulation. a) A subset of dopamine neurons is kept in a hyperpolarized, non-firing state due to GABA-ergic inputs from the ventral pallidum (VP). By controlling the number of dopamine neurons firing, the VP determines the potential for phasic burst firing. Glutamatergic input from the pedunculopontine tegmentum (PPTg) causes active, spontaneously firing dopamine neurons to generate phasic bursts of dopamine release. b) & c) The behavioral context determines the number of dopamine neurons which are spontaneously firing, and thereby regulates the level of dopaminergic response to behaviorally relevant stimuli: In a benign, non-threatening context, the number of spontaneously firing neurons is kept low and a salient stimulus will therefore only lead to phasic bursting in a small population of dopamine neurons. In a threatening or opportunistic environment, a larger population of dopamine neurons are disinhibited, leading to a much larger phasic response to the same salient stimulus. Image from Grace[3].

activity has been observed to accompany presentations of unexpected (i.e., not predicted) rewards (e.g., a drop of liquid in the mouth) in primates and the magnitude of the dopamine response is thought to directly reflect the discrepancy between prediction and actual occurrence of reward: the reward prediction error[126].

A popular theory posits that tonic dopamine levels encode the long-term average rate of available reward, and consequently determine the effort an individual is willing to exert - also termed 'response vigor' - in order to obtain a reward[127]. In other words, while the phasic dopamine response signals the magnitude of the immediate reward associated with a behaviorally relevant stimulus, tonic dopamine activity is believed to encode the average availability of this reward in the environment. In consequence, dopamine depletions in humans may lead to effects linked to both phasic and tonic dopamine activity such as blunted prediction error signals and aberrant coding of the cost-benefit ratio of certain actions. In clinical populations, such a hypodopaminergic state may manifest as reduced vigor during action execution (e.g., bradykinesia in PD[128]) or dysfunctional reward processing (e.g., as seen in ASD[129]).

1.3.2. Four dopamine pathways

Besides modulating reward, however, dopamine is hypothesized to regulate a multiplicity of behavioral and physiological functions via four major neural pathways (see Fig. 1.4). The tuberoinfundibular pathway, which originates in the arcuate nucleus of the hypothalamus and projects to the pituitary gland, inhibits prolactin (i.e., a hormone facilitating lactation) release and is therefore involved in the control of lactation[130]. The mesolimbic pathway involves neurons whose cell bodies originate in the VTA and project to the nucleus accumbens in the ventral striatum. The mesolimbic pathway is implicated in the processing of

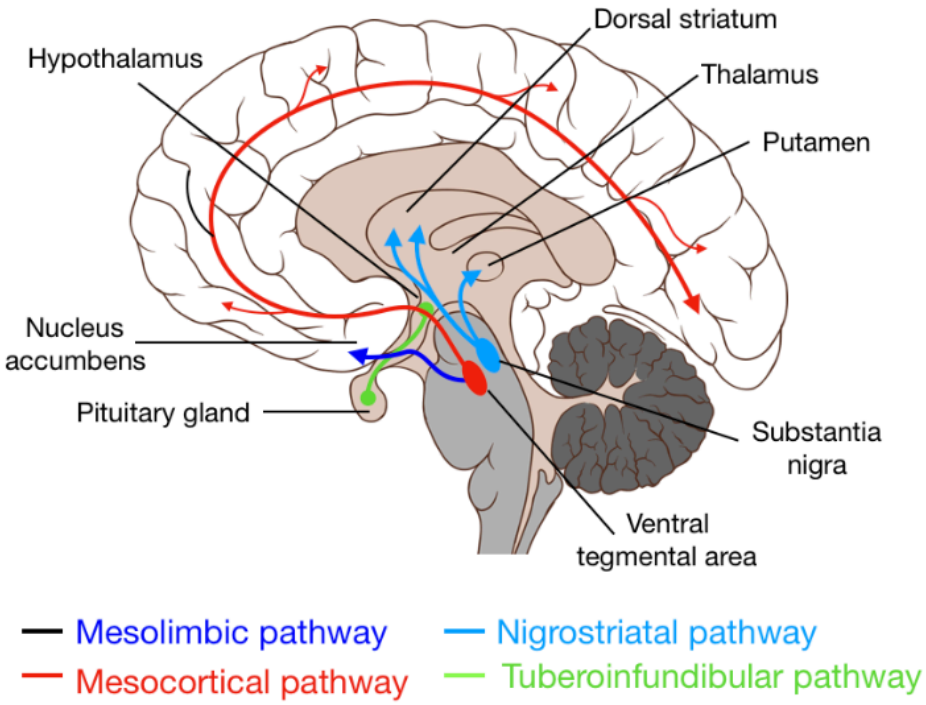

Figure 1.4. Four major dopamine pathways. Image from Nummenmaa et al.[4]

incentive salience and motivation, and overactivity of this circuit is, for example, associated with addiction[131] and psychosis[132]. Dopaminergic neurons in the mesocortical pathway also originate in the VTA, but connect to the prefrontal cortex and are involved in the regulation of executive functions, learning and memory, as well as mood and emotion[133]. Finally, the nigrostriatal pathway projects from the SNc to the dorsal striatum (i.e., caudate nucleus and putamen) and is involved in the regulation of movement. According to a prevailing model of the role of the basal ganglia in movement control, striatal dopamine controls motor function via two cortico-basal ganglia-thalamo-cortical loops (see Fig. 1.5, [134]). In short, the direct ('Go') pathway is linked to the facilitation of movement, where cortical glutamatergic downstream projections excite striatal dopamine release, which via inhibitory action on the globus pallidus internal disinhibits the thalamus, leading to excitatory action on the cortex and finally stimulating movement. The indirect ('NoGo') pathway is by nature inhibitory with the hypothesized purpose of preventing unwanted movements. Dopamine release inhibits neurons

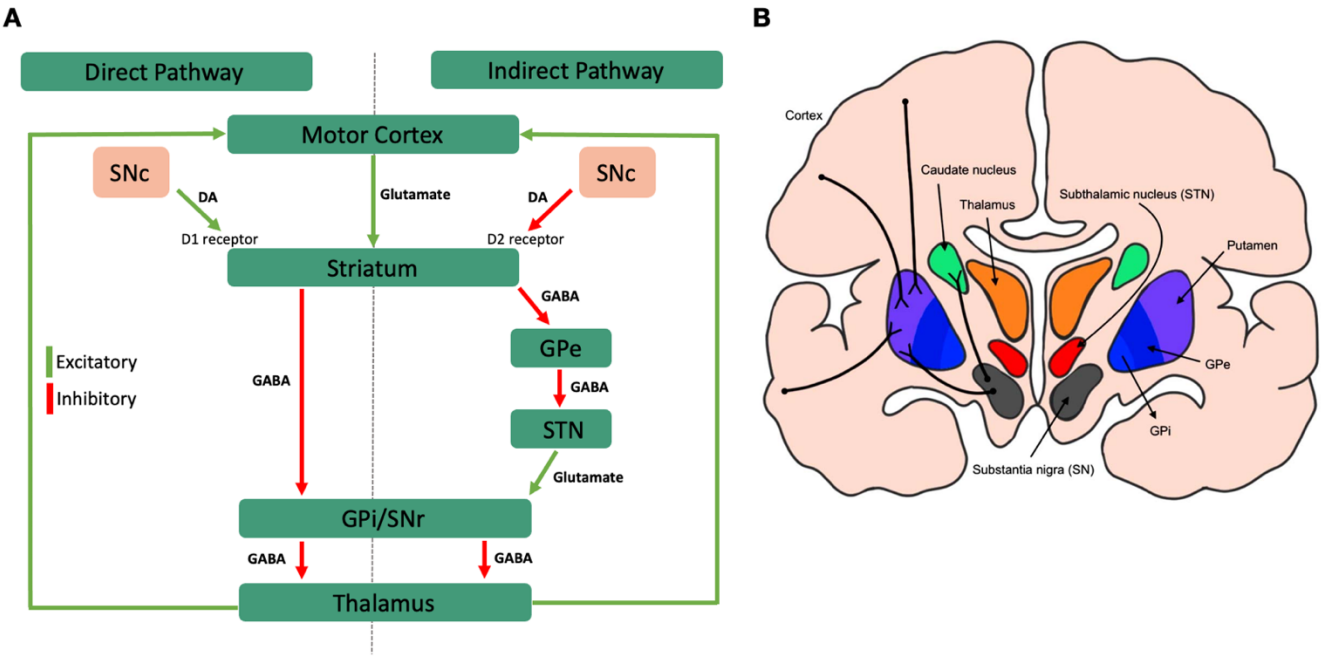

Figure 1.5. Basal ganglia direct and indirect pathways. (A) Model of direct and indirect basal ganglia pathways. SNc = substantia nigra pars compacta; GPe = globus pallidus external; GPi = globus pallidus internal; SNr = substantia nigra pars reticularis. In the direct pathway, dopamine activates medium spiny neurons (MSNs) in the striatum via excitatory D1 receptors, and therefore increases activity of this pathway, resulting in excitatory input into the cortex. By binding to inhibitory D2 receptors of the indirect pathway, dopamine decreases inhibitory activity in this pathway, again leading to excitation of the cortex via decreased inhibition of the thalamus. (B) Diagram of coronal section of basal ganglia nuclei. Image from Aum & Tierney[5].

in the indirect pathway, thereby ultimately leading to disinhibition of the thalamus and cortex, and again resulting in facilitation of movement. Underactivity in the direct- in combination with overactivity in the indirect pathways resulting from a hypodopaminergic state (e.g., as seen in PD), for instance is linked to motor symptoms such as bradykinesia or muscle stiffness. More recently, these two pathways have also been associated with the modulation of cognitive function (e.g., see [135,136], discussed in more detail in Chapter six).

1.3.3. Dopamine receptors and psychopharmacological manipulation of dopamine function

Dopamine function is mediated by five distinct subtypes of G protein-coupled receptors named D1 to D5. These five subtypes can further be divided into two major sub-classes with distinct pharmacological properties: D1-like (D1 & D5; hereafter: *D1 receptors*) and D2-like receptors (D2, D3, D4; hereafter: *D2 receptors*)[137]. D1 receptors are exclusively expressed post-synaptically on dopamine-receptive cells in the striatum, olfactory bulb and cerebral cortex, as well as hippocampus and amygdala. D2 receptors are inhibitory in nature and found at highest densities in the striatum, nucleus accumbens and olfactory tubercle, and in lower densities in the amygdala, hippocampus, hypothalamus and cortical regions (e.g., [138]). While the majority of D2 receptors are found postsynaptically on non-dopamine neurons (i.e., *heteroreceptors*), D2 receptors are also located on the presynaptic terminals of dopamine neurons. These so-called *autoreceptors* act as feedback regulators by decreasing both excitability of dopamine neurons and dopamine release upon activation[139].

Dopamine receptors, in particular D2 receptors, are the primary targets of pharmacological interventions for various neurodegenerative and psychiatric conditions. For instance, most clinically effective antipsychotics are D2 receptor antagonists, suggesting a critical role of this receptor subtype in the pathogenesis of schizophrenia[140-142]. However, the dopaminergic action of agents targeting D2 receptors depends on numerous factors, such as the local ratio of hetero- to autoreceptors[143] and drug dose[135]: Because D2 autoreceptors are presumed to be abundant in the striatum[144], and generally activated at lower doses than heteroreceptors, the same dopamine antagonist can lead to increased dopamine function at low (through the primary blocking of autoreceptors), and to decreased signaling at higher doses. For instance, D2 antagonists, which are used in schizophrenia primarily for their capacity to

decrease tonic dopamine transmission have been observed to lead to *increased* levels of dopamine at low doses (e.g., haloperidol[135]).

1.4. The relationship between motor function and social cognition in clinical populations – two different cases

1.4.1. The case of autism

Autism Spectrum Disorder is a heterogenous neurodevelopmental condition characterized by difficulties in social interaction and communication, as well as restricted, repetitive and stereotyped behaviors and interests[145]. In particular, autistic individuals' social-cognitive functioning has received considerable attention, with an extensive literature attesting to performance differences between autistic and control participants in a variety of ToM and social-cognitive tasks. However, a growing body of work has additionally noted motor abnormalities in this condition and several studies have established links between socio-cognitive and motor symptoms. To provide further insight into the precise relationships between social and motor function, in the following section, I expand on findings regarding social and motor function in ASD and elaborate evidence for putative social-motor links in this condition.

With regard to ToM, differences compared to controls have been reported for autistic individuals in the ability to detect white lies, figures of speech or misunderstandings (e.g., Strange Stories test[64]), detect social faux pas (Faux Pas task[43]), attribute false beliefs (e.g., Sally-Anne task[63]) and infer actors' affective and mental states from short video clips of interacting triangles (e.g., Frith-Happé animations[42]) or people (Movie for the Assessment of Social Cognition [MASC][146]). Furthermore, autistic individuals have been shown to exhibit

differences in the ability to infer emotions, mental states or intentions from both static and dynamic stimuli, depicting just the eye region of a face[44], facial expressions[147-149] and bodily postures[150], as well as body movement[151-153]. In addition, a number of studies point to impairments in the recognition of biological motion, evidenced for instance by reduced ability to discriminate natural from unnatural arm movements[154], and reduced sensitivity to human motion in point-light displays[155].

Although first observations of movement atypicalities in ASD have already been noted by Kanner[156] and Asperger[157], much of the autism literature to date has focused on social impairments. In the recent years, however, atypical motor function in this condition has received growing attention. Retrospective analyses indicate that motor abnormalities are evident in children diagnosed with or at high risk of autism from early infancy on and can emerge before social and linguistic impairments. Motor atypicalities in infants include delays in gross-[158] and fine[159] motor development, abnormal muscle tone[160], postural asymmetries[161] and gait abnormalities[162]. Research suggests that these impairments tend to persist into adulthood, with a meta-analysis reporting persistent deficits in ASD in motor coordination, gait, upper limb movement, and postural stability across three age groups[163]. Furthermore, atypical eye movements[164,165], as well as differences in emotional facial expressions[166,167] have also been found in autistic individuals. Thus, despite the relative paucity in empirical research on motor dysfunctions in ASD, prevailing evidence for motor abnormalities has sparked calls to treat motor symptoms as a 'core' feature of this condition[163,168], as well as proposals to use motor signatures as a biomarker for the identification of ASD[168,169].

In sum, there is ample evidence that autistic individuals exhibit atypical movements from early on in life, and that these atypicalities span a variety of gross- and fine motor behaviors. If it is true that we build action models based on experiences with our own actions,

it is likely that autistic people have atypical action models, built from a lifetime of experience with their own, atypical actions. Consequently, they may struggle to interpret the actions of non-autistic people due to a lack of familiarity with the observed movement. It would follow from this, that individuals with systemic motor atypicalities show stronger impairments in the social domain.

Evidence for a link between social and motor symptoms within ASD comes from developmental longitudinal studies as well as experimental research. For instance, in toddlers at high risk of ASD, delays in motor development at 18 months of age were predictive of a diagnosis of ASD at 36 months[170]. Likewise, in newly diagnosed children, better performance in motor tasks at 2 years was the strongest predictor of loss of diagnosis at age 4[171]. Furthermore, in older children of 6 to 15 years, motor skills have been shown to predict social communicative skills[172].

In an experimental study by Cook et al.[173], autistic and control participants were asked to perform sinusoidal ('waving') arm movements, while their movement kinematics were recorded using motion tracking technology. Subsequently, participants performed a perception task where they were required to classify the movements of a human hand as 'natural' or 'unnatural'. Results showed that the movements produced by autistic participants were characterized by atypically high velocity, acceleration and jerk (i.e., the rate of changes in acceleration and deceleration). What is more, the magnitude of the kinematic atypicalities was positively correlated with a bias towards perceiving biological motion as 'unnatural', as well as autism symptom severity as measured by the Autism Diagnostic Observation Schedule (ADOS-2[174]).

The observation that participants with more atypical movement patterns tended to judge 'typical' movements as unnatural further suggests that autistic participants, like the non-autistic

participants in Edey et al.[2] (who judged others' emotional walks on the basis of their own neutral walking speeds), model observed movements on the basis of their own actions. That is, autistic individuals' internal representations of 'natural' movements may be based on their visual and proprioceptive experience with their own movements, and therefore deviate from what a non-autistic person would constitute as 'natural'. Consequently, the more different the observed movement kinematics are to their own, the less they would spark characterizations as 'natural'. In sum, a number of studies provide support for the idea that that social and motor performance may be linked in ASD.

However, the few existing longitudinal and experimental studies bridging social and motor atypicalities in ASD rely on correlational analyses, thus provide no insight into the direction of the relationship between social and motor function. Although from the evidence discussed it might seem obvious that motor difficulties are causing social dysfunctions, indeed it is possible that abnormal social development precedes atypical motor development in ASD. For example, decreased attention to social movement cues in early life[175] might result in reduced imitation of others' actions and consequently to suboptimal motor learning[176]. What is more, observed relationships between social and motor function may not be causally related at all; it may be that a third, hidden variable influences both functions independently. Finally, even if there is a true causal relationship between social and motor abnormalities in ASD, little is known about the underlying neural and biochemical processes that cause the observed behavioral co-occurences.

Alongside many other neurochemical modulators of brain function proposed to be implicated in the pathophysiology of ASD (e.g., gamma-aminobutyric acid [GABA][177], serotonin[178], oxytocin[179]), dopamine has emerged as another candidate neurotransmitter linked to the condition's etiology. Evidence for altered dopaminergic function in ASD comes from a

number of mouse models, gene studies and molecular imaging studies, as well as from the observation that dopaminergic medication alleviates some of the behavioral presentations of the condition. For instance, atypical antipsychotics (the majority of which are dopamine D2 receptor antagonists) are among the most frequently prescribed medications to autistic individuals[180] and have been shown effective in reducing symptoms such as hyperactivity, aggression, repetitive behaviors, or social withdrawal[181]. In mouse models of autism, administration of dopamine *agonists* have *increased* repetitive and stereotyped behaviors[182] (viewed as proxy measures of ASD), while dopamine *antagonists* have been shown to *reduce* these behaviors[183]. Furthermore, optogenetic stimulation of dopaminergic neurons in the ventral tegmental area (VTA) lead to increased time spent in social interaction[184]. A handful of studies have investigated in vivo dopamine transmission in autistic subjects by use of positron emission tomography (PET) in combination with radioactive tracers that bind to dopamine receptors (such as fluorine-18-labelled fluorodopa [FDOPA]). Two studies report abnormal dopamine function in autistic subjects, including decreased presynaptic dopamine activity in the mPFC in autistic children[185] and increased presynaptic dopamine function in the striatum of autistic adults[186] (though note a recent study reporting no differences in striatal dopamine synthesis capacity between autistic and non-autistic adults[187]).

Based primarily on evidence from mouse models and drug trials, a recent theoretical account proposes two distinct routes via which aberrant dopaminergic signaling could lead to ASD-like behaviors[54]: According to this account, dysfunctions in the meso-corticolimbic pathway may lead to autistic individuals experiencing social interactions as less rewarding, thereby affecting the development of social abilities. In addition, stereotyped and repetitive behaviors are proposed to arise from dysfunctional nigrostriatal projections, due to their suggested role in mediating goal-directed actions. Thus, this 'dopamine hypothesis of ASD'

suggests that dysfunctions in two discrete dopaminergic pathways independently contribute to the emergence of social and motor symptoms in ASD. Indeed, parkinsonian symptoms have been observed at elevated rates in ASD (e.g., bradykinesia, other gait abnormalities, handwriting[188]), strengthening the case for a role of the nigrostriatal dopaminergic pathway in the etiology of motor symptoms in ASD. However, at present much less is known about the involvement of the meso-corticolimbic pathway in socio-cognitive atypicalities in ASD; furthermore, empirical evidence on dopaminergic dysfunctions in ASD is too limited to fully support the two-pathway account of autism (e.g., low consensus among molecular imaging studies). Given evidence on the influence of own action experiences on internal state inferences, an alternative role of dopamine in the relationship between social and motor symptoms in ASD is plausible: Dopaminergic imbalances in ASD may disrupt individuals' motor function, resulting in atypical action models, which in turn lead to socio-cognitive impairments. Chapters three and four of this thesis explore the mechanistic pathways via which dopamine may affect both socio-cognitive and motor functioning in populations like ASD by administering the dopamine antagonist haloperidol to healthy volunteers.

1.4.2. The case of Parkinson's

Parkinson's disease is a neurodegenerative disorder where progressive loss of dopaminergic neurons in the SNc leads to the cardinal motor features bradykinesia, rigidity, resting tremor and postural imbalances. Secondary motor symptoms include hypomimia (reduced voluntary or spontaneous facial expressions), micrographia (abnormally small, cramped handwriting), shuffling gait, and dystonia[189]. Motor symptoms in this disease typically set on in late adult life to old age (median onset age = 60 years), and progressively worsen over time[190]. Whilst the etiology of PD is presumed to be multifactorial (with proposed involvement

of noradrenergic, glutamatergic, serotonergic and adenosine pathways), the cardinal motor impairments in this condition have been primarily ascribed to the degeneration of nigrostriatal dopamine neurons[191], most effectively treated with levodopa, a dopamine precursor[190].

In addition to motor symptoms, PD is accompanied by a range of non-motor symptoms, comprising autonomic and gastrointestinal dysfunctions, sleep disorders and mood disorders (amongst others), some of which occur before onset of motor symptoms[192]. Furthermore, cognitive impairments are common and range from mild (e.g., affecting executive dysfunctions, such as working memory), to severe (dementia)[193]. Although not classically listed alongside non-motor symptoms, there is increasing evidence that socio-cognitive deficits are prevalent in PD. For example, while emphasizing high variability of results, a meta-analysis[194] and a recent review[195] suggest deficits in facial emotion recognition in PD, with evidence pointing towards a greater deficit for negative, relative to positive emotions. Highly variable findings, with some studies not reporting any differences in emotion recognition between PD patients and controls, have been attributed to confounding factors such as pathological heterogeneity, disease severity, psychiatric comorbidities, or dopaminergic medication.

Furthermore, PD patients have been shown to exhibit lower performance than controls in various tasks of ToM, signaling impairments in attributing internal states to pictures of eyes (RMET, e.g.,[196,197]) or to agents of naturalistic stories (Happé stories, e.g.,[198,199]), in identifying social faux-pas (faux-pas test, e.g.,[196,199]), and in attributing (false) beliefs (e.g.,[200,201]). A meta-analysis confirms a significant impairment in PD patients across cognitive and affective measures of ToM[202].

Whilst the dopaminergic involvement in motor dysfunctions in PD is well-established, much less is known about the role of dopamine depletion in socio-cognitive deficits in this condition. Although few studies to date have directly investigated the effect of dopaminergic

medication on emotion recognition in PD, there is evidence for a restorative effect of dopamine replacement therapy (DRT) on neuroscientific markers of emotion processing (e.g., amygdala activity[203]; N170 event related potential[204]) and on emotion recognition performance[205,206]. Intriguingly, however, in the early stages of PD, levodopa administration has been observed to result in reduced amygdala activation[207] as well as impaired emotion recognition performance (with particular deficits in anger recognition[208]). This observation has been proposed to reflect overdose effects of DRT on emotion processing[195], which were ascribed to the meso-corticolimbic pathway being relatively unaffected by dopaminergic depletion in the early stages of the disease[209,210]. Further evidence for an involvement of the meso-corticolimbic pathway in emotion recognition in PD comes from a study of a sample with juvenile parkinsonism, where patients exhibited more severe depletion of the nigrostriatal, relative to the meso-corticolimbic pathway[211]. In this study, authors failed to find differences in emotion recognition performance between patients and controls.

Dopaminergic pathways have been further hypothesized to be implicated in ToM deficits in PD. It has been suggested that the sequential occurrence of cognitive and affective ToM impairments in PD reflects the differential involvement of different parts of the striatum[212]. In early disease stages, where the dorsal striatum is more severely affected than the ventral striatum, patients appear to exclusively show deficits in cognitive ToM. In contrast, impairments in affective ToM tend to occur as the disease progresses and are associated with depletions in the ventral striatum.

In sum, evidence is suggestive of socio-cognitive deficits in PD, including impairments in emotion recognition and cognitive and affective ToM. Moreover, severity and domain of impairments appear to depend on disease stage and have been associated with dopamine dysfunction in nigrostriatal and mesco-corticolimbic systems. However, it is possible that

dopamine does not directly influence socio-cognitive processes in PD. In fact, a number of studies failed to establish a link between DRT and emotion recognition performance in PD[195]. Rather than directly modulate, dopamine may affect emotion recognition indirectly, for example by affecting patients' movements, which in turn may alter or disrupt internal motor representations associated with affective states. Although the evidence is not fully conclusive and may depend on sensitivity of the diagnostic scale used, several studies report a link between motor symptom severity and emotion recognition ability, supporting a possible role of motor function in emotion perception processes in PD[213-216]. For instance, Marneweck et al. reported positive correlations between patients' ability to discriminate and recognize emotional facial expressions and the degree to which they were able to voluntarily control their facial muscles. More importantly, these effects were found to be independent of disease severity and selective towards emotion recognition, as patients' ability to recognize and discriminate facial identity was not related to motor dysfunctions, indicating a specific role of motor simulation in emotion recognition. At present it is unclear, however, whether PD patients exhibit socio-cognitive deficits before, simultaneous with, or after onset of motor symptoms. If, as previously hypothesized, internal action models built on individuals' own motor experiences contribute to the understanding of observed actions, it is possible that PD patients at early disease stages still benefit from a lifetime of experiences with typical actions, and that difficulties in action understanding arise only later, after gradual change of internal action representations. Indeed, in support of this idea, a range of studies report relatively spared socio-cognitive functioning alongside impaired motor function in early-stage PD patients[196,211,217]. However, in studies claiming to use more sensitive measures of socio-cognitive function, difference to controls were also found in PD patients at early disease stages[199,218]. Thus, whether motor symptoms precede socio-cognitive symptoms in PD is currently not fully established. Chapters three and four

discuss evidence in support of early socio-cognitive impairments in PD alongside spared internal action models. Chapter six elucidates possible mechanistic pathways via which dopamine dysfunctions may affect social understanding independent of motor function.

1.4.3. Dopamine as a key player in mechanisms underlying symptomatic commonalities between Parkinson's disease and autism spectrum disorders?

Intriguingly, a large number of motor and social dysfunctions seen in PD and ASD are strikingly similar. For example, autistic individuals exhibit difficulties in movement initiation[121,219], which is a cardinal motor feature of Parkinson's[220]. Further shared motor abnormalities affect postural control (e.g., ASD[221,222], PD[223]) and handwriting (e.g., ASD[224,225], PD[226]). This overlap in motor difficulties, as well as indications of genetic overlaps (e.g., in the Park2 gene[227]) between ASD and PD, are potentially responsible for increased rates of diagnoses of parkinsonism in older autistic individuals (20% across the whole ASD sample)[228]. Furthermore, both populations exhibit difficulties in attributing and reasoning about internal states in a variety of socio-cognitive tasks (e.g., ASD[43,64], PD[196,199]). With dopaminergic processes confirmed to be implicated in motor dysfunction in PD, symptomatic commonalities between the two conditions may hint at dopamine as a key contributor to social and motor dysfunctions. As previously outlined, it is conceivable, that dopamine dysfunction primarily affects individuals' motor function, which in turn may impact upon their social abilities. Motor abnormalities may lead to dysfunctional social interactions in two ways: On the one hand, in both ASD and later-stage PD patients, extended time of visuo-motor experiences with atypical movements could lead to atypical action models, potentially resulting in activation of inappropriate internal state representations upon observing others' actions and thus leading individuals to draw inaccurate inferences about others' internal states. On the other hand, it may

be that short-term disruption of motor function acutely affects the internal state representations associated with mirrored actions which might interfere with long-term internal action models. In other words, if low dopaminergic tone slows down an individual's movements but leaves their mood unaffected, that person might now associate slower movements with a neutral affective state, which would contradict their original internal action model (wherein slow speed was associated with sad mood). This interference may result in a bias in judgements towards the current association between movement speed and internal state, or alternatively in more general inference errors. Importantly, whereas the former hypothesis would predict socio-cognitive deficits in PD patients only at later stages of the disease, the latter hypothesis would be in line with early-stage impairments in socio-cognitive ability in PD. Due to the acute nature of the dopaminergic manipulation employed in the following studies, the present thesis is suitable to test the latter question, but no inferences about any potential long-term influences of aberrant dopamine function on socio-cognitive function can be made. Furthermore, it is conceivable that conditions with dopaminergic dysfunctions show co-occurring motor and social symptoms as a function of the same underlying domain-general processes. For instance, predictive coding accounts provide a unifying model for both action understanding and action production[229], and predictive processing has been argued to be aberrant in PD[230], ASD[231], as well as schizophrenia[124]. Finally, it is possible that dopamine affects domain-specific processes underlying social and motor functions independently, via separate neural pathways.

Lastly, socio-cognitive impairments in conditions like PD or ASD could not be associated with dopaminergic dysfunction at all, but instead stem from psychological or psychosocial changes patients experience with ongoing disease severity. For example, motor symptoms such as reduced facial expressiveness or dystonia can lead to PD patients being judged as hostile, less sociable or less cognitively competent[232,233]. This could in turn lead to

social withdrawal, and ultimately to decline of cognitive resources which may be necessary for social interaction. Moreover, conditions like PD, HD or ASD exhibit high levels of co-morbid mood disorders[234,235], and mood is known to affect emotion perception processes[236,237]. Thus, various other processes are possible that may lead to a coincidental co-occurrence of socio-cognitive and motor processes in the discussed clinical populations.

By means of investigating socio-cognitive and motor performance in healthy subjects after acute pharmacological challenge of dopamine using haloperidol, Chapters three and four of this thesis attempt to disentangle the contribution of dopaminergic processes to the relationship between social and motor function. Investigating dopaminergic modulation of motor and social processes in healthy subjects is advantageous for several reasons. First, acute dopaminergic challenge in healthy participants bears the potential to disentangle effects of short-term dopaminergic depletion from long-term effects of dysfunctional dopamine signaling typically observed in patients, furthermore it allows the investigation of dopaminergic effects on socio-cognitive and motor abilities isolated of potentially confounding psycho-social changes. Second, high functional and pathological heterogeneities within clinical populations can complicate inferences due to increased variance within those samples. Third, using healthy subjects allows the exploration of the dopaminergic modulation of certain functions without imposing on patients which may not tolerate long experimental studies very well due to a variety of co-morbid psychiatric and physical difficulties. Finally, Chapter six applies the empirical findings presented in this thesis to draw conclusions about the potential mechanisms via which dopamine system dysfunctions may affect socio-cognitive abilities in various clinical populations.

1.5. Summary

This chapter provided an overview on the existing literature on the expression of internal states in, and inference of internal states from body movement cues, as well as elucidating how similarity in movement between two interaction partners may lead to facilitated social interactions. Chapter one further summarized key knowledge on the neurophysiological processes via which dopamine affects cognition and behavior, as well as illustrating how dopamine system dysfunctions may lead to the co-occurrence of atypical social and motor function using the example of two clinical populations, ASD and PD. The primary question of this thesis concerns the role of the neurotransmitter dopamine in the co-occurrence of socio-cognitive and motor deficits. I address this question by investigating (1) how our own bodily actions and the similarity to others' actions influence our perception of others' affective and mental states, and (2) whether dopamine signaling has acute effects on social ability via its effects on motor performance.

To shed light on this question, Chapter two presents empirical evidence that individuals make use of a variety of kinematic and spatial cues to infer mental states from the movements of two triangles, and that similarity in those cues between an observer and agent promotes the accurate decoding of these movements. Thus, Chapter two sets the scene for the further investigation of dopamine's influence on movement and mental state attribution by confirming that movement similarity contributes to accurate mental state attribution. Following on, Chapter three investigates whether the effects of dopamine manipulation on motor function have cascading effects on participants' mental state attribution abilities by decreasing similarity between their and the triangle's movements. To anticipate, Chapter three provides evidence that pharmacological manipulation of dopamine has dissociable effects on motor and social function. Chapter four goes on to explore the role of dopamine in emotion recognition from

whole-body movement, adding further support for the idea that dopamine independently modulates motor ability and socio-cognitive performance whilst presenting hypotheses for possible underlying mechanisms. As the fourth empirical chapter, Chapter five addresses current methodological shortcomings of the emotion recognition literature, thereby providing important implications for the results demonstrated in Chapter four. Finally, Chapter six presents a synthesized discussion of all findings of this thesis, concluding that dopamine signaling has short-term effects on internal state inferences which are independent from its influence on motor function and likely reflect domain general processes. The chapter closes by proposing three candidate mechanistic pathways via which the dopamine system may independently modulate socio-cognitive function, discussing implications for clinical populations and by providing some directions for future research.

Chapter 2: Kinematics and observer-animator kinematic similarity predict mental state attribution from Heider-Simmel style animations

The Introduction outlined how two individuals who move distinctly different from each other, as might be for instance the case in a dyad of a non-autistic and an autistic person, may have difficulties in inferring each other's internal states. This may be specifically evident in situations where movement kinematics are the most obvious, or only, cues conveying information about underlying mental phenomena, such as in animations tasks. Edey and colleagues[1] have shown that two populations who on average move with significantly different levels of kinematic jerk have trouble attributing the correct mental states to videos of interacting triangles when these were created by the respective other group. These findings led the authors to speculate that the dissimilarities in jerk between the two groups were causally related to the observed performance differences. This chapter presents a study which tests whether movement jerk, and similarity in jerk between animator and observer, are predictive of mental state attribution performance in the animations task. In addition, other animation features which are potentially important in conveying mental state information are explored.

Publication 1:

Kinematics and observer-animator kinematic similarity predict mental state attribution from Heider-Simmel style animations

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Abstract

The ability to ascribe mental states, such as beliefs or desires to oneself and other individuals forms an integral part of everyday social interaction. Animations tasks, in which observers watch videos of interacting triangles, have been extensively used to test mental state attribution in a variety of clinical populations. Compared to control participants, individuals with clinical conditions such as autism typically offer less appropriate mental state descriptions of such videos. Recent research suggests that stimulus kinematics and movement similarity (between the video and the observer) may contribute to mental state attribution difficulties. Here we present a novel adaptation of the animations task, suitable to track and compare animation generator and -observer kinematics. Using this task and a population-derived stimulus database, we confirmed the hypotheses that an animation's jerk and jerk similarity between observer and animator significantly contribute to the correct identification of an animation. By employing random forest analysis to explore other stimulus characteristics, we reveal that other indices of movement similarity, including acceleration- and rotation-based similarity, also predict performance. Our results highlight the importance of movement similarity between observer and animator and raise new questions about reasons why some clinical populations exhibit difficulties with this task.

2.1. Introduction

Seminal work by Heider and Simmel[84] demonstrated that humans readily attribute mental states to two triangles moving around a rectangular enclosure. Since their inception in 1944 such "animations tasks" (also referred to as Frith-Happé Animations[42] and Social Attribution Task[85]) have grown dramatically in popularity and have been used in a wide variety of clinical populations, including autism spectrum disorder (ASD)[42,238], schizophrenia[87], antisocial personality disorder[239], Huntington's disease[46] and Tourette's syndrome[47]. Though animations tasks have been scored and administered in a number of ways (some studies count the number of mental state terms used to describe the movements of the triangles[42,238], other studies have asked participants to rate the type of interaction or the mental state word depicted in the animations[1,240]) it is generally agreed that "poor performance" indicates a problem with ascribing appropriate mental states to the triangles. We refer to this process here as 'mental state attribution'.

Though mental state attribution has been found to be atypical across a range of clinical populations, little is known about *why* some individuals struggle to attribute appropriate mental states to the triangles. One explanation is that individuals who struggle with the animations task would exhibit atypicalities in other tests of mental state attribution because of a deficit in the ability to attribute minds and ascribe appropriate mental states (i.e., Theory of Mind [ToM]). However, animations tasks tend to be more sensitive to mental state attribution difficulties compared to other tests, as shown by Abell et al.[42]. At present it is unclear why some individuals find this task particularly challenging.

A recent study highlights that kinematic similarities between the triangles' movements and the participant's own movements may influence performance in the animations task[1]. Edey and colleagues asked autistic ('condition-first' terminology is used in line with the majority

preference expressed in a survey of the autistic community[241]) and non-autistic participants to complete the animations task, and also to produce their own animations using triangles that could be moved around an enclosure with magnetic levers. In line with a growing literature concerning jerky body movements in autism[173,242-244], the authors found that animations produced by autistic individuals were more jerky (i.e. exhibited greater changes in acceleration and deceleration) than those produced by non-autistic individuals. Furthermore, whereas non-autistic participants could readily attribute mental states to animations created by other non-autistic participants, they had difficulties attributing mental states to the jerky animations that had been produced by the autistic participants. Conversely, autistic participants in Edey's study did not show improved performance when rating their own group's, relative to the control group's, animations. The authors proposed that *jerk similarity* significantly contributes to performance in the animations task: that is, non-autistic individuals were better able to correctly identify animations created by other non-autistic participants because the kinematic jerk in the videos was comparable to the amount of jerk they themselves would exhibit when moving the triangles. Autistic participants did not, however, benefit from jerk similarity because high variability in jerk present within this group led to a reduced number of animations sufficiently similar to facilitate mentalizing performance.

Although Edey et al.[1] inferred - on the basis that jerk differed between the ASD and control group - that jerk similarity was a likely contributor to animations task performance, they did not empirically demonstrate this to be the case. To test Edey et al.'s, hypothesis and better understand why some individuals struggle to attribute appropriate mental states in the animations task, the first aim of the current study was to test whether a significant amount of variance in performance in a Heider-Simmel style animations task would be accounted for by

the kinematic jerkiness of the animation and the *similarity* between the jerkiness of the animation and a participant's own movements.

Kinematic jerk and jerk similarity are not the only factors which plausibly influence performance in animations tasks. Previous studies have highlighted potential roles for stimulus features including the rotation of, and distance between, the triangles[245], and the shape of the triangles' trajectories[246]. For instance, Roux et al. documented highly distinguishable trajectory paths for random, goal-directed and mental state animations, thus suggesting that trajectory path may be an important cue that observers can use to attribute appropriate mental states. Furthermore, it is plausible that, in addition to jerk, other kinematic parameters such as speed and acceleration may predict performance. That is, beyond jerk similarity, *movement similarity* more generally may predict the accuracy of mental state attribution in the animations task. The proposal that movement similarity may affect performance in the animations task is bolstered by recent empirical work showing that observers more accurately estimate a human actor's underlying intentions when the trajectory of the actor's arm movements closely approximates the observer's own movements[247]. Furthermore, a role for movement similarity in mental state attribution is in line with theoretical accounts suggesting that inferences about others' actions are facilitated by mapping visual representations of these actions onto our own visual/motoric representations of the same actions[29,106,248,249], and is broadly consistent with simulation accounts of ToM which claim that one uses one's own mental processes to simulate others' mental states[250]. The movement similarity hypothesis would propose that mental state attribution difficulties in classic animations tasks may, at least in part, be explained by differences between the way the triangles are animated and the way an observer would move the triangles if required to create their own animation.

Correspondingly, the second aim of the current study was to explore the extent to which a range of other stimulus features (including trajectory shape, rotation of and distance between the triangles, and various indices of kinematics) influence the ease with which participants correctly attribute a mental state to an animation. By doing so, we shed light on a multiplicity of factors which may explain why some clinical groups find the animations task so challenging.

For this latter analysis we made use of the fact that, similar to a sound wave, a triangle's trajectory comprises a complex wave and thus can be decomposed with Fourier transform and represented as spectral density (i.e., energy) in different frequency bands[251]. In other words, Fourier transform can be used to characterize the shape of a trajectory. For example, a trajectory which approximately follows an elliptical orbit oscillates in speed and curvature twice during every full rotation and consequently would be characterized by high spectral density in a band centered around an angular frequency of two. Adapting a method developed by Huh & Sejnowski, we explored whether there are particular angular frequency bands which differentiate mocking, seducing, surprising, following and fighting animations and whether spectral density in these bands is predictive of accuracy.

Currently available animations task stimulus sets are not suitable to test our hypotheses regarding jerk, jerk similarity and movement similarity for two reasons: First, having been created by experimenters or graphic designers, the stimuli in these tasks typically represent a narrow range of kinematics and thus lack the variation necessary for quantifying the contribution of kinematics and other stimulus features to performance. Second, tasks to date offer no option to track animator (or observer) kinematics at sufficient sampling rates to reliably make inferences about the role of jerk/movement similarity. Here we created a novel Heider-Simmel style animations database (available upon request) by asking 51 members of the general population to animate two triangles to depict mental- (mocking, seducing, surprising) and non-

mental- (following, fighting) state interactions on a 133 Hz touch screen device. The distinction between mental and non-mental states, and the choice of individual words used within these conditions, was based on the ToM and Goal-Directed conditions used in the original Frith-Happé animations[42]. That is, ToM animations depict "[…] one character reacting to the other character's mental state […]" whereas Goal-Directed animations represent "[…] reciprocal interaction, but no implication that one character was reading the other's 'mind'" (p. 5). This distinction has since been widely used across the literature[1,238,240]. Following database creation, an independent sample of 37 members of the general population watched a selection of videos from our new database. To ensure that participants were exposed to a wide range of kinematics, they watched 8 exemplars for each word, ranging from slow to fast speed. Participants rated the extent to which each animation depicted the words mocking, seducing, surprising, following and fighting, in addition to also creating their own animation for each word (Fig. 1). In a four-step analysis procedure, we first used Bayesian mixed effects models to test our hypotheses that kinematic jerk and the similarity in jerk between observer and animator are significant predictors of the accuracy of mental state attributions (*confirmatory analysis*). In a second step, we used Fast Fourier Transform (FFT) combined with bootstrapped F-tests to investigate whether mocking, seducing, surprising, following and fighting animations could be reliably distinguished according to their profile of spectral density across a range of frequency bands (*exploratory analysis 1*). Thus, enabling us to identify potential differences in trajectory shape between animations of different words. In a further exploratory analysis, we employed a random forest procedure to determine the relative contribution to accuracy of a multiplicity of factors including speed, acceleration, jerk, the amount of simultaneous movement of both triangles, the relative distance between triangles, triangles' average rotation and trajectory shape as indexed by the magnitude of spectral density in the frequency bands identified in the

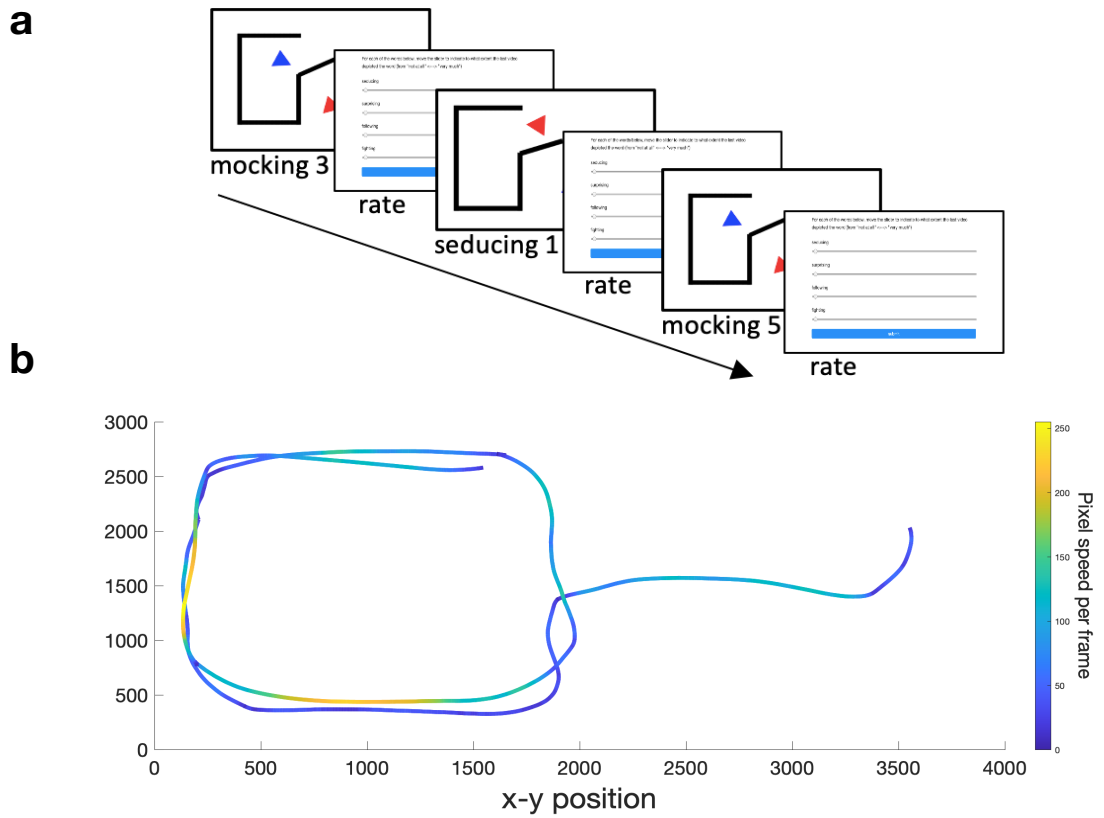

Figure 1. (a) Schematic depiction of three successive trials in the animations task. 37 participants watched videos from the database and rated the extent to which each video depicted mocking, seducing, surprising, following, or fighting. (b) Example trajectory of an animation stimulus. Each participant used a touchscreen device to create their own triangles animations.[4] For each animation (both observed and generated by participants) we calculated *jerk* as the mean of the third order non-null derivative of the raw positional data across all frames, jerk similarity was calculated as the difference in mean jerk between an animation stimulus and the participant's own animation of the same word (*jerk difference*). Depicted is an example of a *following* animation (one triangle's trajectory).

second analysis step (*exploratory analysis 2)*. Finally, in *exploratory analysis 3* we take the top three predictors from exploratory analysis 2 and use these to calculate novel indices of movement similarity; Bayesian mixed effects models are employed to test whether these novel indices are significant predictors of animations task performance.

[4] For a more detailed description of triangle movements and more examples of trajectories please see Appendix 1.1

2.2. Results

Accuracy for each trial was calculated by subtracting the mean rating for all non-target words from the rating for the target word (e.g., the target word was *seducing* on trials where the participant watched a video wherein the original animator had attempted to depict the triangles seducing each other). Consequently, a high, positive accuracy score for a seducing animation indicates that an observer rated this animation as depicting seducing to a higher extent than mocking, surprising, following or fighting. For a comparison of mean accuracy scores for each word category see Supplementary Materials [Appendix 1]. For each video that participants observed and for each animation that they created themselves, mean jerk magnitude (hereafter: *jerk*) was obtained by taking the third order non-null derivatives of the raw positional data and calculating the mean across all frames in the video. Jerk similarity was calculated as the difference in mean jerk between an animation stimulus and the participant's own animation of the same word (hereafter: *jerk difference*), where lower difference values indicate higher jerk similarity (see **Methods: Data Analysis and Processing**).

Mental state animations are rated less accurately than non-mental state animations

A Bayesian linear mixed effects model with the maximal random effects structure allowed by the design[252] was fitted to jerk, jerk difference (lower values reflect higher jerk similarity) and the dummy-coded factor *mental state* (mental state [seducing, surprising, mocking] versus non-mental state [following, fighting]) as well as their three-way interaction. Random intercepts were fitted for *animation ID* (unique identifier for each animation) and *subject ID;* random slopes were fitted for the interaction between jerk and mental state varying by *animation ID* and jerk difference varying by *subject ID*. For all relevant model parameters, we report expected values (E_μ) under the posterior distribution and their 95% credible intervals

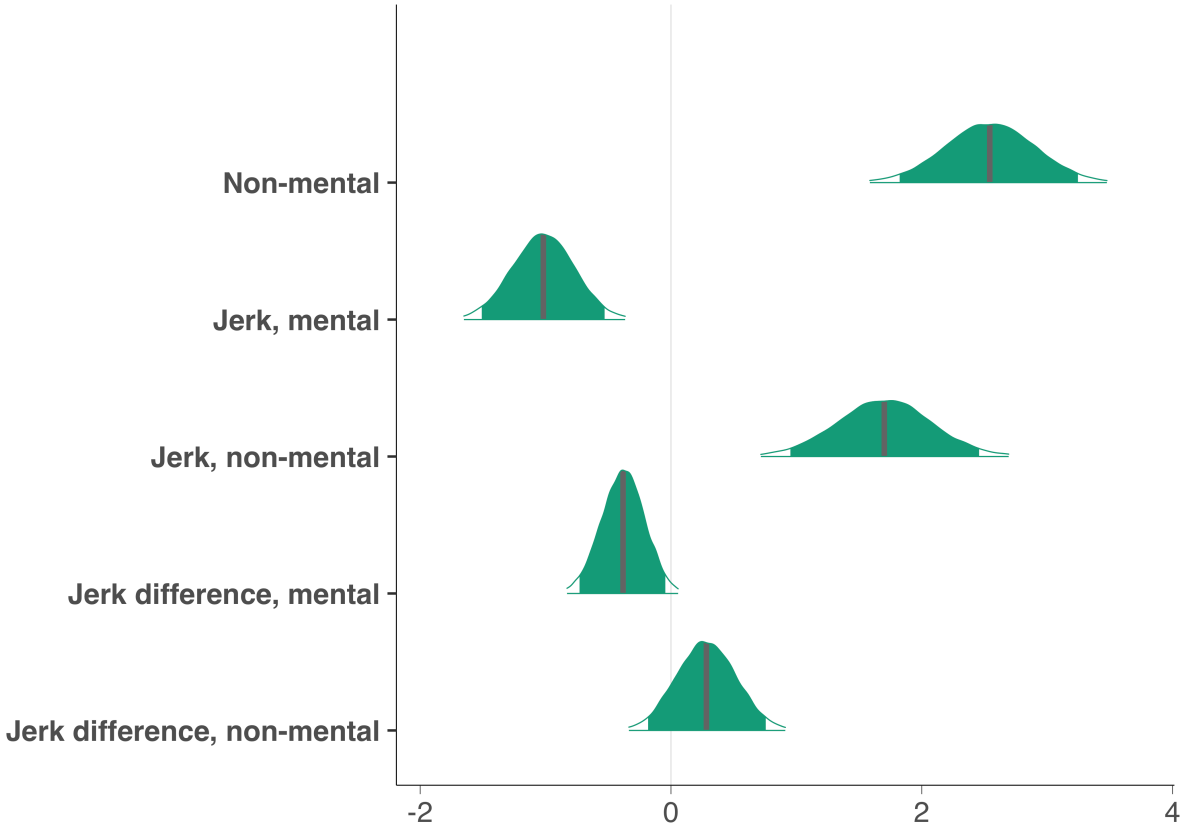

Figure 2. Posterior probabilities of model parameters predicting accuracy. Filled green areas represent 95% credible Intervals around parameter estimates. Grey lines represent means of parameter estimates.

(CrIs)[253], as well as the posterior probability that an effect is different to zero ($P(E_\mu < 0)$ / $P(E_\mu > 0)$). In line with Franke & Roettger[254], if a hypothesis states that an effect $E_\mu \neq 0$ (e.g. effect of jerk similarity on accuracy), we conclude there is compelling evidence for this effect if zero is not included in the 95% CrI of E_μ and if the posterior probability P($E_\mu \neq 0$) is close to 1. The model indicated that accuracy was higher in non-mental state videos relative to mental state videos ($E\mu_{mentalVSnon-mental}$ = 2.54, CrI= [1.81, 3.28]), with the posterior probability that the difference is larger than zero being P($E\mu_{non-mental} > 0$) = 1 (see Fig. 2 for prior and posterior distributions of all estimated parameters).

Jerk affects performance differently for mental- and non-mental state animations

In line with our hypothesis, accuracy was associated with mean jerk, furthermore jerk interacted with mental state: For mental state animations, lower mean jerk was associated with higher accuracy ($E\mu_{jerk,mental}$ = -1.03, CrI = [-1.52, -0.53]), whereas in non-mental state animations higher mean jerk led to higher accuracy scores ($E\mu_{jerk,mentalVSnon-mental}$ = 1.65, CrI = [0.88, 2.41]). Thus, while mental state animations with mean jerk values 1 standard deviation (SD) above the (mental state condition) mean were rated 1.03 points less accurately (compared to a mental state video with a mean jerk value), non-mental state animations with jerk values 1 SD above the (mental state condition) mean were rated 0.62 points more accurately ($E\mu_{jerk,mental} + E\mu_{jerk,mentalVSnon-mental} =$ – 1.03 + 1.65). Since the posterior probabilities for both effects (P($E\mu_{jerk,non-mental} > 0$), P($E\mu_{jerk,mental} < 0$)) were in fact 1, we conclude that, given our model and the data, there is compelling evidence in favor of our hypothesis that an animations' jerk impacts mental state attribution performance in the animations task. To probe whether such effects varied as a function of the word depicted in the video, we conducted separate exploratory models for non-mental state and mental state animations for which we included *word category* (non-mental state: following, fighting; mental state: mocking, seducing, surprising) as a predictor in addition to jerk and jerk difference. These models revealed that, for non-mental state animations there was a strong positive effect of jerk for fighting, but not following, animations ($E\mu_{jerk,fighting}$ = 1.88, CrI = [0.67, 3.11], P($E\mu_{jerk,fighting} > 0$) = 1; $E\mu_{jerk,following}$ = 0.30, CrI = [-0.30, 1.05]). For mental state animations, the overall negative effect of jerk was driven by a tendency towards a negative effect of jerk on accuracy in mocking and surprising animations ($E\mu_{jerk,mocking}$ = -0.58, CrI = [-1.56, 0.40]; $E\mu_{jerk,surprising}$ = -0.94, CrI = [-2.69, 0.76]). There was no effect of jerk in seducing animations ($E\mu_{jerk,seducing}$ = 0.26, CrI = [-1.40, 1.85]).

Higher observer-animator similarity in jerk is associated with higher accuracy

In line with our hypothesis, accuracy was also associated with jerk difference. The model revealed a negative relationship between jerk difference and accuracy for mental state animations ($E\mu_{jerkDiff,mental}$ = -0.38, CrI = [-0.72, -0.03]; P($E\mu_{jerkDiff,mental} < 0$) = 0.98). Jerk difference did not affect accuracy differently in non-mental state animations, indicated by high uncertainty surrounding the coefficient for the contrast of mental state and non-mental state ($E\mu_{jerkDiff,mentalVSnon-mental}$ = 0.25, CrI = [-0.27, 0.76]). Thus, jerk difference had a negative effect on accuracy in both mental- and non-mental state animations. Consequently, higher jerk similarity was associated with higher accuracy. To probe whether such effects varied as a function of word category we conducted an exploratory mixed model which included the word categories mocking, seducing and surprising. This model revealed that the negative main effect of jerk difference was mainly driven by mocking animations ($E\mu_{jerkDiff,mocking}$= -0.70, CrI = [-1.22, -0.18]; P ($E\mu_{jerkDiff,mocking} < 0$) = 0.99; $E\mu_{jerkDiff,seducing}$= 0.98, CrI = [-0.49, 2.46]; $E\mu_{jerkDiff,surprising}$= 0.63, CrI = [-0.29, 1.52]).

A combination of ten kinematic and spatial variables best predicts accuracy in the animations task

In order to explore the relative importance of trajectory path alongside a variety of other stimulus features, we first identified which components of triangle trajectories can reliably distinguish between the five target words (i.e., mocking, seducing, surprising, following, fighting). For this we used FFT to decompose the triangles' trajectories and represent them as an amplitude spectral density profile across a range of angular frequencies. We then employed bootstrapped F-tests (with 1000 boots) to identify angular frequency "bins" wherein spectral density significantly differs between the five target words (see Methods: Data Analysis and

Processing). We reasoned that these bins contain signal that participants may be using in the mental state attribution task. This analysis revealed nine significant clusters, defined as clusters of difference that occurred in less than 5% of comparisons with resampled distributions (see Figure 3A).

To examine whether spectral density in these nine frequency clusters was predictive of accuracy we used the maxima and minima of each significant cluster as bin edges and calculated the *angular frequency spectral density (AFSD)* as the area under the curve between the bin edges (cluster bin edges: 0.21 – 1.49, 1.61 – 2.39, 2.64 – 2.87, 3.04 – 3.40, 3.91 – 4.27, 4.79-5.19, 6.19-6.68, 7.6-7.93, 8.75-10). AFSD in the nine bins refers to the relative amount of specific trajectory components (i.e., "shapes") present in each animation. That is, an animation that predominantly features elliptical trajectory components would be characterized by high AFSD in a band centered around an angular frequency of two (i.e., bin 2 which covers angular frequencies from 1.61 to 2.39).

The relative contribution to accuracy of the presence of these trajectory components was then assessed, alongside a selection of other kinematic and spatial variables, which were chosen based on indications in previous literature for their putative role in mental state attribution[245,246]. For this purpose, mental-state, speed, acceleration magnitude (hereafter: *acceleration*), jerk, *simultaneous movement*, *relative distance* and *mean rotation* were entered into a random forest model[255] using the *Boruta*[256] wrapper algorithm (version 7.7.0). Boruta trains a random forest regression model on all variables as well as their permuted copies - so called "shadow features" - and classes a variable as *important* when its permutation importance is significantly higher than the highest permutation importance of a shadow feature (for more details see Methods: Exploratory analysis). Note that because this analysis technique does not account for random effects, values corresponding to the same animation were averaged across participants, this

permits indices such as jerk and acceleration which are features of a particular animation but excludes jerk difference which depends on the relation between an animation and an individual participant.

Out of all 16 variables tested, 10 were confirmed *important*, two were confirmed *unimportant*, and four were classed as *tentative* on the basis that their permutation importance was not significantly different from the maximal importance of a shadow feature (see Fig 4). Fig 4 illustrates that the important role of mental-state and jerk in predicting accuracy is confirmed by the random forest model, with mean importances of 16.0 and 7.82 respectively. However, the model identifies a third variable as even more important than jerk: mean rotation (mean importance = 11.78). In addition, an animation's acceleration and speed, AFSD in bins 1, 6, 9 and 8, as well as the amount of simultaneous movement of both triangles notably contribute to explaining performance in the animations task (mean importances: acceleration = 7.91; speed = 4.70; AFSD-bin 1 = 7.03, AFSD-bin 6 = 6.37, AFSD-bin 9 = 5.04, AFSD-bin 8 = 3.89; simultaneous movement = 4.74). A final model of all 10 important variables predicting accuracy was evaluated by training a random forest on a subset of 70% of the data (training set) and using it to predict the remaining 30% (test set). The regression model of the training set predicting the test set was highly significant ($p < .001$) and indicated that the selected variables explained 37% of accuracy values.

We subsequently conducted post hoc random forests separately for mental state- and non-mental state animations. These post hoc analyses revealed that, in mental state animations, five factors were predictive of accuracy, with jerk and acceleration being the most prominent predictors, followed by speed, which was ranked third (see Supplementary Fig 2 [Appendix 1]). In addition, AFSD in bin 6 and simultaneous movement were classed as important in predicting accuracy. In non-mental state animations, a total of eight predictors were identified

as important variables, with mean rotation being ranked highest by a considerable margin. In addition to mean rotation, a combination of AFSD in bins 1, 6, 7 and 9, and acceleration, jerk and speed were identified as important features of non-mental state animations.

Similarity measures calculated from the three variables identified as most important in the random forest predict mental state attribution accuracy.

In order to assess whether the effect of movement similarity between animator and observer on successful mental state attribution extends beyond jerk, we calculated similarity measures for the two variables (acceleration and rotation) which were identified as most important in the random forest analysis alongside jerk. Subsequently we employed two Bayesian mixed effects models to assess the strength of these difference scores in predicting accuracy. The first featured acceleration difference, rotation difference and mental state (dummy-coded) as predictors, and the second featured rotation difference, jerk difference and mental state. Model 1 revealed a negative effect for rotation difference in mental state animations ($E\mu_{rotationDiff,mental}$= -0.34, CrI = [-0.68, -0.01]; P($E\mu_{rotationDiff}$ < 0) = 0.98), and this relationship did not differ for non-mental state animations ($E\mu_{rotationDiff,mentalVSnon-mental}$= 0.40, CrI = [-0.13, 0.93]) indicating that overall, higher rotation similarity was associated with higher accuracy. For acceleration difference, the model revealed an interaction with mental state, where acceleration difference was negatively associated with accuracy in mental state ($E\mu_{accelerationDiff,mental}$= -0.48, CrI = [-0.88, -0.09]), but not related to accuracy in non-mental state animations ($E\mu_{accelerationDiff,mentalVSnon-\ mental}$ = 0.53, CrI = [0.01, 1.05]; note that this coefficient represents the *difference* in coefficients for acceleration difference between mental and non-mental state animations, the coefficient for the relationship between acceleration difference and

accuracy in non-mental state animations is close to zero: 0.53 – 0.48 = 0.05). The second model revealed comparable results ($E\mu_{rotationDiff,mental}$= -0.35, CrI = [-0.66, -0.04]; $E\mu_{rotationDiff,mentalVSnon-mental}$= 0.35, CrI = [-0.14, 0.85]; $E\mu_{jerkDiff,mental}$= -0.48, CrI = [-0.85, -0.11]; $E\mu_{jerkDiff,mentalVSnon-\ mental}$ = 0.58, CrI = [0.09, 1.06]).

2.3. Discussion

This study evaluated the relative contribution of jerk, jerk similarity and other stimulus characteristics to mental state attribution performance indexed using a novel adaptation of the animations task, suitable to track and compare animation generator and -observer kinematics. Our results confirm our hypothesis that animation jerk and jerk similarity are predictors of the accuracy of mental state attribution. In addition, we highlight that stimulus features including the shape of the triangles' trajectories and the amount of rotation of the triangles can also affect the ease with which participants are able to appropriately label the target states (*exploratory analysis 2*). Finally, we show that the similarity between an observer and generator is also beneficial when considering other movement characteristics beyond jerk, such as triangle rotation and acceleration (*exploratory analysis 3*).

In the first part of our confirmatory analysis step, we found that mental state was the primary predictor of animations task performance. Mental state videos were strongly associated with lower accuracy, correspondingly non-mental state videos were rated more accurately. The extant literature is mixed and there are some studies in which mental state animations are rated less accurately than non-mental state animations[240,257]. However, our observation that our healthy participants performed worse when interpreting mental, relative to non-mental, state animations, is inconsistent with most previous findings: In Abell et al.'s and other studies, non-

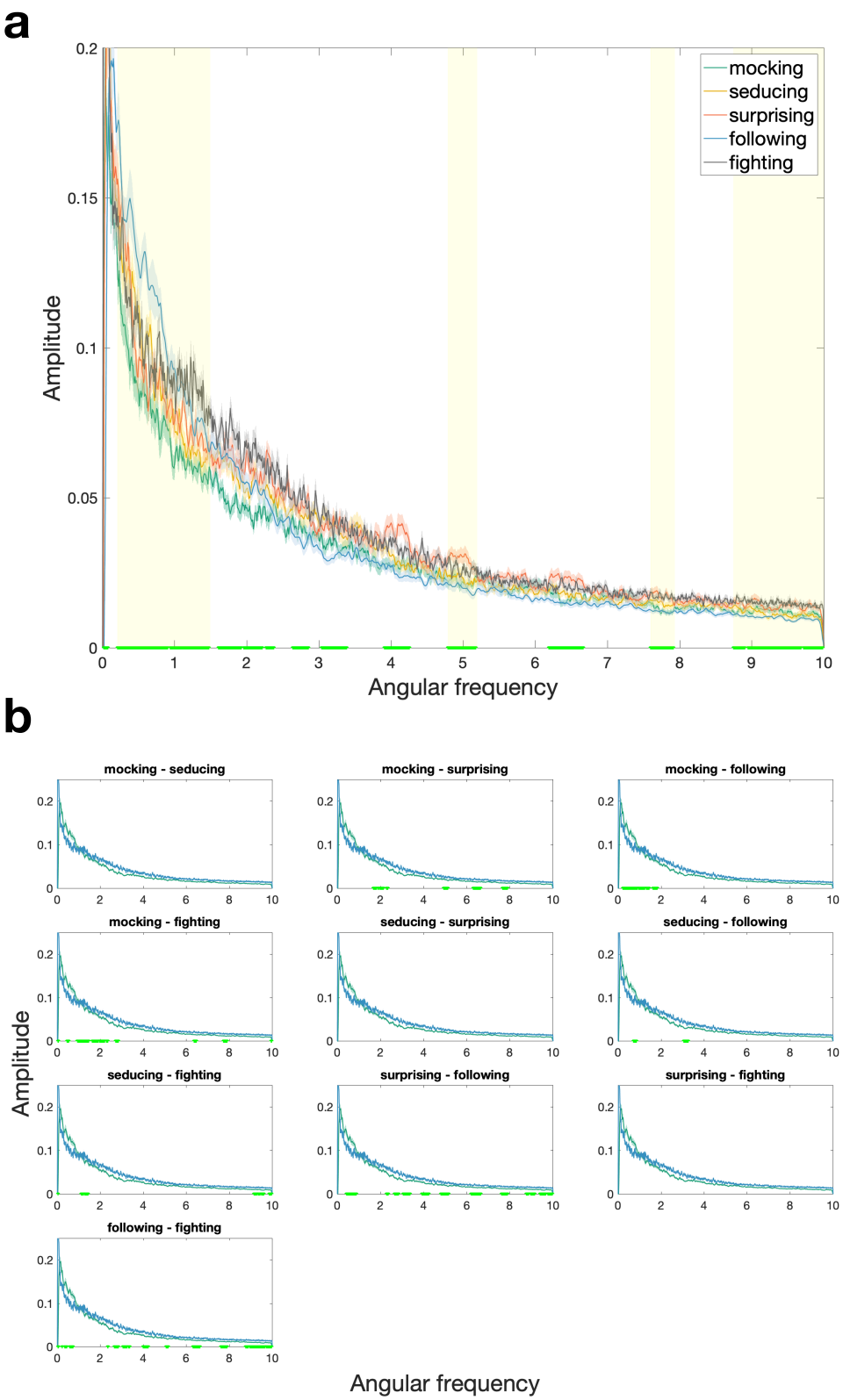

Figure 3. (a) Significant clusters of difference in angular frequency spectral density (AFSD). Solid colored lines represent spectral density as a function of angular frequency per word (=AFSD), the corresponding shaded areas represent 1 SEM (standard error of the mean) below and above the mean values. Yellow bars on x-axis represent clusters where AFSD significantly differs between mocking, seducing, surprising, following and fighting. Clusters that are predictive of accuracy are highlighted in yellow. Note that the lowest

angular frequency derived from the data varied between 0.02 and 0.09, resulting in extrapolated values for some participants. For this reason, the first cluster of difference ranging from 0.02 to 0.09 was considered not representative of actual movements and disregarded. (b) Post-hoc comparisons of AFSD.

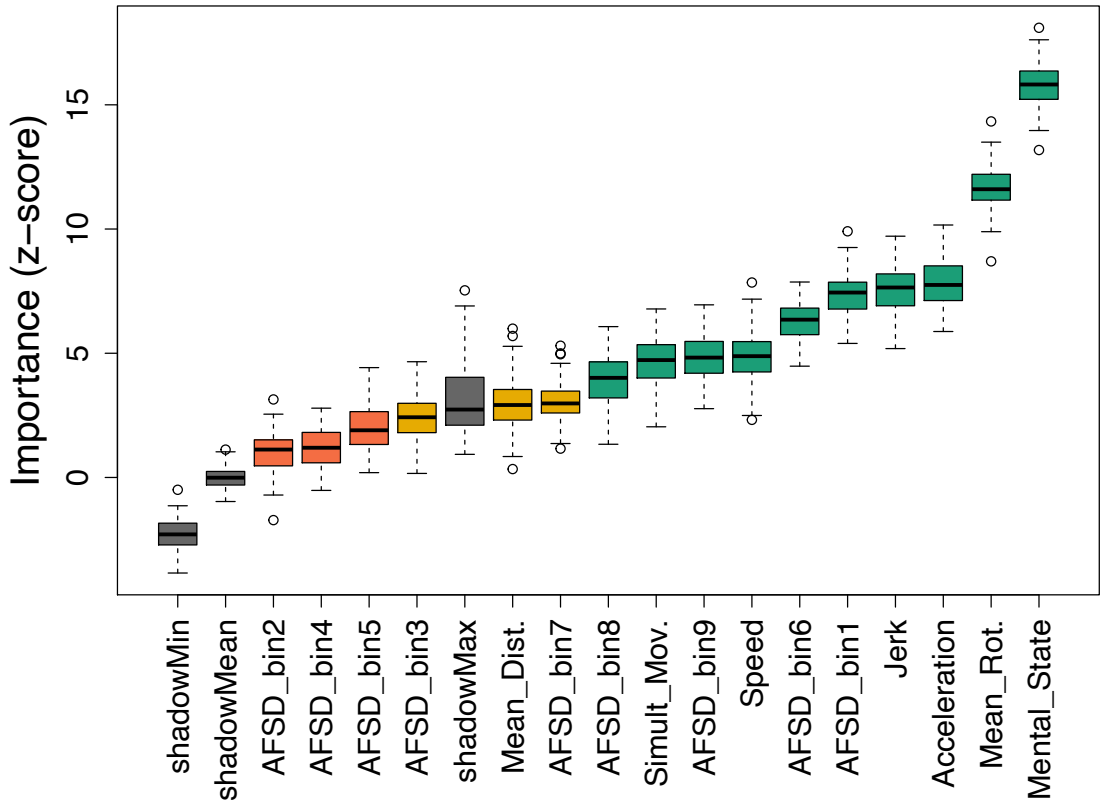

Figure 4. Random forest variable importances. Variable importances of all 16 features entered into the Boruta random forest, displayed as boxplots. Box edges denote the interquartile range (IQR) between first and third quartile; whiskers denote 1.5 * IQR distance from box edges; circles represent outliers outside of 1.5 * IQR above and below box edges. Box color denotes decision: Green = confirmed, yellow = tentative, red = rejected; grey = meta-attributes shadowMin, shadowMax and shadowMean (minimum, maximum and mean variable importance attained by a shadow feature).

autistic adult participants performed at least equally well[42,238,257-259] on mental state and non-mental state animations. It is possible that our findings illustrate a true difference in difficulty between mental and non-mental state attribution that is revealed only when participants are presented with a wide range of animation stimuli from a population-derived database. This

difference may have been overlooked because previous studies employed animations created by a single graphic designer, or small group of experimenters and thus lack variation. However, this possibility demands empirical testing. Indeed, a direct comparison between our paradigm and previous studies is not possible due to task related differences (e.g., in indices of performance, and number of words animated per condition). If superior performance for non-mental, relative to mental, state animations were replicated, future studies may proceed to explore whether non-mental state videos are perhaps richer in cues (such as acceleration and ASFD in bin 6) which contribute to the correct inference of both mental- and non-mental states in the current dataset.

In this first analysis step it was further revealed that the triangles' mean jerk in an animation plays a substantial role in interpreting that animation. For mental state attributions jerk was *negatively* predictive of accuracy, whereas for non-mental state animations jerk was *positively* predictive of accuracy. Post hoc analyses revealed that this latter result was primarily driven by fighting animations, and that the former was most notable with respect to mocking and surprising animations (though caution is advised with regards to the effect of surprising animations, since credible intervals of coefficient estimates did not exclude zero). In previous work, Edey and colleagues[1] observed that non-autistic participants were more accurate in their mental state attributions for animations generated by non-autistic participants compared to those generated by autistic participants. They also observed that animations generated by autistic participants were more jerky compared to those generated by controls. However, in Edey et al.'s study there were a number of additional dimensions along which the two groups' animations may have varied, making it impossible to know whether the autistic participants' animations were difficult to interpret *because of* the jerky kinematics. Our results show that jerk meaningfully contributes to the accuracy of mental state attributions, thus our data supports

the conclusion that jerk is highly likely to be one of the driving factors in the group differences observed by Edey et al.

Our results also highlight *jerk similarity* as a potential driving factor for the differences observed by Edey et al.[1]. That is, we observed a positive relationship between jerk similarity and accuracy. Post hoc analyses revealed that evidence of this relationship was particularly compelling in the case of mocking animations: The more closely a mocking animation's mean jerk approximated the participant's own jerk when animating the same word category, the more accurately that animation was rated. We speculate that Edey et al.'s non-autistic participants performed poorly when attributing mental states to animations produced by autistic individuals not only because these animations were jerky, but also because the kinematics of the animations were *dissimilar* from the way in which the observer would have produced the same animation. In other words, it is plausible that, in the minds of Edey et al.'s non-autistic observers, the animations generated by non-autistic animators triggered suitable mental state labels because the animation kinematics were similar to the kinematics that observers themselves would have produced. However, because the atypically jerky videos generated by autistic animators were presumably not, in the minds of non-autistic observers, associated with any mental state labels, it was difficult for observers to correctly identify the underlying mental state. This interpretation is in line with theoretical accounts[29,106,248,249,260] suggesting that visual and/or motoric representations of one's own actions may influence interpretations of others' actions and is reminiscent of simulation accounts of theory of mind which claim that one uses one's own mental processes to simulate others' mental states[250].

The second aim of the current study was to explore the extent to which a range of other stimulus features, including trajectory shape, influence mental state attribution accuracy. To quantify trajectory shape we used FFT to decompose trajectories into spectral density in angular

frequency bins. Animation identity could be differentiated by AFSD in nine bins and random forest analyses confirmed that four of these bins - bins 1, 6, 8 and 9 corresponding to angular frequencies 0.2-1.5, 4.8-5.2, 7.6-7.9, 8.8-10 - were 'important' predictors of mental state attribution accuracy. Relative to the other words, following animations had the highest AFSD in the angular frequency range 0.2-1.5 (bin 1; Fig. 3). A high amount of AFSD in this range indicates a trajectory characterized by complex doodle-like movements (see Supplementary Fig. 3 [Appendix 1]) with low angular-frequency oscillation in speed and curvature. Thus, one may speculate that animations which are most easily identifiable as 'following' comprise doodle-like triangle trajectories, with between 0.2 and 1.5 curvature oscillations per 2π radians. In the angular frequency range 4.8-5.2 (bin 6), surprising animations had highest AFSD relative to the other words (See Fig. 3). This angular frequency range centers around the pure-frequency trajectory of a pentagon and thus is reflective of movements with around five speed-curvature oscillations per 2π radians. Whilst our stimuli did not necessarily contain trajectories in the shape of actual pentagons, high AFSD in bin 6 reflects curves and speed-curvature patterns similar to those required to produce a closed-form pentagon. Finally, relative to the other words, both surprising and fighting had high AFSD in angular frequency ranges 7.6-7.9 (bin 8) and 8.8-10 (bin 9). A high amount of AFSD in these ranges indicates trajectories characterized by octagonal (bin 8) and decagonal shapes (See Fig. 4) with 8-10 speed-curvature oscillations per rotation. Together these results clearly illustrate that trajectory shape comprises an important cue with respect to the identity of the word that is depicted in an animation. At present one can only speculate about why some shapes (e.g., pentagons) are more indicative of particular mental/non-mental states (e.g., surprising).

For the third step in our four-part analysis, we employed random forests to ascertain the relative contribution to accuracy of a range of stimulus features. The random forest

methodology was chosen for its robustness against (multi-)collinearity and suitability for evaluating contributions of a large number of variables with limited data points[261]. Our random forest analysis confirmed ten features as important predictors of accuracy. In order of relative importance these are: mental state, mean rotation, acceleration, jerk, trajectory shape (AFSD in bins 1, 6, 8, 9), simultaneous movement of the triangles and speed. Post hoc analyses (see Fig. 3B) revealed that with respect to mental state attribution specifically, five of these features were of confirmed importance: jerk, acceleration, speed, AFSD-bin 6 and simultaneous movement. There was one feature which was uniquely important for mental state accuracy: The amount of simultaneous movement of blue and red triangles. By decomposing the animations task into features which predict accuracy, this random forest analysis deepens understanding of individual differences in animations task performance and raises testable empirical hypotheses for further research. For example, our analysis illustrates that simultaneous movement of the triangles is a stimulus feature which predicts mental state attribution accuracy. This observation raises the possibility that poor performance on the animations task in some clinical groups may be related to differences in processing this stimulus feature. That is, processing the simultaneous movement of the triangles requires distributed attention to two objects simultaneously. It may be that individuals with some clinical conditions (e.g., autism[262]) exhibit a deficit in the perception of global relative to local motion stimuli, making it more difficult for them to process the simultaneous movement of two triangles (though note contradictory evidence from Zwickel et al.[263] that autistic participants distribute their attention evenly across both triangles). Given our finding that simultaneous movement cues are uniquely important for mental (but not non-mental) state accuracy, we speculate that difficulties processing the simultaneous movement of both triangles may impact selectively on the accuracy of mental-, not non-mental-, state attributions.

Finally, exploratory analysis 3 investigated whether similarity effects also exist with respect to other movement features such as triangle rotation. The random forest technique, due to its inability to account for random variance among individuals, does not allow for the inclusion of indices relating to movement similarity (which depend on the *relation between* an animation and an individual participant). We therefore conducted an additional set of Bayesian mixed effects models where we tested whether similarity between an observer and animator in the top three features identified by the random forest also predicted accuracy. Results revealed that, alongside jerk similarity, acceleration similarity and rotation similarity predict accuracy in the animations task. Whereas our *confirmatory analysis* was hypothesis-driven, this analysis illustrates that, even when a more data-driven approach is applied, jerk similarity is a strong predictor of accuracy. The results of this last exploratory analysis step are consistent with motor simulation accounts of mentalizing and extend the effect of jerk similarity to other movement features. It remains to be seen whether apparent mentalizing deficits in autism are ameliorated when autistic people are provided with stimuli which match closely to features of their own movement including mean rotation, trajectory shape and kinematics. If it were the case that movement similarity facilitates mental state attribution in clinical populations including autism and healthy people alike, it may be feasible to develop support systems to improve bi-directional communication between (for example) autistic and non-autistic people, by teaching counterparts to move more similarly in order to find a "common body language". Although such support systems could be extremely helpful for autistic and non-autistic dyads who interact frequently, for instance in caregiver-caretaker relationships, there is much work that must yet be completed to build a bridge between the current findings and this future possibility.

This study has several limitations worth noting. First, with respect to generalizability, it should be noted that our 84% female sample lacked variation in terms of gender, age and

educational background. In order to know whether our results apply to the wider population, future studies with more varied samples are needed. Second, since all of our participants first created their own animations *then* rated others' animations, we cannot comment on whether the order of tasks influenced the results. The create-then-rate order was chosen to minimize the risk that, after *first* watching others' animations, participants' own movement kinematics would be biased towards the observed animations. However, we acknowledge that further studies are necessary to explore whether the jerk similarity effect here observed is weaker under rate-then-create conditions and/or when the delay between creating and rating animations is increased. Third, the current study demonstrates a role for jerk similarity in the accuracy of mental state attributions as indexed by performance on a Heider-Simmel style task but the extent to which these results extend to other ToM tasks is unknown. Although it is possible that movement similarity influences the accuracy of mental state attributions across a range of mentalizing tasks which require interpretation of body movement cues (e.g., the Movie for the Assessment of Social Cognition [MASC]-[146] or the Silent Films[264] task), this speculation must be confirmed with empirical testing. Finally, we note that our task does not allow inference of the direction of causality regarding movement jerkiness and mentalizing abilities. Movement jerkiness may precede mentalizing difficulties in some clinical conditions, whereas mentalizing difficulties emerge before motor symptoms in others (for detailed discussion see Eddy and Cook[50]). For instance, in autistic individuals, motor atypicalities have been noted from as early as one month of age[265], whereas socio-cognitive differences tend to gradually emerge over the first few years of life[266]. Conversely, in Huntington's disease, social cognitive symptoms have been found to occur before the onset of motor symptoms[267]. To clearly disentangle the direction of the relationship between socio-cognitive and motor development longitudinal studies that study these relationships within the same individuals, whilst accounting for potential mediating

factors (see Happé et al.[268], for further discussion about establishing cause and effect in socio-cognitive studies), are needed.

The present findings highlight particular kinematic- and trajectory features (specifically, acceleration, jerk, speed and energy in bin 6 (angular frequencies around 5); see Supp. Fig. 2) as being important for mental state attribution in the context of the animations task. Based on our results one may speculate that individuals who experience difficulties with processing kinematic cues, or with trajectory tracking, may struggle to attend to, and/or process, the cues in Heider-Simmel style animations that are most relevant for accurate mental state attributions. That is, our results raise the possibility that individual differences in mentalizing may be related to individual differences in the perceptual processing of kinematics and trajectory information. Future studies which investigate the relation between kinematic processing, trajectory tracking, and mental state attribution accuracy are required to test this hypothesis. Our findings further show that similarity in a variety of movement features between observer and animator facilitates mental state attribution. Consequently, individuals with certain clinical conditions might find the animations task particularly difficult due to differences in perceptual processing and/or reduced movement similarity. Our data paves the way for studies which empirically test whether mentalizing deficits in clinical populations persist when participants are provided with stimuli which closely match features (including kinematics, trajectory shape and amount of simultaneous movement) of their own movements.

2.4. Methods

2.4.1. Building the animotions database

Animotion online task

We created a browser-based application that enables us to record and replay participants' animations in the style of Heider & Simmel's original movies[84] while captu[268][268]ring the triangles' positions at 133Hz. For this purpose, we adapted a web application developed by Gordon & Roemmele (*The Heider-Simmel Interactive Theatre*[269], https://hsit.ict.usc.edu/) to fit our task design and allow instantaneous calculation of mean speed, acceleration and jerk (change in acceleration), thus enabling the selection of stimuli according to predefined criteria for replay. Gordon's web application employs scalable vector graphics (SVG) objects that allow simultaneous translation and rotation of each object with input from a single finger per object. To ensure object motion follows the direction of movement of the finger, and to suppress sporadic rotations (which can occur if dragging is initiated too close to the object center), object motion is suppressed until the pointer is dragged sufficiently far away from the center point (see https://asgordon.github.io/rotodrag-js/ for a more detailed description of the library used for this application).

Participants

We asked 51 healthy volunteers (46 females, mean (M) [SD] age = 20.23 [2.71] years, range 18-34 years) to animate two triangles in order to depict three mental state (mocking, seducing, surprising) and two non-mental state (following, fighting) words. Participants were recruited from the University of Birmingham research participation scheme, gave written informed consent and received either course credit or money (£8 per hour) for their

participation. All experimental procedures were conducted in line with the WMA declaration of Helsinki[270] and approved by the University of Birmingham Research Ethics Committee (ERN 16-0281AP5).

Procedure

Data was collected at the University of Birmingham. Individuals were seated in front of a WACOM Cintiq 22 HD touch screen, tilted at an angle of approximately 30 degrees upon the desk. They were presented with the starting frame, comprising a black rectangular enclosure and two equally sized equilateral triangles (one red and one blue) on a white background (see Supplementary Figure S1.5 [Appendix 1]). In a 45-second-long practice phase, participants familiarized themselves with how to use their finger movements in order to navigate the triangles around the screen. Participants were subsequently instructed to '*represent certain words by moving the triangles around the screen*', assured they could move the triangles in any way they saw fit and encouraged to use their index fingers on both the left and right hand to move the triangles simultaneously (for a complete transcript of task instructions see Supplementary Materials [Appendix 1]). A dictionary was provided in case participants did not know the word in question. No further explanations were given.

Following instructions, participants were presented with the first word and a 30-second-long presentation of the stationary starting frame, allowing participants to plan their subsequent animation of that word. Finally, individuals were given 45 seconds to animate the given word. This process was repeated for the total of three mental state- (mocking, seducing, surprising) and two non-mental state words (following, fighting), and on each trial participants were given the option to discard and repeat their animations if they were unhappy with the result. Only the final animations were analyzed.

The mental state words were chosen to be the same as used in Edey et al.[1], these words were based on the ToM animations used by Abell et al.[42]. After pilot testing revealed that participants found it difficult to understand the meaning of the word 'coaxing', even after consulting the dictionary, we removed this word. The non-mental state words were selected on the basis of the Goal-Directed animations used in Abell et al.

Stimulus selection

Our procedure resulted in a total of 255 animations (51 for each word), recorded at a frame rate of 133 frames / second. Animations were then visually inspected for sufficient length and movement coverage of more than two quadrants of the screen. 53 animations failed these quality control checks. The final stimulus set comprised 202 animations (42 mocking, 38 seducing, 36 surprising, 44 following, 42 fighting). Note that while our choice of words for the new animotions stimulus set was based on previous work by Abell et al.[42] and Edey et al.[1], none of their animation stimuli were used in this study.

2.4.2. Ratings collection

Participants

Thirty-seven healthy volunteers (31 females, M [SD] age = 21.30 [2.68] years, range = 18-32 years) were recruited from the University of Birmingham Research Participation Scheme and gave written informed consent to participate in this study. Post-hoc power calculations based on an online application by Judd et al.[271] (https://jakewestfall.shinyapps.io/two_factor_power/) confirmed that this study had 91.2 % power to find an effect of size Cohen's d (d) = 0.4 for the main hypothesis (1). An a priori

power analysis of the complete study was not performed due to the lack of applications available to estimate effect sizes for the present analyses (a mixed effects model with more than one fixed effect). Participants received either course credit or money (£8 per hour) for their participation. None of the participants had previously taken part in stimulus development.

Task

The Ratings Collection phase comprised two tasks. First, all participants carried out a **production task**, where they created one 45-second-long animation for each of the five target words mocking, seducing, surprising, following and fighting, as described above. Following this, participants completed a **perception task**, where they viewed 40 animations from the full stimulus set and rated the extent to which the animations depicted each of the target words (mocking, seducing, surprising, following, fighting). Participants viewed eight exemplars of each of the five target words, presented in random order. The eight animations were selected from the stimulus pool (N = 202, see **Building the animotions database**) such that the mean speed of the triangles represented one of eight percentiles of the speed frequency distribution for a word (see Figure 5). Thus, for each word, each participant viewed a selection of animations such that they were exposed to the full range of kinematic variation in the population used to create the stimulus pool.

Finally, after watching each animation, participants were asked to rate on a visual analogue scale ranging from one to ten the extent to which they perceived the video to display the target word (e.g., mocking) and each of the four non-target words (e.g., seducing, surprising, following and fighting). The whole process of creating five and viewing and rating 40 45-second animations lasted between 40 and 50 minutes. Task order was fixed (production task then perception task) to allow participants' animations to be unaffected by the animations they

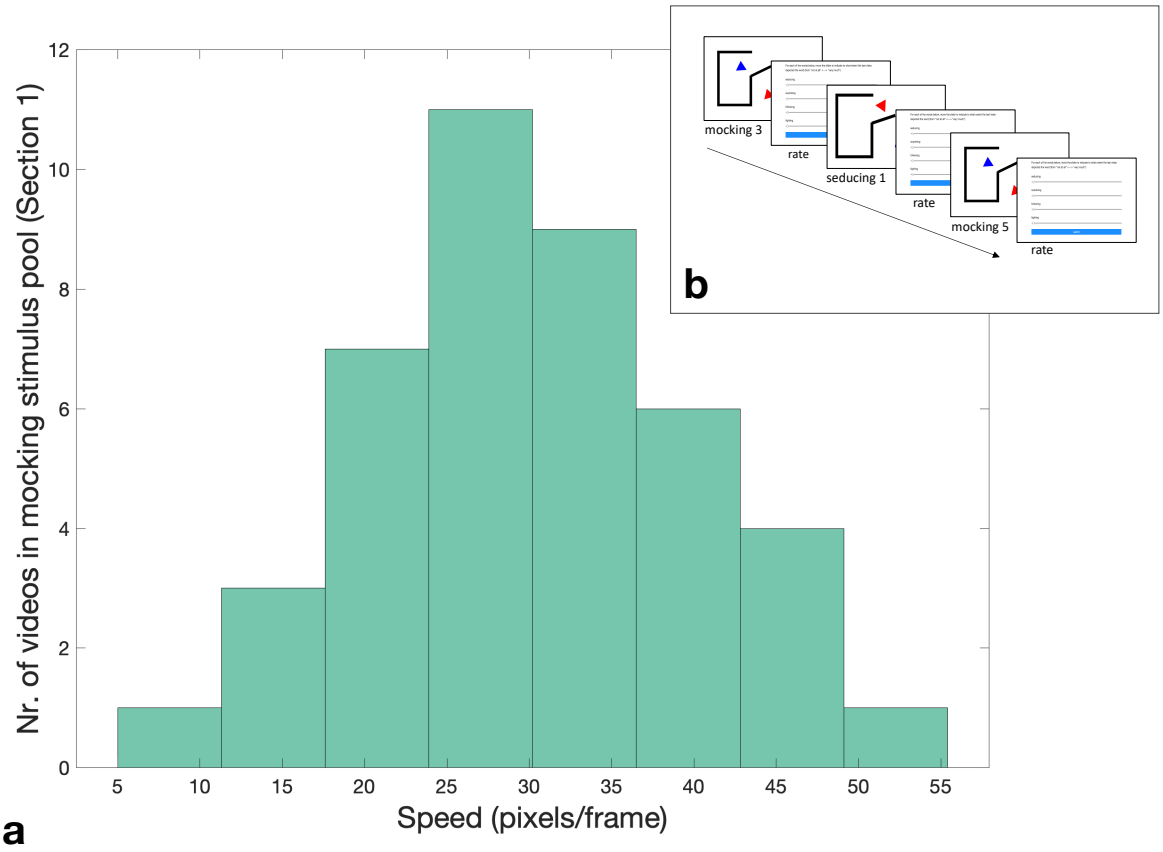

Figure 5. Example of stimulus selection method. (a) Example of the stimulus selection method for the word mocking. The selection method was the same for all five word categories. From each of eight percentile bins of the speed frequency distribution for a word category, one animation was selected at random and replayed to the participant. (b) Schematic depiction of 3 successive trials in the perception task. Numbers next to words represent the order number of the percentile bin from which the stimulus was selected (e.g., mocking 3 represents a mocking animation from the 3rd bin, which includes animations between the 25th and 37.5th percentile of the speed frequency distribution). Animations presented were selected at random; each animation was followed by a separate screen with five visual analogue sliding scales (one for each of the five word categories), ranging from 1 to 10.

would see in the perception task. Due to the upper limit on the WACOM monitor refresh rate, videos were created with a 133 Hz sampling rate and displayed at 60Hz.

Procedure

Individuals sat in front of the WACOM Cintiq 22 HD touch screen, tilted at 30 degrees, and first completed a practice phase in which they familiarized themselves with moving the triangles around the screen. They were then instructed that they would first create an animation for each of the five words themselves (instructions were the same as in 'Building the animotions database'; see Supplementary Materials [Appendix 1]) and subsequently would view and rate animations which had been created by other people. Participants then completed the production and perception tasks as described above.

2.4.3. Data analysis and processing

All data was processed in MATLAB R2020a[272] and analyzed in R[273]. Code required to reproduce data analysis and figures for this study will be freely available under (https://osf.io/pqn4u/).

Accuracy ratings

Accuracy for each trial was calculated by subtracting the mean rating for all non-target words from the rating for the target word. Thus, a positive score indicates that the target word was rated higher than all non-target words, with higher accuracy scores reflecting better discrimination between target and non-target words. See Appendix 1 for further analysis of accuracy scores.

Spatial and kinematic predictors

All variables were calculated from positional data derived from the center points of the blue and red triangles. All steps of data processing mentioned below were performed on both the animations created by participants (= production data) and the animations from the full stimulus set used as perception task stimuli (= perception data).

Stimulus kinematics

Instantaneous speed, acceleration magnitude and jerk magnitude were obtained by taking the first-, second- and third order non-null derivatives of the raw positional data, respectively (see [1], [2] and [3], where x and y represent x- and y positions of red and blue triangles in the cartesian coordinate system, $v, a,$ and j denote instantaneous velocity, acceleration and jerk, respectively, and t denotes time).

$$\vec{v} = \sqrt{(x_{t-1} - x_t)^2 + (y_{t-1} - y_t)^2} \quad [1]$$

$$\vec{a} = \frac{d\vec{v}}{d\vec{t}} \quad [2]$$

$$\vec{j} = \frac{d\vec{a}}{d\vec{t}} \quad [3]$$

As the 'diff' function in MATLAB amplifies the signal noise, which compounds for higher derivatives, we employed a smooth differential filter to undertake each step of differentiation (filter adopted from Huh & Sejnowski, 2015). The Euclidean norms of the x and y vectors of velocity, acceleration and jerk were then calculated to give speed, acceleration magnitude and jerk magnitude. That is, speed is calculated as the distance in pixels moved from one frame to

the next. Acceleration magnitude comprises the change in speed from one frame to the next, and jerk magnitude comprises the change in acceleration. Mean speed, mean acceleration magnitude and mean jerk magnitude were then calculated by taking the mean across red and blue values, respectively. Lastly, kinematic values were converted from units of pixels/frame to mm/s.

Observer-animator jerk similarity

In order to measure the similarity between participants' and stimulus kinematic jerk, absolute observer-animator jerk difference was calculated by first subtracting the mean jerk of each video a person rated from their own jerk values when animating the same word, and then taking the absolute magnitude of those values. Lower jerk difference values indicate *higher* observer-animator jerk similarity.

Angular frequency spectral density (AFSD)

For the purpose of quantifying animation trajectories, we adapted a method developed by Huh & Sejnowski (2015). Huh and Sejnowski have shown that the two-thirds power law varies according to shape trajectory, such that the gradient of the relationship between angular speed and curvature (in the Frenet-Serret frame[274,275]) is a function of the shape's angular frequency. Angular frequency here is defined as the number of curvature oscillations within one full tracing (360° or 2π radians) of a closed-form shape. We extended the method to derive the angular frequencies of arbitrary trajectories (i.e., not closed-form shapes) from the frequencies of speed oscillations within every 2π radians of a triangle's angular displacement in the Frenet-Serret frame.

First, absolute instantaneous curvature k was calculated (angular speed divided by speed). This enables the calculation of Frenet-Serret speed v. Periodicity in v, in every 2π radians, allows the determination of angular frequencies present in the triangles' movement. Asymmetrical FFT was employed on log v, which returned the amplitude spectral density of all angular frequencies present for each triangle in each animation. Angular Frequency values returned by the FFT were then interpolated to obtain uniformly sampled values at 1001 points. Because the FFT assumes an infinite signal, when addressing a finite sample such as the log angular speed here, the first and last values of each sample must be continuous to avoid artefacts in the FFT results. We addressed this and any general drift in the signal (e.g., from participants generally slowing their movements due to fatigue) by removing a second order polynominal trend. The area under the amplitude spectral density curve was normalized to allow like to like comparison between differing lengths of red and blue triangle movement within and across participants. Across red and blue triangles' trajectories a weighted mean was then taken by multiplying each AFSD value with a factor reflecting the proportion of curved movement available for a triangle before averaging. See Figure 6 for an example of an amplitude spectrum and the related trajectory path.

Further spatial variables

A variety of other variables were created to further quantify spatial aspects potentially affecting inferences from the animations. First, simultaneous movement was calculated as the proportion of all frames where both red and blue triangles' speed was greater than zero (as seen in [4]), reflecting simultaneous movement of both triangles in a video. Furthermore, relative distance - the average distance between red and blue triangles - was quantified by taking the mean of the square root of the absolute distances between the triangles' x and y coordinates,

respectively (see [5]). Finally, mean rotation reflects the average rotation of blue and red triangles around their own axis, measured in angle degrees and weighted by proportion of movement present across all frames for each color ([6]).

$$\frac{\sum(speed_{red} \& \, speed_{blue} > 0.01)}{\sum all \; frames} \quad [4]$$

$$\underline{x}\left(\sqrt{\left(abs(x_{red} - x_{blue})\right)^2 + \left(abs(y_{red} - y_{blue})\right)^2}\right) \quad [5]$$

$$\frac{\left(\underline{x}\left(abs(r_{blue\,t-1} - r_{blue\,t})\right)\right) + \left(\underline{x}\left(abs(r_{red\,t-1} - r_{red\,t})\right)\right)}{2} \quad [6]$$

2.4.4. Statistical analysis

Data analysis overview

This study investigates the role of a large number of different predictor variables in explaining accuracy in the animations task. For two of these variables we present specific hypotheses (jerk, jerk difference); in addition, we wanted to investigate the role of a larger set of variables on an exploratory basis. For this reason, analyses were conducted in two stages: First, in a confirmatory stage, the roles of jerk and jerk difference were examined using Bayesian mixed models. Second, in an exploratory stage, a random forest model was performed, investigating the relative contribution of all predictor variables together.

Data cleaning and transformations

For all analyses, variables that were not normally distributed were either log- or square-root transformed to approximate normal distribution. Any outliers, as defined by values exceeding three scaled absolute deviations from the median, were replaced with the

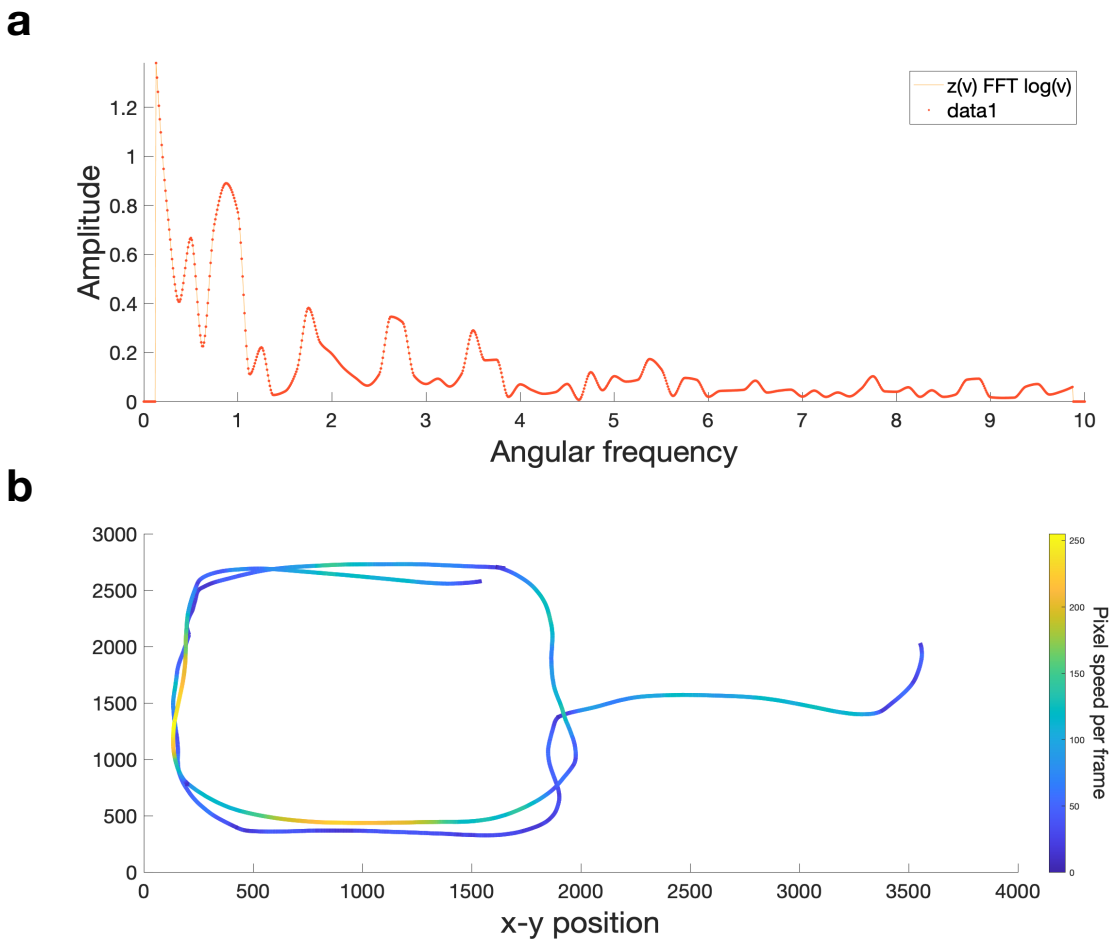

Figure 6. Example of trajectory shape and related angular frequency spectrum. (a) Example of angular frequency spectrum for following animation. (b) Related trajectory (of one of two triangles). Trajectory colors indicate speed (pixel/frame).

respective lower and upper threshold values. Finally, all predictor variables were z-scored.

Confirmatory analysis

A Bayesian linear mixed effects model was fitted in R using the *brms* package[276] to evaluate the relative contribution of jerk and jerk difference to accuracy as a function of word category, as well as their three-way interaction. A maximal[252] random effects structure was defined, allowing the intercept, the predictors of interest and their interactions to vary by

participants (subject ID) and items (animation ID). Jerk and jerk difference were entered as covariates and word category was entered as dummy coded factor. We used brms default priors for the intercept and the standard deviation of the likelihood function as well as weakly informative priors (following a normal distribution centered at 0 and SD = 10) for all regression coefficients. Each model was run for four sampling chains with 5000 iterations each (including 1000 warmup iterations). There was no indication of convergence issues for any of the models (all Rhat values = 1.00, no divergent transitions).

Exploratory analysis 1

Bootstrapped F-tests were performed to test for differences, between the five target words, in the presence of angular frequencies at each of the 1001 points on the amplitude spectrum. Bootstrapping amplitude spectrum values 1000 times revealed nine significant clusters, defined as clusters of difference that occurred in less than 5% of comparisons with resampled distributions (see Fig. 3A). The maxima and minima of each significant cluster were then used as bin edges for calculating the amplitude spectral density as the area under the curve within those nine bins, for both red and blue triangles' trajectories in each animation (cluster bin edges: 0.21 – 1.49, 1.61 – 2.39, 2.64 – 2.87, 3.04 – 3.40, 3.91 – 4.27, 4.79-5.19, 6.19-6.68, 7.6-7.93, 8.75-10). Finally, the weighted mean (weighted by amount of curved movement present in a triangle's full trajectory) was taken across red and blue triangles' spectral density values to form a single value of mean AFSD for each of nine bins for each animation. The final spectral density values are reflective of the relative proportion of curved movement available in a video in each of the nine areas of interest. Thus, a video that had high spectral density in bin 3 would be dominated by shapes with angular frequencies between 2.64 and 2.87. That is,

relative to all other animations, the triangles in this video would be predominately moving with a speed and acceleration profile that lies between that of elliptical- and triangle trajectories.

Exploratory analysis 2

Relative variable importance of 16 variables in predicting accuracy was assessed using random forest models[255] and the feature selection wrapper algorithm *Boruta*[256]. Random forests are ensembles of decision trees, where each tree is grown from a pre-specified subset of bootstrapped samples and where, for each tree, only a randomly selected subset of variables are considered as splitting variables. Boruta makes use of the *ranger* package[277] to train a random forest regression model on all variables as well as their permuted copies - so called "shadow features". First, *normalized permutation importance* (scaled by standard error, see[255]) of all features is assessed. Permutation importance of a given variable is the reduction in prediction accuracy (mean decrease in accuracy, MDA) of the model when this variable is randomly permuted. A variable is then classed as important when the Z-score of their importance measure is significantly higher than the highest importance Z-score achieved by a shadow feature. Overall performance of the model was evaluated by fitting a random forest with the ranger package with 500 trees and 10 random variables per tree.

Due to the known correlational structure within the data and the present lack of random forest models which can account for random effects, this analysis was performed items-based. For this purpose, for every variable, values corresponding to the same item were averaged across subjects, resulting in a total of 202 data points. Note that, due to the reliance on between-subject variance of variables relating to own-stimulus kinematic difference, these variables were excluded from this analysis.

Exploratory analysis 3

Acceleration difference and *rotation difference* were calculated as the difference in acceleration and mean rotation between an animation stimulus and the participant's own animation of the same word, where lower difference values indicate higher movement similarity. Subsequently, we used Bayesian mixed effects models, with the maximal possible random effects structure, to quantify the strength of these difference scores in predicting mental state attribution accuracy. However, high variance inflation factors (VIFs) for the predictors jerk difference (VIF = 33.31) and acceleration difference (VIF = 33.84) indicated collinearity. To avoid the problem of inflated standard errors associated with high VIFs[278], we used two mixed effects models: the first, with acceleration difference, rotation difference and mental state predicting accuracy, and the second with the predictors rotation difference, jerk difference and mental state.

Chapter 3: The dopamine antagonist haloperidol modulates mental state attribution independent of motor function

The previous chapter illustrated how in the widely used animations task, individuals make use of stimulus motion properties, including the triangles' jerk, acceleration, or rotation, to successfully attribute labels to animations. What is more, the chapter demonstrated that similarity in those cues between an observer and the original animation creator facilitated the correct labelling of mental and non-mental state animations. These results suggest that reduced movement similarity may at least in part be responsible for the bi-directional difficulties previously observed between autistic and non-autistic adults in interpreting the respective other group's animations. Atypical motor function has been reported not only for autistic individuals (e.g., [173]), but for a variety of other clinical conditions (e.g., HD[279], TS[280], schizophrenia[281]) which all show difficulties in the animations task[42,46,47,282]. As outlined in Chapter one, a further commonality between these populations is that those disorders all have been linked to dysfunctions of the dopamine system[3,37,53,54], indicating a role for dopamine in the putative relationship between aberrant motor production and decreased performance in the animations task. Aiming to shed light on the pathways via which dopamine disruptions may contribute to atypical performance in the animations task, the following chapter presents a pharmacological model of dopamine system dysfunction in healthy individuals.

3.1. Introduction

Parkinson's disease (PD), Huntington's disease (HD) and Tourette's syndrome (TS) are commonly thought of as motor disorders. However, a burgeoning literature reports that socio-cognitive impairment is common across these conditions and is associated with negative outcomes including increased disease burden and poor quality of life[41,283,284]. An important aspect of social cognition is the ability to accurately attribute mental states to others (also referred to as mentalizing, mindreading or Theory of Mind [ToM]). So called animations tasks, which require participants to attribute mental states to two interacting triangles, have consistently revealed atypicalities in HD, TS, and other disorders that exhibit co-occuring motor and social atypicaltities such as Autism Spectrum Disorders (ASD) and schizophrenia. However, although difficulties in mental state attribution are worryingly prevalent across these conditions, little is known about the origin of these difficulties.

In addition to motor atypicalities, all previously mentioned populations share another salient commonality: PD, HD, schizophrenia, ASD and TS all have been linked to disruptions of the dopamine system, suggesting a causal role of dopaminergic signaling in mentalizing abilities. Indeed, a line of evidence implicates dopamine in ToM function[212], with perhaps the strongest support coming from studies reporting improvements in ToM abilities in schizophrenic and PD patients after treatment with dopamine antagonists (schizophrenia[285-287]) and dopamine supplementation (PD[288]). However, since the restorative effect of antipsychotics on ToM function is typically only observed after several weeks to months, it cannot be excluded that the improvement is owed to other factors associated with longitudinal testing. These potentially confounding factors include practice effects due to repeated exposure to the same ToM tasks, behavioral interventions patients may have received during the period of

observation, or generally improved wellbeing as a result of alleviated primary symptoms (e.g., schizophrenia: positive symptoms such as hallucinations; PD: motor symptoms) after dopaminergic treatment. To the best of our knowledge there is only one study directly comparing ToM abilities within PD patients on, and after acute withdrawal of, dopaminergic medication. This study found no differences between drug states, leading the authors to conclude that dopaminergic pathways are not involved in ToM processes[196]. However, Péron et al. only compared drug on- with off states in their early-stage PD group and found no performance differences to controls for this group in either the on or off condition. Thus, as their early-stage PD patients already showed intact performance off dopaminergic medication, it would have been unlikely for the dopaminergic medication to improve ToM ability beyond a level comparable to controls. Consequently, the current evidence base is inconclusive regarding whether the dopamine system is involved in socio-cognitive function. Furthermore, little is known about the underlying mechanisms via which aberrant dopaminergic signaling may lead to atypical responses in ToM tasks in clinical populations.

There are several ways in which dopamine may modulate socio-cognitive function. For instance, the majority of individuals with known or hypothesized dopamine dysfunctions display motor atypicalities[173,279-281], and changes in dopaminergic tone have been linked to changes in body movement (e.g., reduced movement vigor[127]). Importantly, motor function plays an integral role in social cognition: As illustrated in Chapter two, one's own body movements influence the interpretation of others' movements such that it is easier to correctly identify mental states when others' movements are similar to one's own[289]. Consequently, abnormal dopamine signaling could affect socio-cognitive functioning indirectly, via affecting patients' movements, which in turn may disrupt internal motor representations associated with mental states. Insights into the plausibility of this hypothesis may come from reports of

statistical relationships between social and motor dysfunctions in conditions linked to dopamine system disruptions. However, the picture here is far from clear, and involves findings in support of[173,290,291], and against[283,292-294] a link between social and motor symptoms in these populations (for a review on social-motor links in a range of clinical conditions see [50]).

Alternatively, it is possible that dopamine modulates social cognitive function directly and independent of motor function. As discussed above, a handful of studies exist that report restorative effects of ToM function after dopaminergic treatment, albeit with limited implications due to potential confounds associated with the longitudinal testing of drug effects. Nonetheless, any statistical relationships between dopaminergic treatment and mentalizing skills may still be mediated by drug effects on motor function. To the best of our knowledge, to date no study has tested the influence of acute dopaminergic challenge on both mentalizing abilities and motor function, as well as potential relationships between drug effects in social and motor domains.

Using the paradigm established in Chapter two, here we first investigated whether disruption of dopamine system function plays a causal role in mentalizing. Second, by indexing effects of dopamine challenge on motor function via three different motor tasks, we quantified the extent to which the dopaminergic modulation impacts mentalizing indirectly, via affecting body movements. The Heider-Simmel style paradigm presented in Chapter two lends itself to the investigation of mediating effects of atypical motor function on mental state attribution as here we have already established the influence of movement similarity on accuracy[289]. To anticipate, we did not find any relationship between effects of our dopamine manipulation on motor and mentalizing tasks. Thus, in an exploratory analysis, we used the well-known link between striatal dopamine function and baseline working memory span[295] to dissociate effects of dopamine challenge on motor function and mental state attribution.

3.2. Methods

3.2.1. Participants

Forty-three healthy volunteers (19 females; mean (M) [SD] age = 26.36 [6.3]) took part on at least one of two study days after passing an initial health screening. Participants were recruited via convenience sampling from University of Birmingham campus and city centers, gave written informed consent and received either money (£10 per hour) or course credit for their participation. Four participants dropped out of the study after completing the first day, a further five participants could not complete the second test day due to COVID-19 related University wide closures. All experimental procedures were approved by the University of Birmingham Research Ethics Committee (ERN 18-1588) and performed in accordance with the WMA Declaration of Helsinki (1975).

3.2.2. Pharmacological manipulation and general procedure

Participants' eligibility for the study was evaluated by a clinician via a review of their medical history, an electrocardiogram assessment and blood-pressure check (for details on exclusion criteria see Appendix 2.1). Eligible participants then completed a range of baseline measures and questionnaires (Appendix 2.1). The main study took place on two separate test days, between one and four weeks apart, where participants first completed an initial blood -pressure and -oxygenation check with the medic. Subsequently, in a double-blind, placebo controlled cross-over design, participants received tablets containing either 2.5mg haloperidol or lactose (placebo). Haloperidol is a dopamine D2 receptor antagonist, limiting dopamine transmission by blocking dopamine D2 receptors in the brain. Reported mean values for peak concentration and elimination half-life of oral haloperidol administration lie between 1.7 and

6.1 and 14.5 – 36.7 hours, respectively[296]. After drug administration, participants rested for 1.5 hours to allow for drug metabolization. Subsequently participants began the task battery, including the animations task and three motor tasks. Throughout the day, participants' blood -pressure and -oxygenation was checked hourly between tasks. All data was collected at the Centre for Human Brain Health (CHBH) at the University of Birmingham, UK.

3.2.3. Animations task

The main task, task setup and procedure were the same as in Chapter two (see also [289]), with the following differences: (1) In both the animations generation and perception phase, two instead of three mental state words were used, resulting in the following animation types: *Seducing*, *surprising* (mental state), *following*, *fighting* (non-mental state). (2) The maximum time given for creating an animation and thus the maximum duration of animations presented in the perception task was 30 instead of 45 seconds. Note that, due to the pseudo-random selection of animation stimuli from the pre-defined bins (see Chapter two), animations viewed by each participant in haloperidol trials were not necessarily the same as in placebo trials.

3.2.4. Movement tasks

Walking task

Individuals were asked to walk continuously between two sets of cones (placed 10 meters apart) for 120 seconds at their preferred walking speed. Each participant completed two walks (á 120 seconds) approximately 30 minutes apart. Acceleration data was recorded, using the SensorLog app [297], with an iPhone 6s attached to the outer side of the participants' left ankle.

Shapes drawing task

The same task set-up and device was used as for the animations generation phase (see Chapter two), with the exception that participants used a stylus pen, rather than their fingers, to complete the task. Subjects were first presented with written instructions to continuously trace each of the following presented shapes with their dominant hand as precisely and as quickly as possible. Subsequently, participants traced three different shapes (each shape was presented until 10 rotations were completed) of varying angular frequency which were displayed on the WACOM touchscreen, while positional data of their movements was recorded. Per condition, each shape was presented repeatedly 10 times across two individual blocks, resulting in a total of 10 trials per shape and 30 trials overall. Blocks were presented in pseudo-random order.

3.2.5. Data processing and analysis

All data was processed in MATLAB R2020b (The MathWorks Inc., 2020) and analyzed in R (version 4.0.2, R Core Team, 2020), following the procedure used in Chapter two[289].

Movement Kinematics

Movement data was processed, and kinematics were calculated for three different movement tasks. Kinematics from the animation production phase were calculated following the procedure outlined in Chapter two[289]. For details on the pre-processing of walking task kinematics see Chapter five (5.2. Methods: Data processing).

Shapes drawing task. Velocity for each trial was calculated as the square root of the sum of the squared delta of x and y vectors. Subsequently, velocity vectors were low-pass filtered at 5 Hz, before acceleration and jerk were calculated as the first and second order derivatives

of velocity, respectively. Absolute speed, jerk magnitude and acceleration magnitude were calculated following the procedure used to calculate kinematics in Chapter two (see 2.4.3. Data Analysis and Processing: Stimulus Kinematics). Subsequently, individual trial kinematics were averaged across all trials for each individual condition.

Statistical analysis

All statistical analyses followed the procedure used in Chapter two[289]. There was no indication of convergence issues for any of the models (all Rhat values = 1.00, no divergent transitions).

3.3. Results

As in Chapter two, accuracy for each trial was calculated by subtracting the mean rating for all non-target words from the rating for the target word. Thus, a positive score indicates that the target word (e.g., surprising) was rated higher than all non-target words (e.g., seducing, following, fighting) with higher accuracy scores reflecting better discrimination between target and non-target words. Effects of haloperidol on fine motor control were indexed by recording the speed of participants' arm movements when producing, using a touchscreen device, their own mental and non-mental state animations (by using their fingers to move triangles around) and tracings of simple shapes. Haloperidol's effects on gross motor control were indexed by recording participant's natural speed of walking. Participants also completed additional assessments of general cognitive function and emotion perception to facilitate exploratory analyses (described in more detail in Chapter four).

Haloperidol resulted in decreased accuracy in labelling animations

A Bayesian mixed effects model with random intercepts for *subject ID* and *animation ID* (unique identifier for each animation) and a random slope for drug effects varying by subject ID was fitted to *accuracy* and the two dummy-coded predictors *drug* (haloperidol vs. placebo) and *mental state* (mental vs non-mental), as well as their two-way interaction. The model indicated a main effect of drug, where haloperidol resulted in lower accuracy in labelling the animations ($E\mu_{HALvsPLA}$ = -0.68, CrI = [-1.13, -0.21]). The posterior probability that there was a truly negative effect (P($E\mu_{HALvsPLA} < 0$)) was .99. Thus, when participants had taken the drug, their ability to correctly classify an animation decreased by 0.68 points compared to when they had taken the placebo (see Fig. 3.1). There was, however, no interaction with mental state,

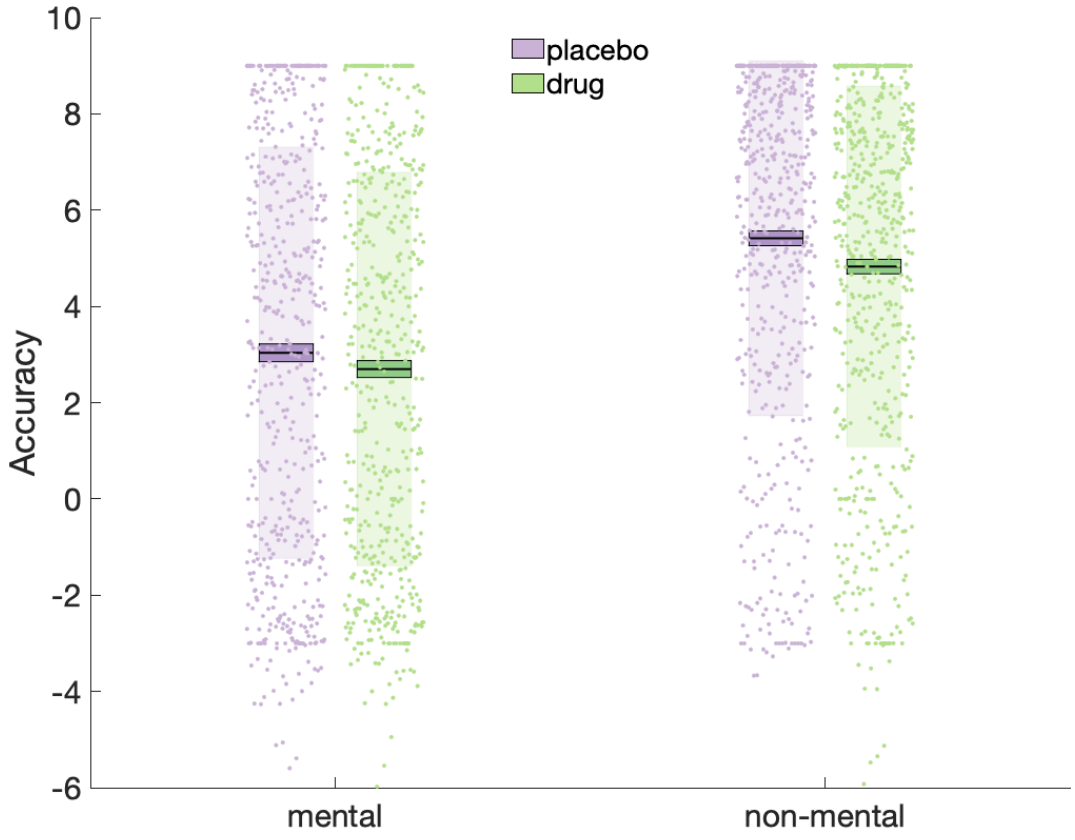

Figure 3.1. Animations task accuracy for placebo and haloperidol trials by mental state. Boxes represent 1 SEM above and below the mean (i.e., horizontal lines within boxes), shaded areas surrounding boxes represent 1 SD above and below mean values.

indicating that haloperidol decreased attribution accuracy to a comparable extent for mental state and non-mental state animations ($E\mu_{HAL,mentalVSnon-mental}$ = 0.23, CrI = [-0.33, 0.78]). Consequently, disruption of dopamine signaling using the D2 receptor antagonist haloperidol resulted in less accurate attribution of mental states to animations of interacting triangles. However, in addition we show that this effect of haloperidol is not restricted to inferring *mental* states and also extends to *non-mental* state inferences. These results raise the possibility that dopamine causally affects mental and non-mental state inferences due to its role in general cognitive functions, such as working memory and attention, which play a key role in inferential reasoning[298]. We return to this question in our exploratory analyses after first testing our second hypothesis.

Jerk and Jerk similarity predict mental state attribution performance in placebo and haloperidol trials

To test whether our observation reported in Chapter two (see also Schuster et al.[289]) that both jerk and observer-animator similarity in jerk predict mental state attribution accuracy replicates, a Bayesian mixed effects model with random intercepts for subject ID and animation ID was fit to *jerk*, *jerk difference* and the dummy coded factors drug and mental state predicting accuracy. Under placebo, there was a main effect of mental state on accuracy, indicating that accuracy for mental state animations on average was 3.55 points lower than accuracy for non-mental state animations ($E\mu_{PLA,mentalVSnon-mental}$ = -3.55, CrI = [-4.59, -2.53]). The model further revealed an interaction of jerk and mental state, where in non-mental state animations higher jerk was associated with higher accuracy ($E\mu_{PLA,jerk,non-mental}$ = 0.53, CrI = [0.04, 1.02]; P($E\mu_{PLA,jerk,non-mental} > 0$) = 0.98)) but in mental state animations negatively predicted accuracy ($E\mu_{PLA,jerk,mentalVSnon-mental}$ = -2.52, CrI = [-4.03, -1.01];

P($E\mu_{PLA,jerk,mentalVSnon-mental} < 0$) = 1). Thus, whereas in non-mental state animations with mean triangle jerk higher than 1 SD above the mean accuracy increased by 0.53 points, mental state animations with the same level of jerk were rated 1.99 points less accurately ($E\mu_{PLA,jerk,non-mental}$ - $E\mu_{PLA,jerk,mentalVSnon-mental}$ = 0.53 – 2.52 = -1.99). Furthermore, there was a main effect of jerk difference on accuracy, indicating that in both mental and non-mental state conditions, lower jerk difference was associated with higher accuracy in labeling the animations ($E\mu_{PLA,jerkDiff,non-mental}$ = 0.34, CrI = [-0.63, -0.04]; $E\mu_{PLA,jerkDiff,mentalVSnon-mental}$ = 0.37, CrI = [-1.12, 0.37]; P($E\mu_{PLA,jerkDiff,non-mental} < 0$) = 0.99; note that the latter contrast reflects that the effect of jerk difference in mental state animations was *not* different from non-mental state animations). In conclusion, in placebo trials, the effects observed in Chapter two (see also [289]) were replicated in this study.

Contrasts between PLA and HAL trials further revealed that there was no difference between placebo and haloperidol in any of the observed effects ($E\mu_{PLAvsHAL,jerk,non-mental}$ = -0.04, CrI = [-0.51, 0.42]; $E\mu_{PLAvsHAL,jerk,mentalVSnon-mental}$ = -0.28, CrI = [-1.65, 1.04]; $E\mu_{PLAvsHAL,jerkDiff,non-mental}$ = 0.09, CrI = [-0.31, .50]; $E\mu_{PLAvsHAL,jerkDiff,mentalVSnon-mental}$ = 0.80, CrI = [-0.33, 1.93]; Fig. 3.2B). Consequently, the drug did not affect the extent to which participants used jerk as an informative cue for attributing labels to animations, moreover, disrupting dopamine signaling did not affect the effect of jerk similarity on our healthy participants' ability to accurately decode animations (Fig. 3.2).

Haloperidol affects mentalizing accuracy independent of drug effects on body movement

To index drug effects on movement, jerk change scores were calculated for two different motor tasks: Drug effects on movement jerk in the animations task were calculated from

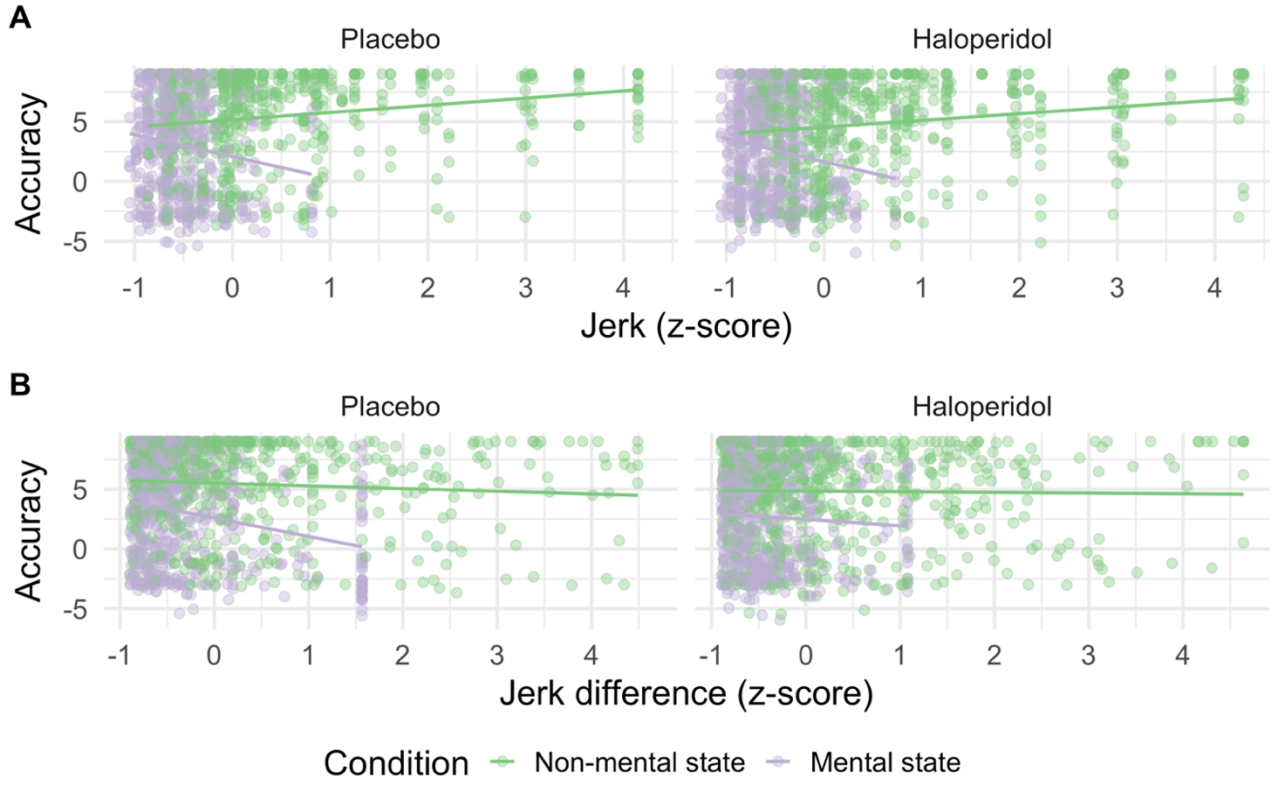

Figure 3.2. Relationships between jerk and accuracy (A) and jerk difference and accuracy (B).

triangle kinematics of animations the participants had created themselves. For each of the four word types, jerk change scores were calculated by subtracting the mean jerk values of placebo trials from mean jerk values of haloperidol trials. Correspondingly, jerk change values for the shapes drawing task were calculated by subtracting the mean jerk values of placebo trials from mean jerk values of haloperidol trials. Note that we were not able to calculate jerk values for the walking task due to the lack of positional data, causing issues relating to signal drift (see Chapter five [5.2]). Based on our previous findings that animation mean jerk is a major predictor of accuracy (Chapter two, [289]), drug effects on animations task accuracy were calculated by first selecting pairs of animations viewed by each participant in PLA and HAL conditions which were most similar in jerk. Subsequently, for each animation pair, *accuracy* change *scores* were calculated by subtracting PLA accuracy scores from HAL accuracy scores.

Two separate Bayesian mixed effects models (with random intercepts and slopes for subject ID and random intercepts for jerk level [i.e., individual rank of animations pairs with equivalent jerk levels which were used to calculate accuracy change scores]) were fitted to accuracy change scores with the predictor jerk change scores (using animations task and drawing task change scores, respectively). There were no main effects of jerk change scores and this was true irrespective of whether signed or unsigned values were used as a predictor, and irrespective of whether the jerk difference scores pertained to the animations task (signed: $E\mu_{jerkChange}$ = 0.15, CrI = [-0.32, 0.60]; absolute: $E\mu_{jerkChange}$ = 0.34, CrI = [-0.20, 0.86] or the shapes drawing task signed: $E\mu_{jerkChange}$ = -0.33, CrI = [-1.15, 0.37]; absolute: $E\mu_{jerkChange}$ = -0.13, CrI = [-1.36, 0.86]). Consequently, drug effects on participants' mental state attribution accuracy were not related to drug effects on participants' motor function, regardless of whether the direction of change was taken into account or not.

In sum, there was no convincing evidence to support the idea that dopaminergic modulation impacted mentalizing indirectly, via affecting participants' body movements. This pattern of results raises the possibility that D2 receptor antagonism has dissociable effects on mentalizing and body movement. If this is indeed the case this would make it possible that in clinical conditions such as PD, HD, schizophrenia and TS dopamine affects both mental state attribution and body movement, but these effects are dissociable.

Exploratory analysis: Can the effects of haloperidol on (mental and non-mental) inferences be formally dissociated from effects on body movements?

The extant literature concerning the role of dopamine in motor control and movement kinematics strongly emphasizes a role for striatal dopamine. Theoretical work suggests that dopamine in the ventral striatum may determine the general motivation to work for a reward

while, in the dorsal striatum, it may control how much energy is put into the specific actions/motor sequences selected to obtain rewards[299,300]. In line with this, rats with dorsal-striatal lesions exhibit reduced running speed[301] and striatum-wide manipulation of the type-2 dopaminergic receptor modifies the energy expenditure of rats engaged in a foraging task[302]. Furthermore slower arm reaching movements are apparent in early-stage PD patients, in which dopamine depletion is primarily affecting dorsal regions of the striatum[128]. Consequently, both dorsal and ventral striatal dopamine levels are strongly implicated in movement (with roles in energizing action and general motivation respectively). Whilst it is possible that striatal dopamine is also strongly implicated in mental state inference, there is no existing data to support this claim. Furthermore, neuroimaging studies of the animations task do not implicate the striatum and instead show activity primarily in 'social brain' regions such as the mPFC[303]. Consequently, it is possible that though dopaminergic modulation affects both movement and mentalizing, these effects are mediated by dissociable neural pathways.

Effects of dopaminergic drugs such as haloperidol have been noted to vary as a function of individuals' striatal baseline dopamine synthesis capacity[295]. In the absence of direct measures, such as positron emission tomography, dopamine synthesis capacity can be estimated using indices of working memory capacity[295]. Here we reasoned that if the effects of haloperidol on movement and mentalizing shared a common striatal pathway we would see that the magnitude of the effect of haloperidol on both movement and mentalizing is predicted by baseline working memory capacity. If, however, we were to see that working memory capacity predicts drug effects on one, but not both, outcomes (i.e., movement or mentalizing) this could be considered evidence of a dissociation.

Drug effects on movement depend on WM span

Individual baseline WM span was assessed using an adaptation of the Sternberg[304] visual WM task, where participants were required to determine if a single consonant had been part of a previously displayed list of consonants. For more details on the task procedure see Chapter four: Visual WM task.

As elaborated above, the majority of evidence for the modulation of motor function by striatal dopamine concerns speed. Thus, to evaluate effects of haloperidol on movement speed, first three separate Bayesian mixed effects models with random intercepts for subject ID were fit to the dummy-coded factor drug (PLA, HAL) predicting animations task, shapes drawing task, and walking task mean speed values, respectively (for details on processing and calculation of speed values see Methods). There was a negative main effect of drug on speed in all three tasks (albeit with varying levels of certainty about the true effect, as indicated by Credible Intervals and posterior probabilities P; drawing task: $E\mu_{HALvsPLA}$ = -0.11, CrI = [-0.22, -0.00], P($E\mu_{HALvsPLA} < 0$) = 0.98; walking task: $E\mu_{HALvsPLA}$ = -0.05, CrI = [-0.08, -0.01], P($E\mu_{HALvsPLA} < 0$) = 0.99; animations task: $E\mu_{HALvsPLA}$ = -0.12, CrI = [-0.31, 0.07], P($E\mu_{HALvsPLA} < 0$) = 0.90). Adding WM span as covariate to the previous models revealed that drug effects in two of the three movement tasks depended on WM span (drawing task: $E\mu_{HALvsPLA:WM}$ = 0.15, CrI = [0.03, 0.26]; walking task: $E\mu_{HALvsPLA:WM}$ = 0.48, CrI = [-0.02, 0.99]) with post hoc models indicating negative effects of haloperidol on movement speed in the low WM (drawing task: $E\mu_{HALvsPLA}$ = -0.19, CrI = [-0.36, -0.02], walking task: $E\mu_{HALvsPLA}$ = -0.08, CrI = [-0.16, -0.01]) but not the high WM group (drawing task: $E\mu_{HALvsPLA}$ = -0.02, CrI = [-0.17, 0.04], walking task: $E\mu_{HALvsPLA}$ = -0.00, CrI = [-0.04, 0.03]). While there was no interaction of WM span and drug in the model predicting animations task speed ($E\mu_{HALvsPLA:WM}$ = -0.04, CrI = [-0.22, 0.14]), visual partitioning of the data into low and high WM span suggests a trend towards a negative drug effect in the low WM group with no visible

effects of haloperidol on animations task speed in the high WM group (see Fig 3.3C), thereby following the pattern of drug effects observed for the two other measures of motor function.

Drug effects on animations task accuracy do not depend on WM span

To test whether observed effects of haloperidol on accuracy in the animations task depend on individual baseline WM span, a Bayesian mixed effects model (random intercepts for subject ID) was fit to the factor drug (HAL, PLA, dummy coded) and covariate WM span, as well as their two-way interaction, predicting accuracy. The model revealed no interaction of drug and WM span ($E\mu_{HALvsPLA:WM}$ = 0.18, CrI = [-0.29, 0.66]) while leaving the main effect

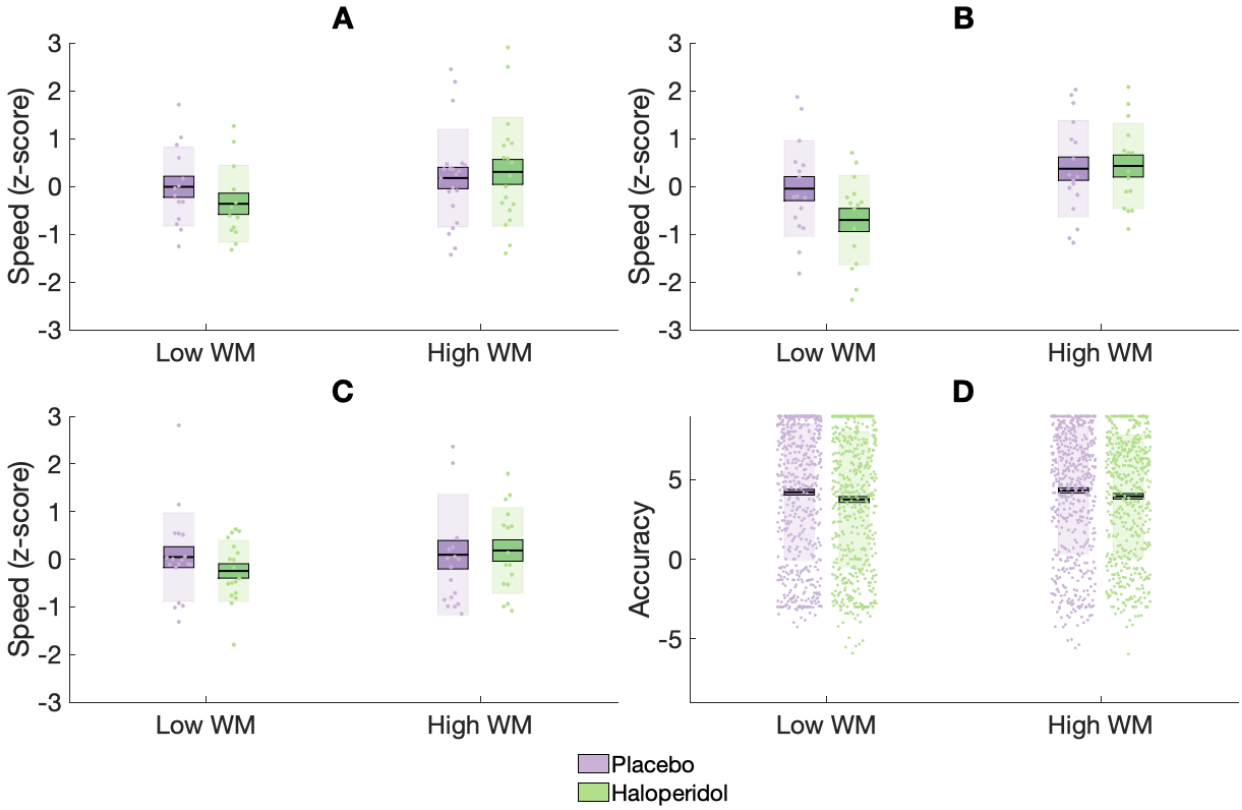

Figure 3.3. Drug effects on movement speed (A-C) and animations task accuracy (D) by WM group. Boxes represent 1 SEM above and below the mean (i.e., horizontal lines within boxes), shaded areas surrounding boxes represent 1 SD above and below mean values. (A) Shapes task speed values. (B) Walking task speed values. (C) Animations task speed values. (D) Animations task accuracy scores. WM was split in groups of low and high by median split.

of drug on accuracy unchanged ($E\mu_{HALvsPLA}$ = -0.67, CrI = [-1.15, -0.1], see Fig. 3.3D).

3.4. Discussion

The present study aimed to investigate dopaminergic contributions to mental state attribution in the animations task and to explore possible mechanistic pathways via which dopamine imbalances may affect performance in various clinical populations. We observed a decline in accuracy in labelling animations after haloperidol compared to placebo ingestion, suggesting that the disruption of dopaminergic function causally impacts on performance in the animations task. Consequently, reported mentalizing differences between control participants and patients with HD, schizophrenia, TS or PD may at least in part be a direct result of dopaminergic dysfunctions. However, we did not observe an interaction between drug effects on accuracy and mental state condition (mental versus non-mental state), indicating that performance differences between patient groups and controls may to some extent be attributable to domain-general processes rather than a specific mentalizing deficit.

Our results raise the possibility that drug-related differences in animations task performance were a result of effects of dopamine disruptions on motion perception. Compared to other mentalizing tasks, animations tasks are unique in that here (mental) states are almost exclusively communicated through motion information. More specifically, to be able to adequately decode an animation's identity, participants are required to integrate two triangles' motion trajectories into one coherent narrative. Thus, it is possible that the observed decrease in labelling accuracy after haloperidol is owed to changes in the lower- or higher-level processing of these motion cues. For instance, the ability to integrate local motion signals across space (i.e., global motion perception[305]) has been found to be impaired in some populations

which show atypical responses in animations tasks (e.g., schizophrenia[306], ASD[262]). Moreover, dopamine replacement therapy (DRT) in PD patients restored global motion perception function to levels comparable to those of healthy controls[307], suggesting a dopaminergic contribution to these processes. These difficulties in global motion perception could be attributed to an imbalance between bottom-up and top-down processing. Bayesian inference accounts (e.g., [308]) explain perceptual inference as an optimal integration of prior expectations and sensory information according to uncertainty (e.g., confidence). In other words, these Bayesian theories assume that humans are 'optimal observers', who track the stochastic properties of perceptual events to minimize surprise (i.e., prediction errors arising from discrepancies between predictions and perceived outcomes). Our expectations of what kind of perceptual events are likely to occur (i.e., priors) limit the number of possible predictions and thereby enhance the efficacy of the perception process. With respect to animations of moving triangles, humans might hold priors at various levels of the motion hierarchy[309]: At the lowest level, priors might relate to the kinematics of both triangles' individual trajectories, and may follow a normal distribution centered around human movement speed. At higher levels, priors may represent the possible motion structure (i.e., spatial configuration) of both triangles' movements, which for instance is constrained by the size of the task window (see Supplementary Figure S1.5, Appendix 1). Finally, these lower-level motion percepts may feed into higher-level predictive processes of action understanding[310], where our previous experiences of associations between particular motion patterns and mental states serve as priors. Support for the idea that top-down information is crucial for the successful interpretation of animations comes from a study investigating mental state attribution in schizophrenia[311]. In this study, patients' ability to provide appropriate interpretations of the triangles' movements was closely related to their ability to use top-down information to categorize stimuli in a different

task. More specifically, the less participants were able to use the contextual information of stimulus color to choose between two types of tasks, the less appropriate were their descriptions of the animations. Importantly, using the same paradigm, a different study demonstrated how schizophrenic patients have specific difficulties with integrating contextual, but not sensory or episodic, information to select the appropriate response[312]. Given recent findings which suggest that dopamine may be involved in encoding perceptual uncertainty independent of reward[313,314], it is conceivable that dopamine imbalances may lead to inadequate inferences from motion information present in the animations. In other words, dopaminergic signaling may reflect the relative weighting of bottom-up sensory information to top-down prior beliefs relating to the motion signals present in an animation. Consequently, difficulties in attributing the correct label to an animation may arise from atypical weighting of the incoming perceptual information in relation to prior beliefs about what a particular motion pattern may represent. More precisely, dopamine imbalances may result in aberrant signaling of the precision of predictions about an animation's identity, leading to systematic biases toward either the motion information or prior beliefs about the context of the motion information.

Further support for the idea that performance differences in the animations task may be driven by difficulties in the processing of motion cues comes from a recent meta-analysis, which reports deficits in autistic populations in interpreting control (both goal-directed [G-D] and random) animations, in addition to slightly larger impairments for ToM animations[315]. The fact that larger difficulties were found for ToM relative to control animations may simply be attributable to more complex motion trajectories present in the ToM animations. Future studies should explore the contributions of motion processing demands to animations task performance by matching ToM, G-D and random animations with respect to trajectory complexity. Finally, two random forest analyses performed separately for placebo and haloperidol trials (see

Appendix 2.4) indicated that under haloperidol, participants did not use different perceptual features to decode animation identities, further suggesting that it was the way in which perceptual cues were processed, rather than which perceptual cues were attended to, that led to performance differences under dopamine challenge.

One may argue that our findings are reflective of an alternative possibility. The lack of interaction of drug effects on accuracy and mental state condition may be due to the possibility that both mental and non-mental state animations require some degree of ToM. Indeed, one may reason that, for instance, a 'fighting' animation can elicit attributions of anger or upset. In fact, previous studies have viewed G-D animations (which are equivalent to our non-mental state animations) as entailing mental-state information, albeit to a lesser extent compared to the so-called ToM condition. This notion is supported by studies reporting graded fMRI signal changes accompanying graded levels of mentalizing demands posed by an animation[238,316]. However, if dopamine modulated animations task performance by affecting domain specific processes (i.e., mechanisms specifically dedicated to the processing of social information), based on the previous findings we would expect to see similarly graded effects on our mental and non-mental state animations. Consequently, our observation that dopamine challenge affected performance in both conditions to the same extent offers further support for a domain-general role of dopamine in mental state attribution.

A further aim of this study was to investigate an alternative mechanism via which dopamine disruption may be associated with impairments in mental state attribution: Based on the observation that disorders commonly classified as movement disorders show consistent atypicalities in social cognition, we hypothesized that dopamine may affect mental state attribution via affecting participants' motor function. More precisely, given the importance of movement similarity for the correct interpretation of an animation (see Chapter two, [289]), we

predicted that the degree to which haloperidol affected participants' movements would be associated with the magnitude of drug effects on animations task accuracy. Indeed, we observed that haloperidol affected participants' movement speed in three different tasks spanning fine- and whole-body motor control, illustrating a global effect of dopamine on motor function (note that the slightly increased uncertainty surrounding the effect on animations task movements is presumably owed to the lack of repeated trials and increased variance due to the non-periodicity of movements in this task). However, drug effects on movement speed and animations task performance were not related in the present study, thus providing no evidence for mediating effects of altered motor production on socio-cognitive processes. What is more, we observed a dissociation of the dependency of drug effects on our proxy of baseline striatal dopamine function, WM span. A slowing down of movements after haloperidol in three motor tasks (with varying levels of certainty) was evident in the low, but not high, WM group. This may be reflective of a drug induced reduction in tonic dopamine levels[135], evident only in the group with hypothesized higher susceptibility to dopaminergic manipulation due to lower dopamine synthesis capacity[295]. In contrast, there was no interaction between WM span and drug effects on animations task accuracy, suggesting that effects of haloperidol on labelling an animation's underlying (mental) state were not dependent on individual baseline dopamine function. These results prompt the conclusion that dopamine likely modulates mental state attribution independent of motor function, via dissociable pathways.

Mental state attribution in the animations task has consistently been associated with activation of a network of brain regions including the posterior and anterior superior temporal sulcus, temporal poles, dorsomedial prefrontal cortex, inferior frontal gyrus and precuneus[317]. Two previous studies found decreased resting state cerebral blood flow (rCBF) in prefrontal (e.g., left middle frontal gyrus), as well as temporal (e.g., left inferior temporal gyrus) areas

following acute, single dose administration of haloperidol[318,319]. Consequently, we speculate that in our study, haloperidol may have affected animations task performance by altering rCBF in these prefrontal and temporal regions shown to be typically recruited when decoding animations. In contrast, the role of the nigrostriatal pathway in the control of movement is well established[320], therefore haloperidol presumably affected movement speed via postsynaptic action within the nigrostriatal pathway. Moreover, the lack of association between drug effects on movement and mentalizing tasks suggests that dopamine challenge did not affect animations task performance by decreasing movement similarity between our participants and the triangles' kinematics.

In line with our previous study[321], participants were better able to identify animations which were more similar in jerk to their own movements, and this effect remained unchanged by the dopaminergic manipulation. It is plausible that haloperidol did not change our participants' movements enough to reduce the range of animations available in the stimulus pool with sufficiently similar kinematics to their own. In particular, drug effects on movements in this study were robust but subtle (see Fig. 3.3.A-C) and may not be representative of the larger movement differences between controls and, for instance, autistic participants found in previous studies (e.g., [1,173]). Thus, the observation of the present study that haloperidol affected participants' ability to accurately decode animations without decreasing movement similarity suggests that reported performance differences between clinical populations and controls are not entirely attributable to differences in movement. Rather, performance differences may at least to some extent be owed to direct contributions of dopaminergic imbalances.

However, the possibility is worth noting that, even if haloperidol had sufficiently decreased movement similarity between observers and animations, internal action models were not affected because they may be based on long-term visual and motor experiences with one's

own actions, which were not atypical in our sample. Therefore, it may indeed be possible that over time, dopaminergic dysfunctions can lead to altering action models via long-term influence on individuals' movements. Yet, this study shows that at least to some extent, dopamine modulates mentalizing ability independent of its influence on motor systems.

There are several limitations to the conclusions that can be drawn from the current study. First, inferences about anatomical correlates of observed effects associated with our dopaminergic manipulation are merely speculative, and no definitive conclusions about the precise local actions of haloperidol on dopaminergic activity and rCBF can be made in this study. Future studies investigating dopaminergic modulation of mental state attribution should employ pharmacological fMRI or PET to gain understanding of the precise dopaminergic mechanisms underpinning atypical responses in the animations task. Second, while the present findings provide support for a domain-general role of dopamine in mentalizing processes, the whole picture of neurochemical modulation of mental state attribution is likely to be far more complex. There is growing evidence that the dopaminergic system modulates social function in interaction with the serotonergic system[212,322]. For example, reports of restored ToM function in schizophrenic patients treated with atypical, but not classical, antipsychotics have been attributed to the fact that atypical antipsychotics (e.g., clozapine) bind to both dopamine and serotonin receptors, whereas classical antipsychotics (e.g., haloperidol) selectively target dopamine D2 receptors[286,287]. Future work is needed to identify the specific contributions of the dopaminergic and serotonergic system to social cognitive function.

In conclusion, the current findings support a causal role of dopamine in the modulation of mental state attribution in the animations task. Our observation that a single, acute dose of haloperidol has deteriorating effects on mentalizing ability bears potentially important implications for individuals who are currently in treatment with classical antipsychotics.

Moreover, the non-selectivity of our observed effects is suggestive of a domain-general contribution of dopaminergic processes to performance in the animations task. Future studies should explore the specific nature of these domain-general processes in addition to possible interactions with other neurochemical modulators of ToM. Insights earned from the current and following studies may help facilitate the development of new pharmacological and behavioral interventions.

Chapter 4: Dopaminergic modulation of dynamic emotion perception

Chapter three illustrated that acute dopamine disruption has detrimental effects on individuals' ability to adequately interpret animations of interacting triangles, confirming our hypothesis that dopaminergic processes are involved in ToM. The lack of a relationship between drug effects on (mental) state attribution and drug effects on motor function suggests that dopamine may modulate mentalizing abilities directly and independently of motor and/or timing processes. In addition to deficits in ToM, disorders with dopamine system dysfunctions also display consistent impairments in emotion recognition[39,195,323]. However, currently there is not enough converging evidence on whether the dopamine system is at all involved in the modulation of emotion recognition nor concerning the putative mechanistic pathways via which dopamine may affect these processes. Chapter one elucidated the importance of motion kinematics for emotion perception based on body movements. While Chapter two confirmed that kinematics (in particular jerk) are important for mental state attribution, it is possible that emotion recognition relies on internal motor processes and/or adequate timing mechanisms to a greater extent than mentalizing. Consequently, this chapter examines the effects of dopamine manipulation on healthy individuals' emotion recognition performance, while additionally investigating potential underlying pathways relating to motor and timing processes.

4.1. Introduction

The ability to recognize others' emotions from facial and bodily cues is an important skill that facilitates the development of meaningful social relationships[324,325]. However, the cues towards genuine expressions of emotions are often highly subtle. When we are sad we do not pull a face that bears much resemblance to the Ekman example, but rather subtly alter the particular spatiotemporal dynamics of the way we move our body and face (e.g., [12,75,80]). Therefore it is perhaps unsurprising that difficulties interpreting emotions are widespread throughout a wide range of clinical conditions. Difficulties with recognizing others' emotions are particularly prevalent in clinical conditions featuring a disruption of the dopaminergic neurotransmitter system (e.g., Parkinson's disease[195], Huntington's disease[39], or schizophrenia[323]), leading to widespread examination of the role played by dopamine in such skills.

An incisive way to establish a causal role of dopamine in emotion recognition is to observe the influence of dopaminergic drugs on emotion recognition in the healthy population. Given the widespread effects of dopamine across different psychological domains, and given expansive dopaminergic projections throughout the brain, one might assume that dopaminergic drugs would have truly striking impacts upon emotion perception. However, while studies have found a range of mixed influences on neural responses (e.g., amygdala activation[326-329]) during emotion processing tasks, they have generally not found drug-related behavioral differences. One explanation for this mixed neural picture and the null behavioral findings is that there is an optimal level of dopamine for such tasks, and that – dependent upon one's baseline levels – dopaminergic modulation brings individuals closer to, or further away from, that optimum[326,327]. This theory has received widespread attention in other domains of

cognition[295,330-332]. Direct examinations of dopamine synthesis capacity and/or receptor binding are possible via positron emission tomography (PET) but are expensive and difficult to implement. Consequently, a large number of cognitive studies approximate striatal dopamine synthesis capacity via measures of working memory span – which are found to comprise a good proxy[295]. Specifically, low working memory scores are associated with low dopamine synthesis capacity, and thus have been suggested to reflect higher susceptibility to the effects of dopaminergic drugs[295]. Correspondingly, for many cognitive tasks, behavioral effects of dopaminergic drugs are found to be different in individuals with low and high working memory span[333-335]. For example, on a number of tests of executive function, performance is boosted by dopaminergic drugs in low-span participants and different effects are found for high-span participants[330,331,336]. Therefore, individuals with low dopamine synthesis capacity as indexed by low working memory span are likely to show a stronger response to a dopamine antagonist than those with higher capacity – or higher span.

It is also notable that while a role for dopamine in emotion perception is suggested by studies illustrating emotion recognition difficulties in clinical conditions linked to dopamine disruption, we do not have good mechanistic models of the nature of that role. Some plausible contenders could relate to the influence of dopamine on temporal, and perhaps relatedly, motor encoding. Specifically, many of the cues signaling emotional state are dynamic, and will therefore be highly dependent upon one's ability to encode temporal features. For instance, whereas rapid, accelerated movements are associated with anger, slower and sluggish movements tend to be interpreted as sadness (e.g.,[2,75,78-80]). It has also been hypothesized – outside of the dopaminergic literature – that recognition of such temporal features relies upon yoking to one's own movements and the emotional state experienced when performing such movements[2,110]. Given the strong link between dopamine and temporal encoding[337,338], as well

as motor performance[127,338], it is plausible that dopamine mediates emotion recognition via its influence on temporal processing.

To examine the role played by dopamine in emotion recognition, this study thereby presented participants with a dynamic whole-body emotion recognition task under the dopamine D2 receptor antagonist haloperidol, and a placebo. We separated our analyses according to working memory span and examined whether influences of the drug were modulated by performance in motor and timing tasks. To pre-empt, in line with our hypotheses we found that effects of haloperidol differed as a function of working memory span. Haloperidol impaired emotion recognition for high-span individuals and improved emotion recognition in individuals with low working memory span, this latter group were the same individuals whose movements were affected by the drug. These results help address conflicts in the literature to date by supporting the notion that the influence of dopamine on emotion recognition varies as a function of baseline dopamine levels and suggest possible mechanisms that may mediate the influence of dopaminergic drugs on emotion recognition.

4.2. Method

4.2.1. Participants

Sample (43 healthy volunteers, 19 females; mean (M) [SD] age = 26.36 [6.3]; 9 participants only completed one of two study days) and recruitment conditions were the same as in Chapter three. All experimental procedures were approved by the University of Birmingham Research Ethics Committee (ERN 18-1588) and performed in accordance with the WMA Declaration of Helsinki (1975).

4.2.2. Pharmacological manipulation and general procedure

The general procedure is described in Chapter three: Methods - Pharmacological manipulation and general procedure. After drug metabolization, participants began the task battery, which included the emotion recognition task, a verbal working memory task and indices of drug effects on movement execution and timing (see Method: Tasks and procedure; for task order see Appendix 2.1). All data was collected at the Centre for Human Brain Health (CHBH) at the University of Birmingham, UK.

4.2.3. Tasks and procedure

The tasks listed in this section were part of a larger task battery which is described in more detail in Appendix 2.2., see also Supplementary Figure S2.1.

Emotion recognition task

Stimuli were whole-body point light displays of male and female actors expressing angry, happy and sad emotional walks (i.e., point light walkers [PLWs]) adopted from Edey et al[2]. For each of the three affective states, the stimulus set contained 100% stimuli, which displayed the walkers at the speed they originally modelled. In line with the literature demonstrating that sadness is conveyed via slow, sluggish movements, anger with fast, jerky kinematics, and happiness intermediate to the two[75,78-80], sad 100% PLWs exhibited the slowest mean speed, followed by happy, and then angry PLWs[152]. In addition, for each emotion, the stimulus set included three levels of velocity adapted stimuli, consisting of morphs between the speed of neutral walkers and the corresponding 100% stimuli. The resulting velocity adapted stimuli thus contained 0%, 33% and 67% of emotion specific speed information with full postural information. A total of 48 velocity adapted and 100% stimuli (4 trials of angry, happy,

and sad PLWs at 4 levels of speed information) were presented in pseudorandom order for an average of 2000 milliseconds (ms). On each trial, participants first viewed a fixation cross for 1000 ms, followed by a PLW stimulus. Subsequently three separate visual-analogue scales were presented one after another, in pesudorandom order, asking participants to rate how intensely they felt the stimulus was expressing an angry, happy, or sad emotional state (Fig. 4.1A).

Walking task

Following the Emotion Recognition task (task order was fixed to enable comparison with a previous study using the same paradigm, and to avoid priming effects of own speed on emotion judgements based on PLWs' speeds; for more details see [2]), participants performed the walking task. The procedure for this task is described in Chapter three.

Visual WM task

Participants completed an adaptation of the Sternberg[304] visual WM task. Participants were first presented with instructions followed by practice trials. Subjects completed 60 trials across five blocks over a total task duration of approximately 10 minutes. On each trial, a fixation cross was displayed in the center of screen (500-1000 ms), followed by a list of letters (5 – 9 characters in length, depending on the block; 1000 ms), followed by a blue fixation cross (3000 ms). A single test letter was then displayed (for a maximum of 4000 ms), asking participants whether the letter was taken from the previously displayed list (Fig. 4.1B). Participants responded by pressing 1-3 on the keyboard (1 – Yes, 2 - No, 3 – Unsure). Responses (accuracy) and response time (time from test letter displayed until participant response) were recorded for each trial. Each block varied in length from 5-9 consonants, with letters randomly

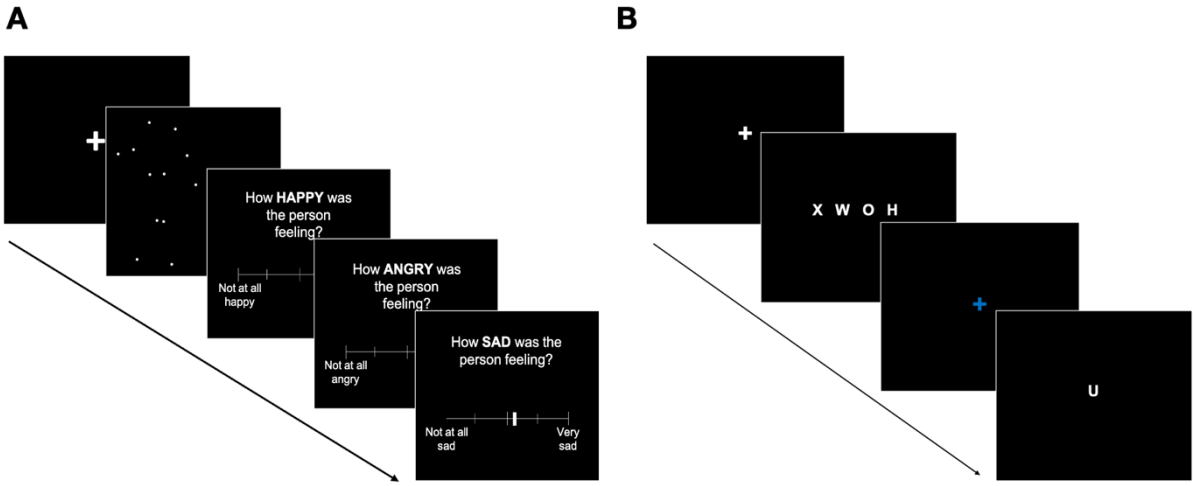

Figure 4.1. Schematic depiction of perception tasks. (A) PLW perception task. (B). Visual WM task. (A) Depiction of one trial of PLW perception task. (B) Depiction of one trial of visual WM task. After presentation of a fixation cross (duration varied between 500-1000 ms), a list of 5-9 characters was presented for 1000 ms, followed by a blue fixation cross (3000 ms).

selected from the alphabet on each trial (Fig. 4.1B).

Time estimation task

In the time estimation control task, participants were asked to estimate temporal intervals by counting the number of seconds that had passed between two auditory signals. Four different time intervals of varying lengths (between 22 and 103 seconds) were presented in a pseudo-random order.

4.3. Results

4.3.1. Effects of haloperidol on emotion recognition

As in Edey et al.[2], *emotion recognition scores* were calculated for each emotion and speed level by subtracting the mean of the ratings for the two non-modelled emotions from the rating for the modelled emotion. For example, for a sad PLW stimulus, we subtracted the mean of the ratings on the angry and happy scales from the rating given on the sad scale. High emotion recognition scores therefore reflect judgements of the PLW intensely expressing the modelled emotion and successful discrimination between the three emotion scales, whereas low or negative emotion recognition scores indicate that participants felt the PLW was weakly expressing the modelled emotion or a lack of discrimination between the three emotion scales.

Haloperidol increased emotion recognition scores in low WM span, and decreased emotion recognition in high WM span individuals

A Bayesian linear mixed effects model with a random intercept for *subject ID* was fitted to the factors *drug* (placebo [PLA], haloperidol [HAL]; dummy coded), *emotion* (sad, happy, angry; effects coded), *speed level* (i.e., emotion specific speed information; 0%, 33%, 67%, 100%; orthogonal polynomial coded) and *WM group* (low, high; effects coded), as well as all possible two- and three-way interactions, predicting emotion recognition scores. Due to the dummy-coding of the factor drug all main effects refer to the placebo level, which are compared to effects under haloperidol via individual contrasts. The first model revealed a strong positive linear trend for the variable speed level ($E\mu_{PLA,speedLevel.L}$ = 1.29, CrI = [0.94, 1.64]), confirming that, overall, participants gave increasing emotional intensity ratings with increasing speed levels (see Supplementary Figure S.3.1). There were no interactions between

drug and speed level, indicating that haloperidol did not affect participants' sensitivity to the speed manipulation (for a detailed summary of model 1 see Appendix 3). Consequently, all following results are reported based on emotion recognition scores collapsed across the four speed levels.

In the subsequent model (Model 2: Bayesian linear mixed effects model with random intercept for subject ID, factors drug, emotion and WM group, dependent variable [DV] emotion recognition scores collapsed across speed level), there was a main effect of emotion for PLA trials, with contrasts revealing that overall, sad PLWs were rated with higher intensity ($E\mu_{PLA,sad}$ = 0.65, CrI = [0.36, 0.93]), while angry PLWs were rated lower than average in terms of intensity ($E\mu_{PLA,angry}$ = -0.59, CrI = -0.88, -0.31). There was no main effect of drug, with the contrast of PLA and HAL emotion recognition scores being close to zero ($E\mu_{PLA-HAL}$ = -0.06 (CrI = [-0.37, 0.24]).

Most interestingly and confirming our primary hypothesis, there was an interaction between drug and WM group, with a 0.94 point difference between drug effects on emotion recognition scores in the low and high WM group ($E\mu_{(PLA-HAL,lowWM)-(PLA-HAL,highWM)}$ = -0.94, CrI = [-1.56, -0.32]). To evaluate drug effects in the two WM groups, two separate post-hoc models were run for low and high WM groups. These models confirmed the predicted nature of differences, revealing superior performance under haloperidol versus placebo in the low WM group ($E\mu_{PLA-HAL,lowWM}$ = 0.40, CrI = [-0.06, 0.87]), probability that this is a true effect: P($E\mu_{PLA-HAL,lowWM} > 0$) = 0.96), alongside poorer performance under haloperidol in the high WM group ($E\mu_{PLA-HAL,highWM}$ = -0.53, CrI = [-0.95, -0.12]), probability that this is a true effect: P($E\mu_{PLA-HAL,highWM} < 0$) = 0.99; see Fig. 4.2). These improvements under haloperidol in the low WM group were generated via increased ratings on the modelled scales and decreased ratings on the non-modelled scales (see Appendix 3) – demonstrating improved discrimination

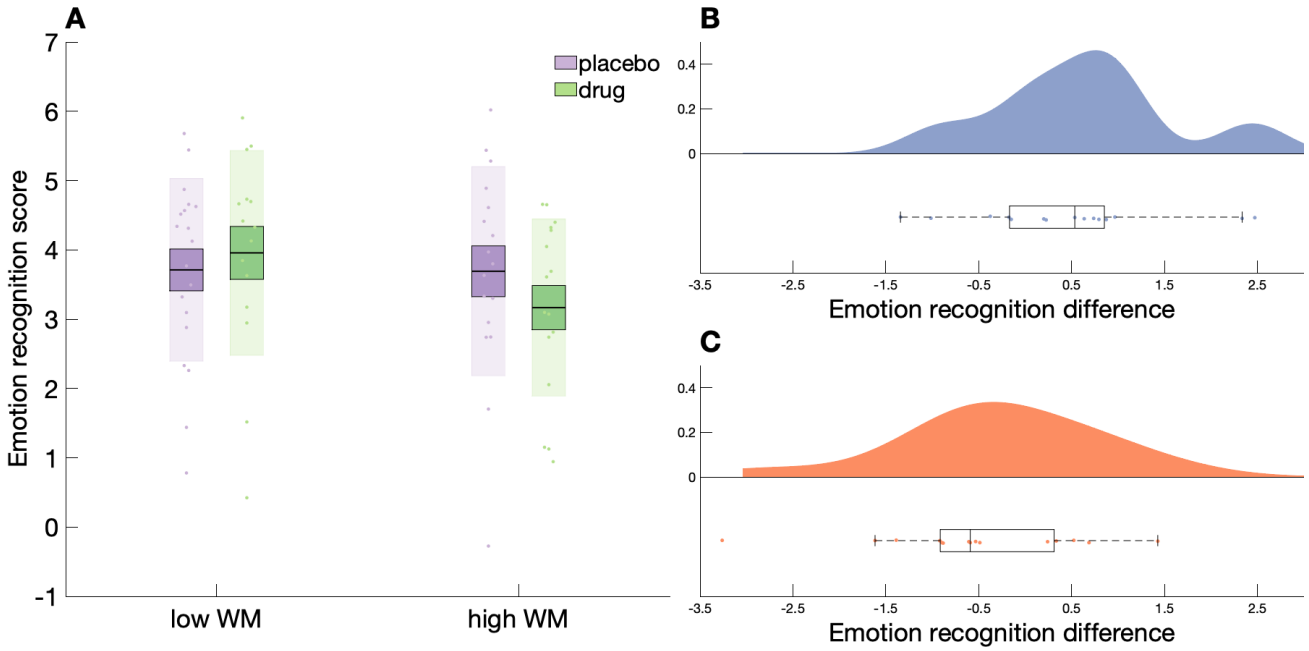

Figure 4.2. (A) Mean emotion recognition scores for placebo and haloperidol trials by WM group. Boxes represent 1 SEM above and below the mean (i.e., horizontal lines within boxes), shaded areas surrounding boxes represent 1 SD above and below mean values. (B-C) Probability density function (PDF) of emotion recognition difference scores for low (B) and high (C) WM groups. The central mark of each of the box plots below PDFs represents the median of each group, the edges represent 25th (Q_1) and 75th (Q_3) percentiles. Whiskers denote ranges of Q_3 + 1.5 x (Q_3 - Q_1) above and Q_1 + 1.5 x (Q_3 - Q_1) below box edges.

abilities under haloperidol. Note that the same picture emerged when using a continuous variable for WM span, hence for illustrative purposes we proceeded with the binary split.

4.3.2. Effects of haloperidol on participants' own movements and time perception

Movements

A Bayesian mixed effects model of drug (PLA, HAL; dummy coded) and WM group (low, high; deviation coded) indicated a negative main effect of drug ($E\mu_{PLAvsHAL}$ = -0.04, CrI = [-0.08, 0.01], P($E\mu_{PLAvsHAL}$) < 0 = 0.94), indicating that, overall, haloperidol reduced walking speed in all participants. In addition, the model revealed a main effect of WM group

($E\mu_{WMgroup}$ = 0.08, CrI = [-0.02, 0.19], P($E\mu_{WMgroup}$ > 0) = 0.94), demonstrating that under placebo, the low WM group exhibited a slower walking pace relative to high WM individuals (low WM: mean [M] = 1.05 m/s, high WM: M = 1.13 m/s). There further was an interaction between drug and WM group ($E\mu_{PLAvsHAL,WMgroup}$ = 0.09, CrI = [0.00, 0.18], P($E\mu_{PLAvsHAL,WMgroup}$ > 0) = 0.98). Separate post-hoc models for low and high WM groups indicated that, whereas the drug slowed movement speed in the low WM group, there were no drug effects on movement in the high WM group ($E\mu_{PLAvsHAL,lowWM}$ = -0.08, CrI = [-0.16, -0.01]; $E\mu_{PLAvsHAL,highWM}$ = 0.01, CrI = [-0.4, 0.6]; Fig. 4.3A).

We indexed individual drug effects on emotion recognition by subtracting emotion recognition scores of PLA trials from emotion recognition scores of HAL trials (i.e., *emotion recognition difference scores*). Positive emotion recognition difference scores thus indicate enhanced emotion recognition under haloperidol. Accordingly, we estimated drug effects on walking speed by subtracting mean speed values from PLA trials from mean speed values from HAL trials for each of the two walks (i.e., speed difference values), where negative speed difference values reflect decreased walking speed in HAL relative to PLA trials. Speed difference was added as a covariate to a Bayesian mixed effects model (random effects for subject ID) fitted to emotion and WM group as well as all two- and three-way interactions, predicting emotion recognition difference scores. The first model revealed no interactions with emotion, therefore all following results are based on a model excluding this factor. There was a main effect of WM group, confirming the dependency of drug effects on WM group as reported above ($E\mu_{WMgroup}$ = -0.79, CrI = [-1.59, -0.00], P($E\mu_{WMgroup}$ < 0) = 0.98). Furthermore, there was a main effect of speed difference, indicating that drug effects on walking speed were negatively related to drug effects on emotion recognition ($E\mu_{speedDiff}$ = -0.66, CrI = [-1.19, -0.12], P($E\mu_{speedDiff}$< 0) = 0.99). A lack of interaction between WM group

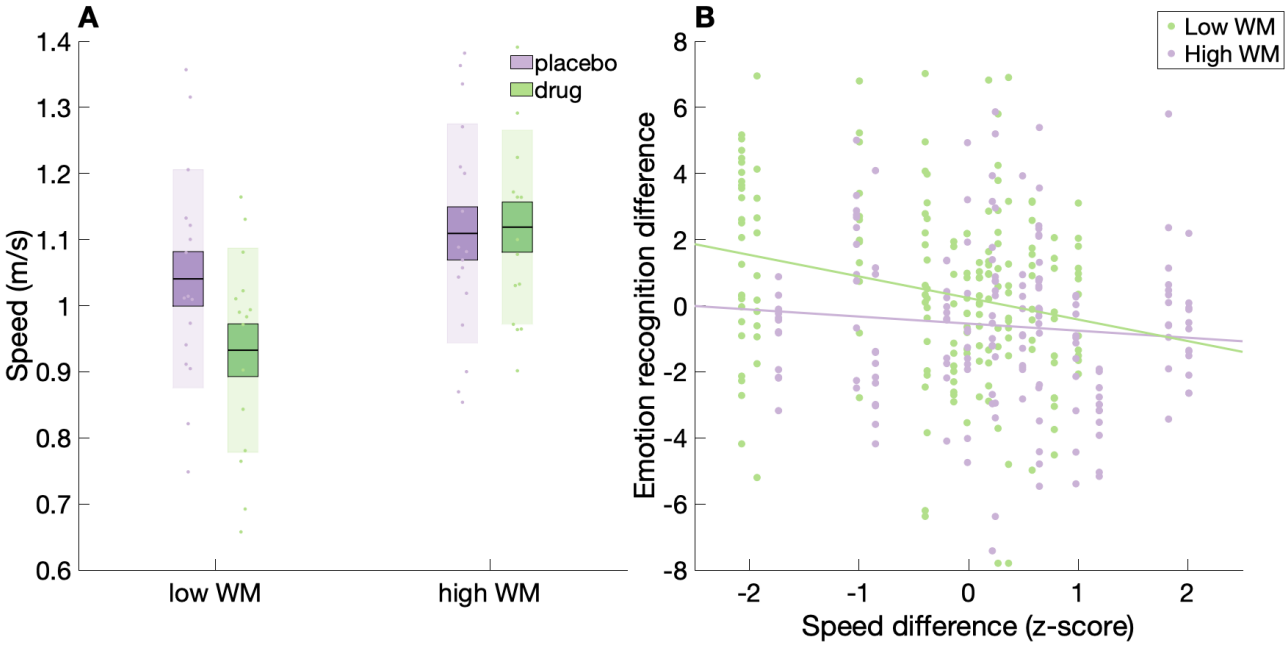

Figure 4.3. (A) Drug effects on walking speed by WM group. Boxes represent 1 SEM above and below the mean (i.e., horizontal lines within boxes), shaded areas surrounding boxes represent 1 SD above and below mean values. (B) Relationship between drug effects on walking speed and drug effects on emotion recognition scores by WM group.

and speed difference scores ($E\mu_{speedDiff,WMgroup}$ = 0.44, CrI = [-0.30, 1.21]) suggests that the relationship between drug effects on movement and drug effects on emotion perception did not depend on WM span. Thus, in both the high and low WM groups, slower movement speed under the drug was associated with increased emotion recognition, however, haloperidol-induced slowing was observed only in the low WM group (Fig. 4.3B).

Timing

Time perception difference scores were calculated as the difference between time perception scores in HAL and PLA trials. Negative time perception difference scores reflect slowed time perception in HAL relative to PLA trials. A model with time perception difference scores added as a covariate revealed no main effect of time estimation difference scores and no

interactions between any of the other predictors (WM group, emotion) and time estimation difference scores ($E\mu_{timeDiff}$ = -0.16, CrI = [-0.58, 0.27]).

4.4. Discussion

The current study tested whether the dopamine D2 receptor antagonist, haloperidol, modulated emotion recognition from dynamic, whole-body, motion cues. Interestingly and as predicted, the influence of haloperidol on emotion recognition was wholly dependent upon working memory stratification. In our low WM group emotion recognition improved under haloperidol, whereas performance deteriorated in the high WM group. The low WM group also demonstrated slower own movements under the drug, with no impact of haloperidol on walking pace in the high WM group. There was no effect of the drug on a supra-second time perception task.

To the best of our knowledge our study is the first to illustrate a clear behavioral impact of dopaminergic manipulation on the recognition of *numerous* emotions and our results thereby highlight the critical importance of accounting for individual differences in measures thought to reflect baseline dopamine function. Such results are consistent with effects of dopamine antagonists on emotion recognition previously reported in a sample of 14 males (Lawrence et al.[339]). However, whereas Lawrence et al.'s results were restricted to anger recognition we demonstrate effects across emotions, likely due to accounting for individual differences in baseline dopamine levels. Indeed, our analyses revealed only an interaction between drug and working memory span, and no main effect of drug. Thus, previous mixed neural findings and the absence of behavioral effects likely reflect such individual differences in drug response.

The observation that the low WM group exhibiting an improvement in emotion recognition also slowed their own walking pace is potentially informative with respect to the

underlying mechanism. Our results illustrated a negative relationship between drug effects on movement and drug effects on recognition of all three emotions. Speculatively, the observed effects on movement speed may reflect modulations of one's internal timer mechanisms that have not been detected via our explicit timing task. The explicit timing task required estimating intervals of long durations and the mechanisms involved here may be quite different from those required for detecting the sub-second information that conveys emotion via action kinematics[340]. It is certainly the case that sub-second and supra-second perception recruit different neural structures, and it is hypothesized that different functional mechanisms are recruited over these different timescales[340]. Alternatively, one could argue that the explicit instruction to count may have prevented the emergence of putative links with more implicit supra-second timing processes. Furthermore, the crucial role for the motor system in time perception has received widespread recent attention[341], such that a temporal influence of haloperidol on movement performance is likely to reflect wider influences on temporal encoding. It is possible that the slower walking pace under haloperidol in our low WM participants is reflective of the slowing down of an internal timing mechanism, which in turn may lead to higher emotion discrimination through increased sensitivity to temporal cues conveyed in the PLWs.

Notably we did not observe that haloperidol-related movement slowing had emotion-specific effects on recognition (slowing simply predicted improved recognition across all emotions). Such emotion-specific effects would have been interesting given previous work[2,110] which indicated that we recognize emotions according to comparisons between observed kinematic features and one's own baseline kinematics – e.g., if the kinematics are faster than the observer's baseline movement kinematics the model must be angry because this is the speed at which the observer herself feels anger. To be consistent with this, haloperidol-induced

slowing should have improved recognition of fast emotions (e.g., anger) yet impaired recognition of slow emotions (e.g., sadness). Nevertheless, given the likelihood that one builds models for emotion recognition across a lifetime of experience[107,110], artificially slowing one's movement pace in a particular setting (e.g., via haloperidol administration) would be unlikely to re-anchor all models. Given these concerns, we did not feel confident to make strong predictions about emotion-specific effects and we are, indeed, unsurprised to see that this pattern was not reflected in the data.

An important question concerns why we would see such dramatically different results in individuals with high versus low working memory. Notably, despite the absence of an effect of haloperidol on movement speed (and supra-second timing) in the high working memory span group, we nevertheless observed that the drug impaired emotion recognition in this group. Thus, suggesting that timing/movement-based effects are not the only mechanism by which haloperidol can affect emotion recognition. One additional mechanism concerns haloperidol's effects on the maintenance of mental representations. Biologically-inspired models[342-345] categorize the effects of haloperidol on mental representations in terms of putative pre- and post-synaptic drug effects. Pre-synaptic effects should correspond to enhanced updating of mental representations linked to dopamine bursts (e.g., representations that are rewarded or highly salient[346,347]). Post-synaptic effects should result in stable representations that are robust against interference from non-target information. Frank and O'Reilly[135] have argued that low-span subjects exhibit significantly greater responses to haloperidol (indexed by prolactin, an indirect measure of DA levels[348]) than high-span subjects and that higher doses are more likely to result in both pre- and post-synaptic effects. Since we used a slightly higher dose than Frank and O'Reilly (2.5mg, versus 2mg) it is feasible that our low-span subjects obtained a high enough dose of haloperidol that they experienced *both* pre- and post-synaptic effects, whereas

our high-span subjects experienced only mild pre-synaptic effects. It would follow from this that our low-span subjects should exhibit enhanced updating of rewarded/salient mental representations (the pre-synaptic effect) *and* more stable representations in general that are robust against interference from non-target information (the post-synaptic effect). In contrast, our high-span participants should have only experienced the former (pre-synaptic) effect.

For accurate emotion recognition in the context of our paradigm one must maintain a stable and robust representation of the target PLW (e.g., angry PLW), and resist replacing it with a non-target representation (for example, an imagined PLW prompted by a sad or happy rating scale). Thus, post-synaptic effects, which promote stable and robust mental representations would benefit emotion recognition, resulting in the pattern (high target ratings and low non-target ratings) we observed in our low-span group. In contrast, since pre-synaptic effects favor flexible, rapidly updated, representations they are more likely to result in the pattern we observed in the high-span group where the target and non-target ratings are confused. Consequently, models of the role of dopamine in the updating of mental representations[342-345] offer a potential explanation for the differing effects we observe in the high and low-span group, and a potential pathway to explain drug effects on emotion recognition in the absence of effects on timing/movement.

Although the importance of accounting for individual differences in baseline dopamine levels has received widespread attention in other domains of cognition[295,330-332], this study comprises the first illustration within the domain of emotion recognition. We observed that individuals in the low-span group exhibited effects of the drug on both emotion recognition and the speed of their own movements suggesting that drug effects on emotion perception could, at least in part, be mediated by effects on movement/timing mechanisms. In contrast, high-span individuals exhibited drug effects in the absence of movement/timing effects, thus revealing

that here other mechanisms must be at play. This work paves the way for future studies to examine how such effects play out with different types of emotion stimuli including static emotion snapshots wherein timing-based mechanisms are less relevant.

Chapter 5: The assessment of emotion recognition and perception on the basis of gait kinematics

While Chapter one discussed how individuals draw on internal action models built from visuo-motor experiences with their own movements when making judgements about others' emotional movements, Chapter four demonstrated how dopaminergic disruption can lead to changes in emotion perception from whole-body expressions. Section one of this chapter addresses a current shortcoming in the present whole-body emotion expression literature, bearing important implications for our understanding of emotion perception in healthy and clinical populations alike: The over-reliance on emotional stimuli generated from actors posing, rather than genuinely expressing affective states in their movements. Furthermore, this section discusses inter-individual variability in the bodily expression of emotions and use of kinematic information when interpreting others' emotional movements. Implications of the results presented in this chapter on conclusions drawn from Chapter four are discussed. Finally, section two of Chapter five presents a validation of the method used to capture changes in gait kinematics in Chapter four: smartphone-inbuilt accelerometry.

5.1. Addressing limitations in the current whole-body emotion recognition literature

5.1.1. Introduction

Body movement is rich in cues relating to an agent's underlying affective state. Recent decades have seen a growing body of work investigating emotion expression in body movement, informing the development of emotion recognition algorithms with applications in forensics, diagnostics, and entertainment. Automated emotion detection has largely focused on facial expressions (e.g., [349]), however, whole-body movement carries numerous emotion-related cues which humans can rapidly detect. Parameters such as ground reaction forces, arm swing, stride length, cadence, speed, and jerk have been found to reliably differentiate discrete emotional states such as anger, sadness, pride or joy (e.g., [73,350,351]). Kinematic measures such as movement speed have been extensively studied for their ability to reliably differentiate emotional states. Specifically, faster movements have been associated with anger and happiness, whereas slower than average body movements are indicative of sadness[2,75,78-80,82,352]. Whilst there have been advances in incorporating whole-body movements into emotion-recognition technologies[350,353], at present this field still lacks behind the facial expression literature.

One issue which has received interest in the context of emotion recognition from faces, but which has been overlooked with respect to whole-body emotion recognition, is the question of differences between posed and spontaneous expressions. Current knowledge on emotion expression in, and emotion recognition from, whole-body movement mainly stems from studies using posed expressions from professional or lay actors[25]. Crucially, when actors are asked to produce a certain emotion, they most likely draw on stereotypical representations of emotions,

resulting in stylized and exaggerated movement patterns. Consequently, kinematic measures derived from studies using posed expressions alone may not correspond to naturally occurring emotional expressions. The few studies that have aimed to measure kinematic changes after genuinely felt emotions used induction methods such as autobiographical recall or emotional music that are likely to bias kinematics such as movement speed through choice of instruction wording (e.g., 'Think about a time in your life when […] you felt like you wanted to jump up and down'[354]) or through the beats per minute of the music[80,350]. Thus, there currently is limited reliable evidence about the natural representation of emotions in the kinematics of human whole-body movement.

With respect to facial expressions, preliminary evidence suggests that induced and posed expressions differ with regard to timing and amplitude[355-357]. Regarding whole-body movement, although Kleinsmith et al.[358] claim that natural bodily expressions of emotion are "subtler, more complex and less separable", the authors do not report any evidence to support their notion. Indeed, to date there is no study directly comparing measures derived from spontaneously felt and posed dynamic bodily expressions. Consequently, the first aim of this study was to address this issue by comparing the kinematics of spontaneous and posed emotional walks.

A second question which has mostly been neglected in the literature investigating spontaneous emotion expression concerns the possibly large interindividual variability in the bodily expression of internal states. Whilst it has been widely acknowledged that there are differences in the extent to which individuals use body movement to express emotions between cultures[359,360], some studies indicate that individuals of the same culture may too differ in their propensity to express internal states via body movement. For example, gender[361-363] and personality[364] have emerged as factors which influence the extent to which people display their

emotions non-verbally. Fujita et al. interpreted their finding of decreased emotional expressivity in their male, compared to the female sample as higher compliance to so-called 'display rules'[365], the culturally induced inhibition of overt displays of affect.

Crucially, it is currently unclear how interindividual differences in the bodily expression of emotion are linked to interindividual differences in emotion perception. On the one hand, is plausible that individuals who heavily rely on their own body movements to express their internal states to a greater extent use others' movements as emotionally informative cues. On the other hand, the reverse relationship could be true: Given that people make use of their baseline walking speed when inferring affective states from others' whole-body movements[2], it is plausible that individuals who tend to deviate highly from their baseline speed when expressing emotions, or who show higher levels of more general variation in gait speed, may lack a stable representation against which to compare other people's walks. In consequence, people with highly variable walking speeds may rely less on kinematic emotion-specific information when inferring emotions from others' walks. Therefore, the second aim of this study was to examine whether within-person kinematic variance determines participants' reliance on kinematic emotion specific information.

To address these aims, we employed a within-subjects design where all participants first completed a production task, consisting of a baseline walk at preferred walking speed, as well as two emotional walk conditions (posed [angry, happy, sad], induced [angry, happy, sad]). Following the production task, all participants completed a perception task where they rated Point-Light-Walker stimuli according to how angry, happy or sad they were perceived.

5.1.2. Methods

Selection and evaluation of film clips for the induction of emotional states

The most commonly used stimulus batteries for emotion induction from video clips were developed in the 80s[366] and 90s[367] and their content may therefore be outdated and less relatable to the current generation of young participants. In addition, most existing video-sets consist of short scenes derived from longer movies with much of the contextual information missing that would be required for both general comprehension and emotional engagement in the scenes. Consequently, a new set of contemporary emotion induction videos which discretely elicit angry, happy and sad emotional states has been developed as follows.

Participants and Procedure

Forty-seven healthy participants (30 females, aged 18-50 years) took part in an online rating task designed to induce specific emotional states in the observer. Participants gave their informed consent online, prior to task completion. All experimental procedures have been approved by the University of Birmingham Research Ethics Committee (ERN 16-0281 AP5).

The online rating task consisted of a total of 15 videos, selected to induce the three target emotions angry, happy and sad (5 videos per emotion condition, average length 2.5 minutes). Videos were presented to participants in a pseudo-random order (6 possible video orders), each video followed by a rating scale requiring participants to indicate how happy, angry, surprised, disgusted, and neutral they felt after viewing each video (order of emotion scales was pseudo-randomized). In addition, participants rated valence (positive/negative mood) and arousal levels (calm/excited) following each video. All ratings were made on a 10-point likert scale, whereby 1 indicated ‘not at all’ and 10 indicated ‘very’. For valence ratings, 1 indicated ‘highly negative’ and 10 indicated ‘highly positive’.

Selection of emotion induction videos

Emotion discreteness scores were calculated by subtracting the mean rating of all non-target emotions from the target emotion rating (e.g., if participants viewed a video selected to induce anger, scores were calculated by subtracting the mean of happy, sad, surprised, disgusted, and neutral ratings from the angry rating). For each emotion, the video that provided the highest mean discreteness score was selected for emotion induction in the production task (induced condition), resulting in three target videos (angry, happy, sad). A neutral film clip with similar length as the target videos was added to the battery as a control for the emotion conditions. In addition, two short informational film clips (average length 1.1 minutes) were selected as 'neutral filler videos' with the intention to reverse any emotion induction effects in between emotion conditions.

Main Experiment

Participants and general procedure

31 healthy participants (24 females, mean age [SD] = 19.94 [3.03]) with self-reported unimpaired motor function gave informed consent to participate and received course credit or a monetary incentive as reimbursement. All participants first completed an emotion production task, where they performed several walks on a pressure gait mat: A baseline walk, three (angry, happy, sad) posed emotional walks, and three walks after induction of angry, happy and sad emotions, respectively. The production task was followed by a computerized emotion perception task, where participants viewed angry, happy, and sad point light walker stimuli (PLWs) and were subsequently asked to rate how angry, happy, and sad they perceived each stimulus to be.

Emotion production task

Kinematic data was recorded using a 5-metre-long Zeno^{TM} Walkway (ProtoKinetics LLC, Havertown, USA) gait mat.

Baseline walk. In order to gain a measure of individuals' non-emotional walking speed, all participants first carried out a baseline walk for a duration of 120 seconds by walking continuously across the mat at their preferred speed and stepping off the end to turn around each time.

Induced emotion walks. Following the baseline walk, participants viewed three target film clips which had been selected for their propensity to induce angry, happy and sad emotional states, as well as a neutral control video. Immediately after watching each film, participants walked continuously across the gait mat, resulting in four spontaneous emotion walks per participant (angry, happy, sad, neutral). Walks were recorded for 30 seconds, resulting in seven passes, across the full length of the gait mat, on average. Emotion induction videos were presented in a counterbalanced order with the neutral control video always second, in between the first and second emotional video, resulting in 6 possible orders. Before and after the third emotional film, participants viewed a 1-minute-long filler clip to reverse their mood back to neutral. After each of the four induced emotion walks, participants rated their current mood (positive – negative), arousal (calm – excited), intensity for the target emotion and four other basic emotions (anger, happiness, sadness, disgust, surprise) and the extent to which they felt emotionally neutral on a 10-point likert scale.

Posed emotion walks. Following emotion induction, participants executed three 30-second-long posed walks, simulating angry, happy and sad emotional states according to the

instruction: “Imagine you were angry (happy/sad). Walk across the mat how you think you would walk if you were angry (happy/sad)”.

Perception task

The stimulus set comprised of PLW stimuli depicting a male or female actor expressing angry, happy, sad and neutral emotional walks, originally created by Nackaerts et al.[152]. These original stimuli contained 100 % of the emotion specific velocity information (i.e., 100% stimuli), with sad PLWs exhibiting the slowest mean velocity, followed by happy PLWs with slightly faster velocities, and with angry stimuli displaying the highest walking speeds. To examine how the use of kinematic affective information varied according to one’s own kinematics, for each emotion velocity adapted stimuli were adopted from Edey et al.[2], resulting in a total of 48 emotion stimuli (mean duration 2.04 seconds). The velocity adapted stimuli had mean velocities that were morphed between the velocities of the corresponding neutral- and 100% animations and thus contained 0%, 33% and 67% velocity information with all postural information (Fig. 5.1B). To assess a possible response bias towards a particular emotion, the stimulus set also contained eight static control images that were derived from the neutral walker videos and contained no dynamic or affective information. In three rating blocks each, participants first viewed 100% stimuli, followed by velocity adapted stimuli. After each PLW stimulus, participants were asked to rate on a visual analogue scale the extent to which they felt it expressed either an angry, happy or sad emotional state (from 0 = ‘not at all’ to 10 = ‘very much’). Rating block order was counterbalanced across participants and stimulus order was pseudo-randomized within each block.

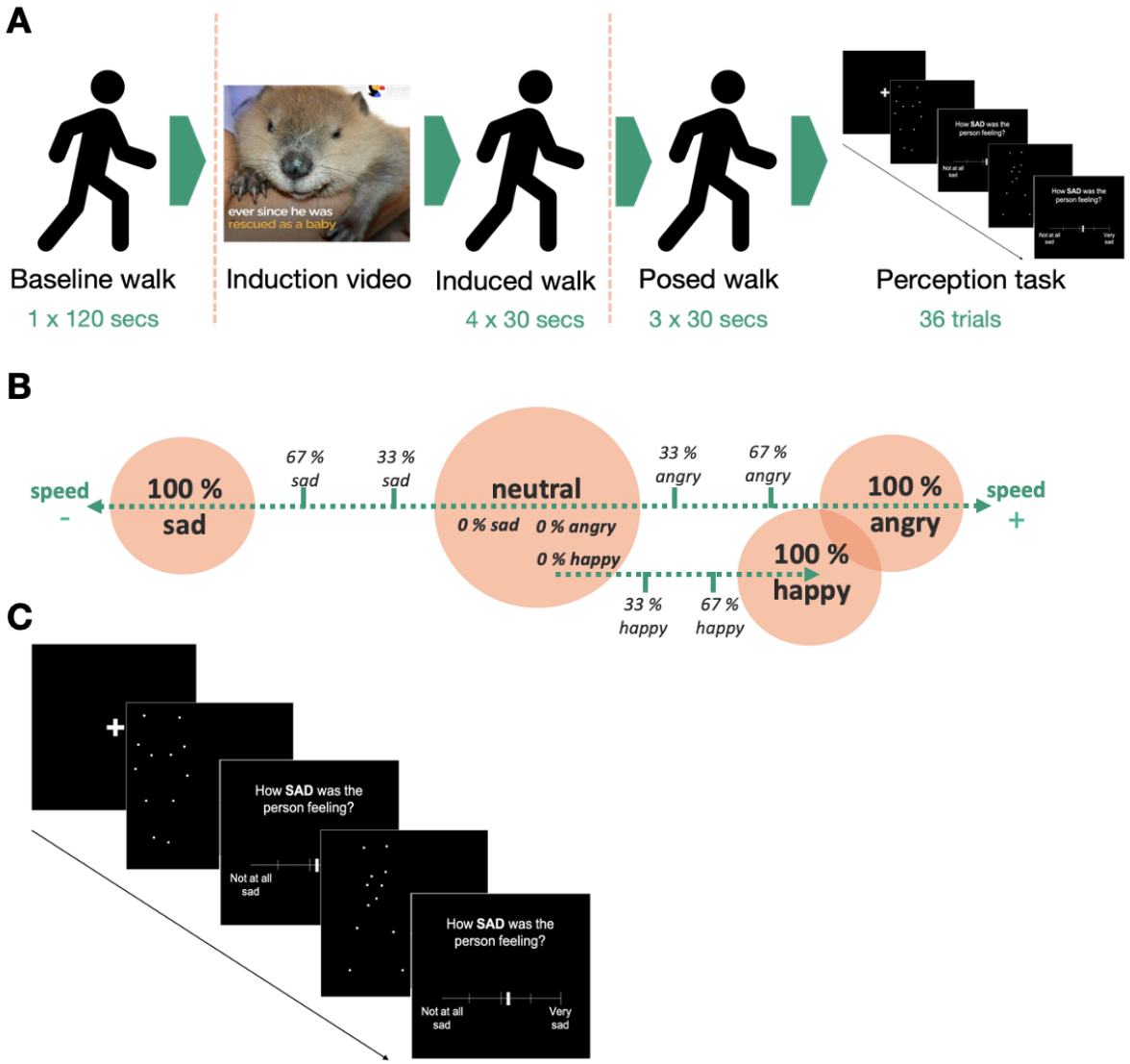

Figure 5.1. General experimental procedure and task stimuli. (A) Schematic depiction of experimental procedure. 'Secs' = seconds. The section in between the orange dashed lines represents four repeated video – walk successions. (B) Emotion perception task stimulus speed levels. (C) Schematic depiction of emotion perception task, example of 'sad' rating block.

Kinematic data processing and analysis

PKMAS software (ProtoKinetics LLC, Havertown, USA) was employed to process each walk and calculate average velocity (distance travelled/ambulation time, centimetres/second [cm/s]) across the walk periods (120 seconds for baseline walks, 30 seconds for all other walks). All data was analyzed in MATLAB R2020a. Data that did not meet

normality assumptions of parametric tests was either log- or squareroot transformed to approximate normal distribution. Any outliers as defined by values exceeding three scaled absolute deviations from the median were replaced with the respective lower and upper threshold values.

5.1.3. Results

Emotion induction successfully changed participants' mood

Due to data loss, all mood ratings data is based on a sample of 28 participants. At baseline, participants on average were in a positive mood, as indicated by valence (mean [M] (standard error of the mean [SEM]) = 6.39 (.45)) and happiness ratings (M (SEM) = 5.96 (.43)) which were significantly higher than the mid-point (i.e., 5) of the scale (valence: $t(27) = 3.06$, $p < .01$; happy: $t(27) = 2.27$, $p < .05$). In addition, ratings for all other emotions, as well as arousal, were significantly lower than the mid-point of the scale (anger: M(SEM) = 1.41(.19), $t(27) = -18.97$; sadness: M(SEM) = 1.97(.29), $t(27) = -10.57$; disgust: M(SEM) = 1.41(.21), $t(27) = -16.79$; surprise: M(SEM) = 2.41(.33), $t(28) = -7.90$; angry: $p = .002$, all other $ps < .001$).

For all four target emotions, discreteness scores were calculated by subtracting the mean ratings of the three non-target emotions from the mean rating of the target emotion. All three emotional films successfully elicited the target emotion as shown by the fact that all target ratings were significantly higher (happy) or lower (angry, sad) than the corresponding rating at baseline (Table 1). In addition, all target emotions were elicited discretely as indicated by all three discreteness scores being significantly different from zero (see Fig. 5.2).

Induced emotion	Target rating M(SEM)	Valence rating M(SEM)	Arousal rating M(SEM)	Discreteness M(SEM)
Angry	8.11(.38)***	2.46(.24)***	7.50(.44)***	3.24(.25)***
Happy	7.32(.47)**	7.61(.43)*	4.82(.49)	4.94(.55)***
Sad	8.61(.45)***	2.11(.18)***	5.54(.42)**	5.32(.40)***
Neutral	7.89(.55)**	5.18(.26)**	2.75(.40)	5.85(.66)***
Baseline walk	-	6.39(.45)**	3.50(.46)**	-

Table 5.1. Mean ratings for target emotion, valence and arousal and mean discreteness scores at baseline and for each of the emotion elicitation videos. Asterisks indicate significant differences from the corresponding rating at baseline (target, valence and arousal ratings for the four emotional videos), from the scale mid-point 5 (baseline ratings for valence and arousal) and from zero (discreteness scores) at p values of .05 (*), .01 (**) and .001 (***).

Walking speed changes as a function of posed, but not induced emotions

A repeated-measures ANOVA with within-subjects factors of condition (posed, induced), and emotion (angry, happy, sad) revealed a significant main effect for emotion (Figure 1; $F(2,60) = 60.09$, $p < .001$, $\eta^2 = .67$). There was no main effect for condition ($F(1,30) = .041$, $p = .841$, $\eta^2 = .00$). Collapsing across posed and induced revealed that angry and happy walks were the fastest, and sad walks were the slowest (angry: M(SEM) = 118.90(3.29) cm/s; happy: M(SEM) = 114.96(2.34) cm/s; sad: M(SEM) = 101.34(2.95) cm/s). Bonferroni-corrected post-hoc t-tests revealed that while there was no difference in speed for happy and angry walks ($t(30) = 2.49$, $p = .019$), sad and angry ($t(30) = 9.56$, $p < .001$) and happy and sad ($t(30) = 8.46$, $p < .001$) were significantly different. However, the ANOVA also revealed a significant condition x emotion interaction ($F(2,60) = 38.16$, $p < .001$, $\eta^2 = .56$). Separate

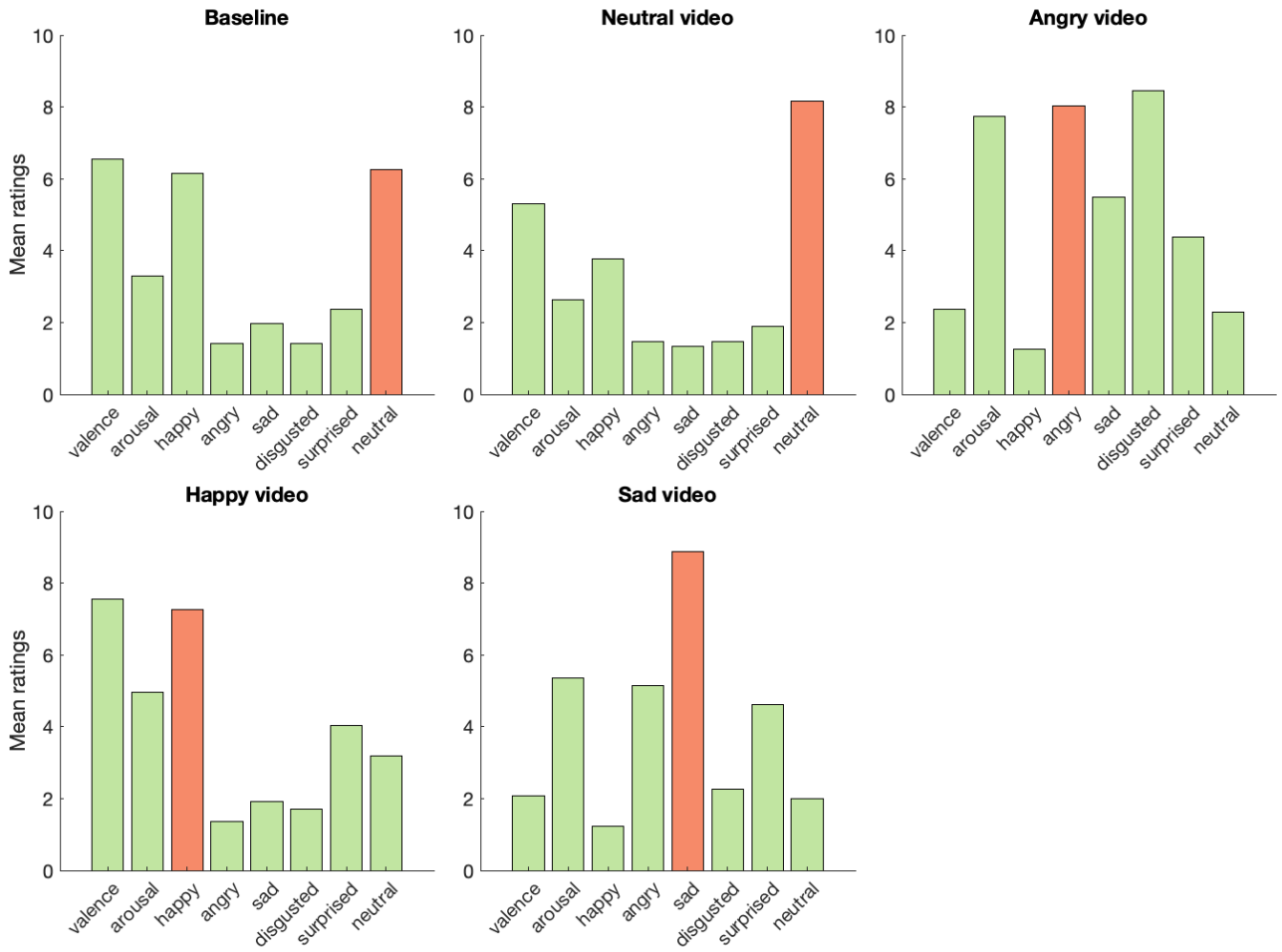

Figure 5.2. Mean emotion, valence, and arousal ratings after induction videos. Orange bars indicate the emotion rating corresponding to the target emotion.

ANOVAs for each condition indicated that, whereas speed differed as a function of emotion for posed walks ($F(2,60) = 57.39$ $p < .001$, $\eta^2 = .66$), this was not the case for the induced emotion condition ($F(2,60) = 2.34$, $p = .105$, $\eta^2 = .07$). Post-hoc tests further showed that, for the posed condition alone, there was no difference in speed for happy and angry walks ($t(30) = 1.98$, $p = .058$). However, mean speeds for posed sad walks were significantly lower than those for posed angry (sad: M(SEM) = 92.35(3.82) cm/s; angry: M(SEM) = 124.50(4.33) cm/s; $t(30) = 9.77$, $p < .001$) and posed happy walks (happy: M(SEM) = 117.85(2.40) cm/s; $t(30) = 9.04$ $p < .001$). The equivalent tests, for the induced condition, showed no difference in speed for

Figure 5.3. Mean speeds for induced (lilac) and posed (green) walk conditions. Boxes represent 1 SEM above and below the mean (i.e., horizontal lines within boxes), shaded areas surrounding boxes represent 1 SD above and below mean values. Dashed lines represent the means of the respective control conditions: walk after neutral video (lilac), baseline walk (green).

sad and angry walks (sad: M(SEM) = 110.32(2.60) cm/s; angry: M(SEM) = 113.31(2.74) cm/s; $t(30) = 2.40$, $p = .024$), sad and happy (happy: M(SEM) = 112.10(2.63) cm/s; $t(30) = 1.10$, $p = .281$) or happy and angry walks ($t(30) = .96$, $p = .343$). Thus, in our study gait speed varied as a function of emotion for posed, but not for induced emotion walks (Fig. 5.3).

In order to explore whether, in absence of speed changes between the three induced emotions, there was a change in mean walking speed from baseline as a result of the video manipulation, a further exploratory analysis was conducted using a repeated measures ANOVA with the factor 'change from baseline' and the five levels baseline, neutral, angry, happy and sad. There was a significant main effect for change from baseline ($F(4,120) = 8.58$, $p < .001$,

η^2 = .22), with post hoc tests revealing that whereas there was no difference in speed between baseline and sad walks (p = .068), neutral, angry and happy walks were all significantly faster than baseline walks (Fig. 5.3; baseline – neutral: p < .001, baseline – angry: p < .001, baseline – happy: p < .01).

Participants made use of emotion specific speed information to infer emotions

Emotion Intensity Scores

To gain a measure of emotion recognition, 'Emotion Intensity Scores' (EIS) were calculated for each emotion and speed level (3 emotions x 4 speed levels) as the mean rating on the target emotion scale (e.g., angry rating for the 0%, 33%, 67% and 100% angry stimuli) minus the mean of the two ratings of the non-target emotion scales (e.g., happy and sad). High, positive EIS indicate that participants rated the PLW as intensely expressing the target emotion, whereas low or negative scores indicate that the PLW was seen as weakly or not at all expressing the modelled emotion.

In order to test whether participants made use of the speed information when rating stimulus intensities, a 3 x 4 repeated measures ANOVA with within-subjects factors emotion (angry, happy, sad) and speed level (0%, 33%, 67%, 100%) was conducted. The analysis revealed a significant main effect for emotion ($F(2,60) = 27.60$, $p < .001$, $\eta^2 = .48$), a significant main effect for speed level ($F(3,90) = 64.38$, $p < .001$, $\eta^2 = .68$) and a significant emotion x speed level interaction ($F(6,180) = 4.12$, $p < .01$, $\eta^2 = .12$). Separate Bonferroni corrected pairwise comparisons showed that stimuli containing more speed information were consistently rated as more intense than stimuli at lower speed levels (M(SEM): See Table 2, Fig. 5.4.A; 100% > 67%: p < .05; 100% > 33%: p < .001; 100% > 0%: p < .001; 66% > 33%: p < .001; 66% > 0%: p < .001; 33% > 0%: p < .01).

	EIS			
Speed level (%)	**Angry M(SEM)**	**Happy M(SEM)**	**Sad M(SEM)**	**Overall M(SEM)**
0	1.95(.35) s**	2.61(.37) s*	4.15(.48) a** h*	2.90(.27)
33	2.36(.33) s***	3.40(.32) s**	5.22(.46) a*** h**	3.66(.22)
67	3.84(.29) s***	4.72(.35) s**	6.10(.40) a*** h**	4.89(.23)
100	4.89(.38) s***	4.32(.30) s***	7.75(.31) a*** h***	5.66(.24)

Table 5.2. Mean Emotion Intensity Scores (EIS) for angry, happy and sad stimuli at four speed levels and for overall EIS averaged across emotions. Asterisks indicate significant differences from EIS for the two other emotions (a = angry, h = happy, s = sad) at p values of .05 (*), .01 (**) and .001 (***).

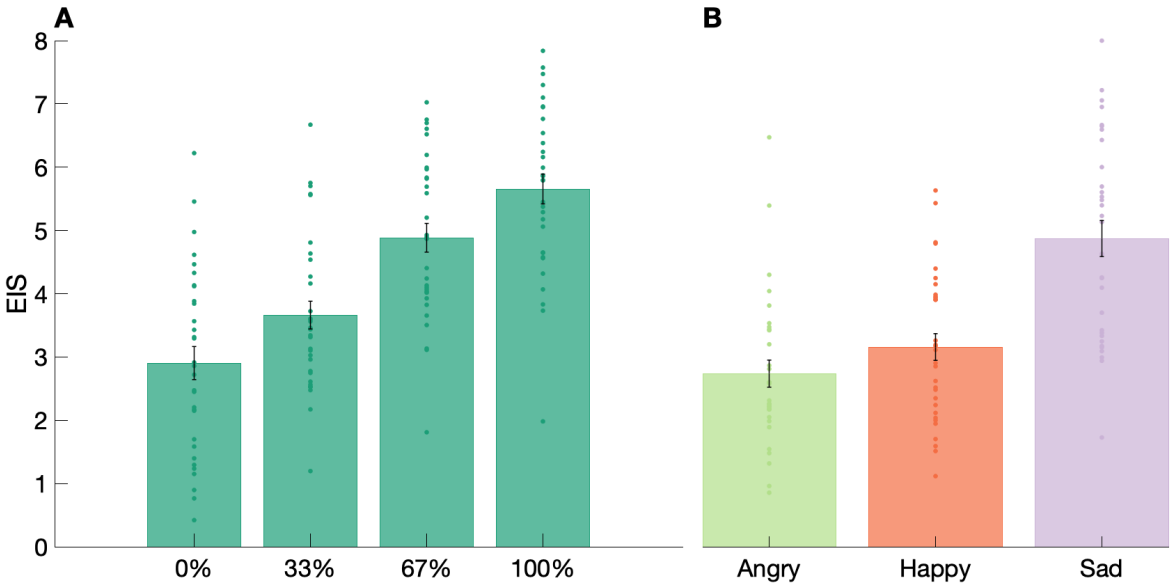

Figure 5.4. Mean EIS values. (A) mean EIS per speed level. (B) mean EIS for angry, happy and sad conditions.

Further separate ANOVAS showed that, on all four speed levels, sad PLW were rated significantly more intense than angry or happy stimuli, whilst there was no difference in intensity ratings between angry and happy animations (Fig. 5.4B, Table 2).

Separate ANOVAS for each emotion with speed level as within subjects factor showed that the extent to which intensity ratings changed as a function of stimulus speed level differed between emotions, with sad stimuli receiving the most differentiated ratings (significantly different EIS between all speed levels at $p < .05$ or higher), followed by angry (significant difference at $p < .05$ or higher between all speed levels except for 0% - 33%), and happy (no significant difference between speed levels 0% - 33%, 33% - 100% and 67% - 100%).

Use of emotion specific speed information depends on between walk variability

To assess interindividual differences in walking variability, we first calculated *speed change scores* as the mean of the absolute difference of baseline walking speed and speeds after each of the emotional videos. As we did not observe any speed change attributable to our systematic manipulation of affective state, this variable was calculated as a general measure of between-trial kinematic variability (see Discussion). We further calculated individual *Kinematic Beta Scores (KIBS)* as the slope of the regression of the stimulus speed level (0% to 100%) against intensity ratings of stimuli at all speed levels (EIS). KIBS thus reflect individual use of kinematic information, with positive values being indicative of increasing emotion intensity ratings with increasing levels of emotion-specific speed information. A simple regression analysis of speed change from baseline against KIBS revealed a significant negative relationship of speed variability with use of kinematic information (Figure 5.5A, $R^2 = .17$, $F(1,30) = 6.05$, $p < .05$), suggesting that the more an individual changed their speed between walks, the less they made use of speed information when judging emotional stimuli.

Use of emotion specific speed information predicts emotion recognition accuracy

To test the exploratory hypothesis that the extent to which individuals made use of the

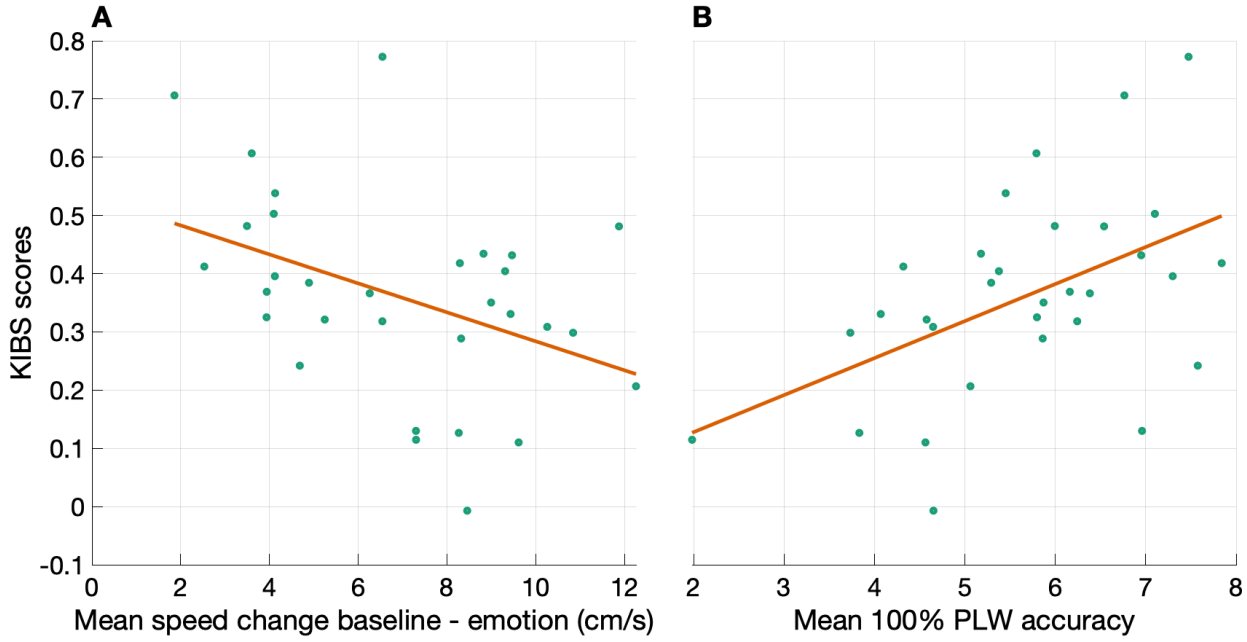

Figure 5.5. Relationship between KIBS scores (i.e., use of kinematic emotion specific information) and (A) kinematic variability, measured as the mean absolute speed change of induced walks from the baseline walk (B) mean EIS scores for 100% PLW stimuli.

emotion specific speed information when judging PLW stimuli affected their overall recognition performance, a further simple regression analysis of KIBS scores predicting the mean of all EIS 100% scores was performed. The analysis revealed a positive relationship between KIBS and EIS scores, indicating that 25 percent of variance in emotion recognition performance could be explained by participants' use of emotion specific speed information (Fig. 5.5B, $R^2 = 0.25$, $F(1,29) = 9.49$, $p < .01$). Thus, the more individuals modulated their intensity ratings according to emotion specific speed information, the better they were able to correctly identify PLWs at the full (100%) speed level.

5.1.4. Discussion

This study aimed to compare the gait speed patterns of induced and posed emotional gait. In line with our predictions and reports from the facial emotion literature[355-357], we

observed different kinematic patterns for our two emotional walk conditions. More specifically, when asked to pose emotional walks, participants walked significantly slower in the sad, compared to the happy and angry conditions. Furthermore, sad walks were markedly slower, and happy and angry walks significantly faster than participants' individual baseline speeds, thus illustrating that participants modulated their gait speeds in accordance with kinematics reported for posed emotional walks in previous studies[2,75,78-80,82,352]. Further in line with several previous findings[78,351,368,369] was our observation that speeds of happy and angry posed walks did not differ, highlighting the possibility that gait parameters like speed may differentiate the affective dimension arousal better than valence or discrete emotional states[25]. For example, Pollick and colleagues[9] found that the perceived arousal of point-light arm movements was strongly and positively related to stimulus kinematics such as speed, acceleration and jerk. This may explain why two emotions on opposite ends of the arousal space like angry and sad are better distinguishable by speed than emotions with different valence, but similar arousal (such as angry and happy).

In contrast to posed walks, analyses revealed no significant differences in speed between the neutral and any of the induced emotional walks, despite successful emotion induction as measured by post video mood ratings. However, comparing participants' walking speeds after the induction videos to their baseline speeds did uncover an increase in speed from baseline to neutral, happy and angry videos. High discreteness scores for neutral mood ratings after the neutral video indicate that this film successfully elicited the target emotional state. Thus, since individuals showed a significant change in speed after the neutral, in addition to after angry and sad videos, it is likely they did not selectively change their speed as a response to the emotion induction conditions. Rather, the speed modulation observed after some of the induction films might be viewed as non-systematic, between-trial variation of walking kinematics. While

human gait speed has been shown to be highly reliable from one trial to the next, the mean between-trial variation of 6.93 cm/s in our sample lies within a range that other studies have found to reflect non-systematic variation[370]. Accordingly, it is possible that any systematic effects of emotion elicitation on movement kinematics were too transient to be still measurable during the walking task. In addition to the gait mat, this study explored the use of iPhone accelerometers as an alternative method to capture gait data. Thus, after watching each emotional video and before the subsequent emotional walk, an experimenter had to switch on the accelerometer recording on the iPhone attached to participants' ankles. This systematic disruption to the flow of the experiment and possible social interactions between experimenter and participant could have been large enough to erase any potentially subtle effects of emotion induction. Future studies investigating the expression of spontaneously felt emotions in movement kinematics should therefore aim for smooth and fast transitions from emotion induction to motor tasks.

Yet, the possibility that our emotion manipulation did indeed affect participants' kinematics in a systematic, however much more subtle way, persists. With respect to facial expressions, several studies have shown that spontaneous expressions are portrayed with smaller amplitude than deliberate movements[356,371,372]. More sensitive methods may be needed to pick up delicate kinematic changes in emotional gait. The lack of distinguishable differences between the different induced emotions, in the clear presence of those differences between posed emotions in this study highlights the necessity for caution when inferring models of emotional gait from acted emotional walks.

A second aim of this study was to investigate whether individual differences in gait speed variability can be related to the perception of affective states from gait. Overall, incrementally reduced intensity ratings for every level of reduced speed information (67%, 33

%, 0%) signify that participants made use of the kinematic information when inferring emotions from PLW stimuli. However, the extent to which individuals used kinematic cues varied. Speed variability, calculated as the mean absolute change of walk speeds after emotion induction from baseline, significantly predicted participants' use of emotion specific speed information when judging the PLWs. Specifically, the higher an individual's speed variability, the less they were influenced by the manipulation of kinematic information when making their ratings. It could be speculated that people with high between-walk variability have a less stable reference basis to compare emotion-specific speed information against. In the same way as individuals with prosopagnosia may compensate for impairments in configural face processing by making use of motion cues[373,374], people with highly variable gait kinematics might rely more on other salient cues, such as the spatial configuration of the body movements, when judging others' gaits. However, it has been argued that point-light stimuli similar to the ones used in the present study contain only limited configural emotion specific information[77]. For example, our PLW displays did not include heads, while head position provides an important form cue of whole body movement[375]. Consequently, with potentially important emotion specific form information missing from our PLWs, in the current study reduced sensitivity to kinematic cues may have resulted in compromised recognition of emotions from these stimuli. Our exploratory analysis confirmed this hypothesis, showing that individuals with reduced sensitivity to the kinematic manipulation also demonstrated lower emotion recognition scores.

Our findings bear crucial implications for emotion recognition research employing dynamic, whole-body expressions of emotions. First, the results of this study support observations from the facial emotion recognition literature[356] in suggesting that, relative to genuine expressions of emotion, kinematics of emotional whole-body stimuli based on posed expressions are likely exaggerated. It follows that any study using emotion stimuli derived from

acted movements possibly overestimates real-world recognition performances in both healthy individuals and clinical samples. Furthermore, we demonstrated that individuals who varied highly in speed between walks made less use of the available emotion specific kinematic information. In addition, use of kinematic cues was positively related to the ability to accurately classify a PLW's modelled affective state. In combination, these latter findings suggest that atypical emotion recognition in individuals who display high kinematic variability (e.g., individuals with movement disorders[376] or autism spectrum disorders[243,377]) may in part be a result of reduced sensitivity to dynamic emotion related cues. Indeed, a recent study by Keating and colleagues[378] demonstrated that autistic individuals showed reduced recognition accuracy of angry facial expressions when these were displayed at original speed, but showed recognition rates comparable to controls when the stimulus speed was increased to 150%. While in non-autistic samples, the perceived intensity of angry emotional states has been shown to proportionally increase with stimulus speed (e.g., [2]; see also: Chapter four; Appendix 3, Supplementary Figure S3.1), the latter results indicate that autistic individuals required higher stimulus intensity to adequately recognize the angry expressions. Future studies could systematically manipulate both kinematic and spatial emotion related cues to test whether individuals with high movement variability rely to a greater extent on spatial features when inferring internal states from observed movements.

In Chapter four I reported that dopaminergic manipulation using a dopamine D2 antagonist altered participants' emotion perception. Specifically, we observed a decrease in emotion recognition performance in a subset of our sample (with high WM span), suggesting that dopamine dysfunctions could play a role in emotion recognition deficits observed in various clinical populations. Furthermore, the present chapter elaborated how genuine whole-body expressions of emotions are likely much more subtle than posed emotional expressions.

Since the stimuli used in Chapter four were developed based on posed, not genuine expressions of affective states, results of the current study suggest that the effect of dopamine disruption on emotion recognition presented in Chapter four likely underestimates the true effect of dopaminergic imbalances on the recognition of genuine expressions of emotion. Furthermore, given dopaminergic dysfunctions have previously been associated with increased movement variability in (e.g., [379-381], note that these studies used within-trial measures of gait variability such as stride length or step time variability, rather than the between-trial speed variability measure used in this study), one may speculate that emotion recognition atypicalities in conditions with dopamine dysfunctions may at least to some extent be explained by increased kinematic variability.

In sum, to our knowledge this chapter presented the first study to demonstrate that genuine expressions of affective states are associated with different gait patterns relative to posed expressions of emotions. Echoing findings from the facial emotion expression literature[355-357], the present results suggest that the kinematics of genuine whole-body manifestations of affect are more subtle compared to those of acted expressions, and thus may require an individual to be highly sensitive to kinematic changes in order to use these cues to infer emotions. In conjunction with our observation that participants who exhibited high movement variability showed reduced sensitivity to emotion-specific kinematic variation, these findings raise important implications for populations associated with high movement variability (e.g., due to dopamine system dysfunctions[379-381]), who might struggle to pick up these subtle emotion-specific cues. Future studies should test whether emotion recognition deficits can indeed in part be attributed to increased kinematic variability in these conditions. If this turned out to be the case, interventions targeted at decreasing kinematic variability may be effective in improving emotion recognition abilities in patients.

5.2. Validation of smartphone in-built accelerometry for the analysis of temporal gait parameters

5.2.1. Introduction

While spatio-temporal parameters of gait, such as step length, stride length or speed, have traditionally been used to assess gait abnormalities in injury, geriatric medicine and movement disorders, they are increasingly becoming a focus of psychological research (e.g., [351,382,383]). For example, gait characteristics have been found to be indicative of personality[382] and psychopathology (e.g., depression[384] or schizophrenia[385]). Until recently, the assessment of gait metrics required specialist equipment such as motion-capture or pressure sensing walkway systems, tools which are costly, require regular maintenance and typically are installed in fixed locations, thus lack portability. However, in the previous few years, mobile phone accelerometers have gained wide popularity as more convenient and cost-effective methods to measure human movement. With the technique originally stemming from applications in the automotive industry, accelerometer-based gait assessment has seen application in a range of fields such as sports (medicine), forensics and health care (e.g., [386-388]). Within experimental and clinical psychology, accelerometry has been used as a non-intrusive, easy to use method to capture changes in gait as a function of, for instance, cognitive load[389] or emotion processing[390,391].

However, currently it is unclear how accurate gait metrics derived from smartphone inbuilt accelerometers are in comparison to methods such as electronic pressure-sensing walkways which are commonly viewed as 'gold-standard'. By recording direct measures of a foot's contact with the ground, pressure walkways provide reliable spatio-temporal gait parameters and are widely used in clinical gait analysis (e.g., [392,393]). In contrast, accelerometry

based gait analysis typically derives foot strikes by analyzing peaks and troughs in acceleration. While several previous studies have attempted to assess the validity of smartphone-derived gait assessment, there are some limitations to existing findings. For example, various studies have used a second accelerometer (i.e., wearable sensors containing Inertial Measurement Units [IMUs]) as the 'ground truth'[394-397], without ascertaining that their reference method is comparable in accuracy to more precise instruments such as pressure walkways. Furthermore, the handful of studies which investigated agreement with a gold-standard tool are limited by small sample sizes, with some being based on a single subject[398-401]. Lastly, the majority of studies seeking to validate accelerometer-based gait parameters investigated metrics such as stride time or step time[399,400], which are often used in the diagnosis of pathological gait patterns (e.g., in Parkinson's disease). However, while gait kinematics such as walking speed have proven informative as markers of cognitive or affective change[354,384,402], studies validating gait speed estimation on the basis of smartphone devices are currently lacking.

Consequently, the present study aimed to compare gait speed collected with two smartphone inbuilt accelerometers at preferred walking speed against gait data collected with a pressure-sensing walkway (ProtoKinetics LLC, Havertown, USA). Successful validation of smartphone accelerometers against a gold-standard tool would open up new opportunities for psychological and clinical research, for example by enabling more ecologically valid and large-scale, population-based data collection outside of the laboratory.

5.2.2. Methods

Participants and Procedure

Forty healthy undergraduate and postgraduate students aged 18-32 (mean [M] = 21.03, standard deviation [SD] = 2.56) years from the University of Birmingham were recruited to take part in this study and received either a small monetary sum or course credit as reimbursement. One participant was excluded from the analyses because of a missing dataset. All experimental procedures were approved by the University of Birmingham Research Ethics committee.

In this this repeated-measures study, each participant performed a 120-seconds-long walk at preferred walking speed along a 5-metre-long walkway. Walking data was recorded (1) with two tri-axial iPhone accelerometers (iPhone 5s, iPhone 6s) using the SensorLog app (version 3.2[297]) and (2) the pressure-sensor walkway system Zeno™ (ProtoKinetics LLC, Havertown, USA), which served as the gold standard reference. Accelerometer data was recorded at 100 Hz, whereas walkway data was recorded at approximately 120 Hz. The two iPhones were attached tightly to participants' left and right lateral ankles using conventional mobile phone armbands. Participants then continuously walked across the walkway, starting with their right foot and stepping off, turning around and stepping back on the mat at the end of each pass. A walk of 120 seconds resulted in 20 passes on average. Immediately before starting each walk, participants were instructed to lift and lower their heels three times, resulting in acceleration peaks which served as a visual marker for matching up the first step of accelerometer and pressure sensor outputs.

Data processing

Accelerometer data

Accelerometer data was processed using MATLAB (version R2020a[272]). Acceleration magnitude (hereafter: *acceleration,* meters/second [m/s]^2) was calculated as the two-norm of raw acceleration values in x, y and z vectors. Each walk was preceded by three, in place, up down heel-lift benchmark motions. The walk starting point was annotated as the first acceleration peak after the three benchmark peaks, and the end point was annotated as the last peak in acceleration (i.e., last footfall, see Fig. 5.6A). Turns between passes were annotated in acceleration envelope minima (occurring approximately every four gait cycles). Subsequently, the duration of each pass was estimated by taking the difference between timestamps for starting and envelope minima points. To obtain an estimation of mean speed across the whole 120 seconds walk, first individual mean speed per pass was calculated by dividing the length of a pass (i.e., mat length, 5m) by its duration. Following this, speed estimates for all passes were averaged across the whole walk. Each data processing step was performed for left and right feet data individually and values were subsequently averaged across left and right. There were eight datasets for which only data from one iPhone was available (for one participant data from one phone was corrupted, for seven participants data was only recorded with one phone). Note that the two iPhones used in this study (iPhone 5s, iPhone 6s) had different inbuilt accelerometers, however the values from the two iPhones were found to be highly correlated (Spearman's Rho = .997, $p < .001$).

Zeno Walkway data

ProtoKinetics Movement Analysis Software (PKMAS, ProtoKinetics LLC, Havertown, USA) was employed to process pressure sensor data and calculate average speed. First, replays

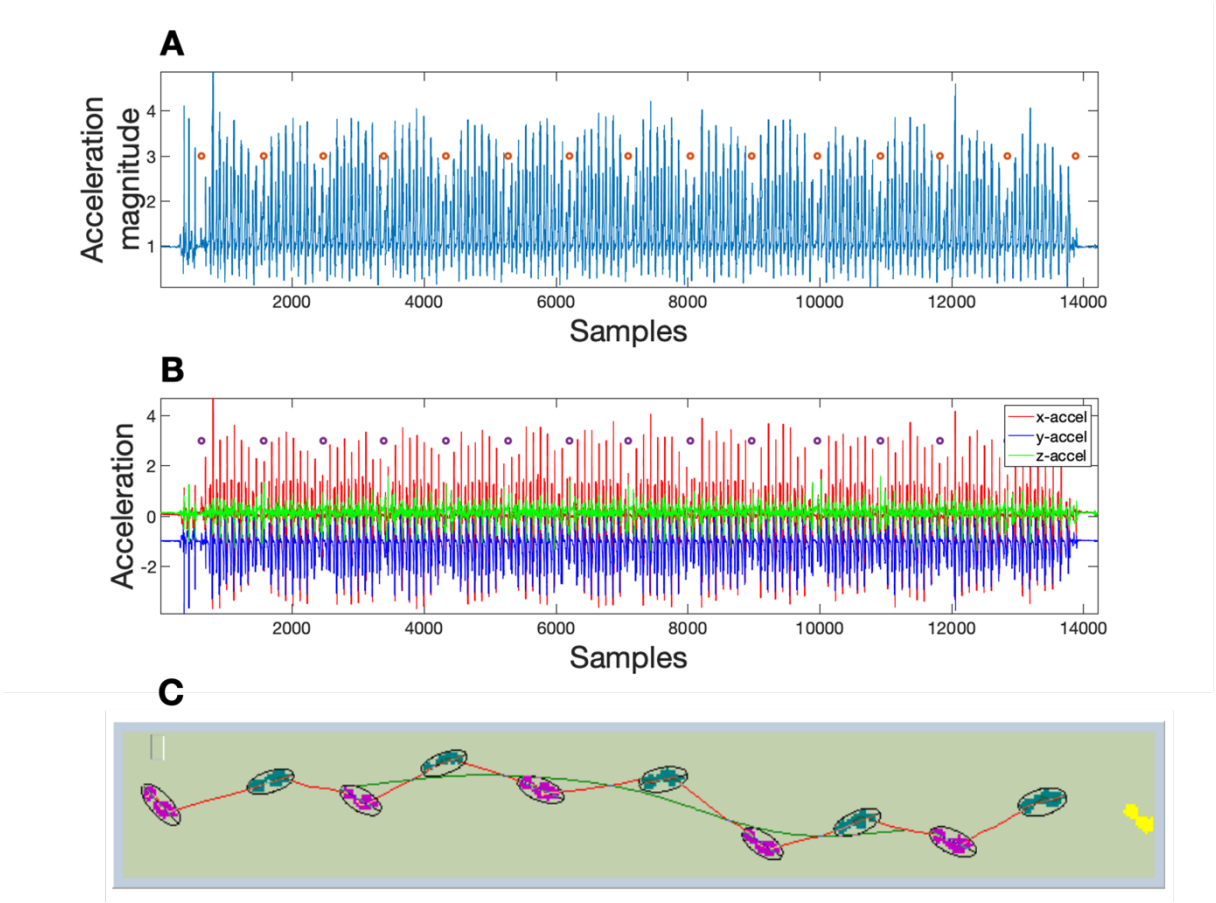

Figure 5.6. (A-B) Example of accelerometer data processing. (A) Orange markers represent manually annotated peak minima in acceleration, reflecting turns between passes. Accelerometer speed data was calculated for each pass by dividing the distance travelled (i.e., mat length) by the difference in time stamps in between markers. Subsequently, average speed across the whole walk was calculated as the mean of individual pass speed values. (B) Raw acceleration in x, y and z planes. (C) Foot strikes as recorded by the Zeno Walkway. Magenta = right foot contacts, green = left foot contacts.

of recorded walks were visually inspected for accurate capture of individual footfalls, and incomplete footfalls removed (see yellow shaded area in Fig. 5.6.C). Subsequently temporo-spatial gait parameters were exported. Mean speed was calculated by the software from the center of pressure recordings of left and right feet as distance travelled divided by ambulation time (cm/s). Finally, walkway data was converted to match units of accelerometer data (i.e., m/s).

5.2.3. Results

Speed data of both methods was normally distributed as assessed by visual inspection of histograms. To assess concurrent validity, average speed values of the two measures were compared using linear regression coefficients and Bland-Altman 95% limits of agreement. Bland-Altman (BA) plots are commonly used in movement analyses to examine the difference between two different instruments. By plotting the difference of two measurements against their mean, BA plots facilitate the evaluation of biases as well as possible relationships between potential discrepancies and true values (i.e., the means between the two measures as best estimations of the true values). According to Bland and Altman[403], evaluation of agreement of two variables presupposes that the differences between two measures are normal distributed. Figure 5.6 shows the agreement between accelerometer derived (iOS) and walkway derived (gait mat) mean speeds. There was a strong linear association between speed values collected with the accelerometer and walkway devices ($r = 0.94$, $p < .001$, Fig. 5.6.A). The mean difference of 0.38 shows that on average, speed values measured with the walkway method are 0.38 m/s larger than accelerometer derived speed values (Fig. 5.6.B). Because the line of equality (i.e., mean difference = 0) is not within the 95% confidence bounds of the mean difference, we conclude this represents a systematic bias. Limits of agreement of 8.6 % further suggest that for 95% of the sample, the range of difference between the two methods lies between -0.24 and -0.51 % (∓1.96*SD). The BA plot further illustrates a negative relationship of the differences, with higher differences between the two instruments for higher speed values.

5.2.4. Discussion

The present study aimed to evaluate the agreement between gait speed data collected with a smartphone accelerometer and a pressure sensing walkway, which served as the gold

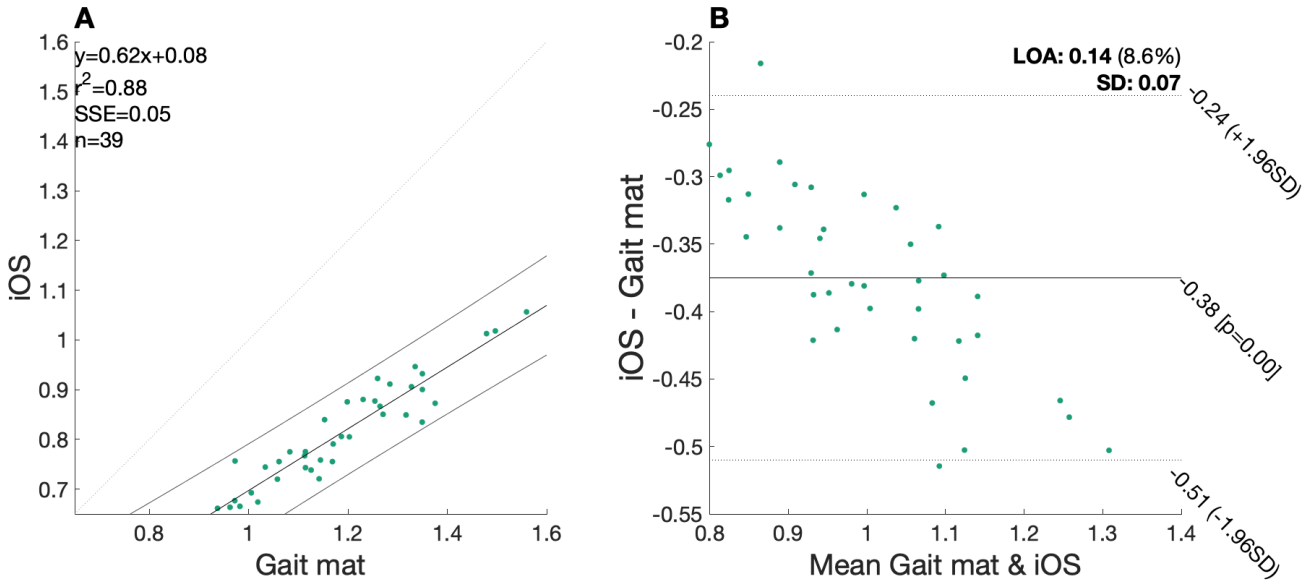

Figure 5.7. Plots for the comparison of accelerometer (iOS) and pressure walkway (gait mat) speed (both m/s). (A) linear model of iOS and gait mat speed measures. Y = model equation, r^2 = coefficient of determination, SSE = Sum of squared error, n = sample size. Solid diagonal lines around fit line represent 95% confidence intervals of fit line. (B) Bland-Altman plot. LOA = limits of agreement (1.96*SD). The solid horizontal line represents the mean difference. Horizontal dashed lines represent upper and lower limits of agreement (mean difference ∓1.96*SD).

standard. Whilst the correlation analysis suggested a strong association between speed values of both methods, the BA analysis revealed a bias for the accelerometer method, indicating that speed values collected with the smartphones were on average 0.38 m/s slower than speed values collected with the pressure walkway. If this bias was constant, future studies could simply add this value to any speed measure derived from a smartphone accelerometer to approximate the true speed value. However, with limits of agreement of 0.14m/s, the difference between iOS and walkway derived speed values ranges from -0.24 m/s to -0.51 m/s. Bland and Altman[403] recommended that criterion values for acceptable limits of agreement between two methods should be decided based on the purpose of the data collection method. With studies which have previously found associations between changes in gait speed and psychological function

reporting mean group differences ranging from 0.17 to 0.36 m/s, it is possible that a smartphone accelerometer employed with the current design may miss meaningful change in walking speed.

It is likely that in the current study, the observed bias and relatively high variation around this bias was a direct result of the study design: In order to gain clear step signals from footfall pressures in the walkway recording, individuals stepped off the mat at the end of each pass and turned around to step back on. Across the whole 120 seconds walk, this likely lead to longer walk durations recorded from the iOS accelerometer, while for both measures the mat length (5m) was used as distance travelled for speed calculation. Our data further showed a negative relationship between difference values and the estimated true value, indicating higher differences between the two methods for faster participants. One may speculate that participants who were faster tended to step further off the mat when turning around, leading to larger biases in the accelerometer derived data, and ultimately to the observed skew in difference values. Thus, we conclude that a large proportion of the difference between accelerometer and walkway derived speed data in this study is owed to a discrepancy between actually travelled and estimated walking distance. In the present study, we chose not to approximate speed by integrating acceleration, as this way of calculating speed is well known to result in inherently noisy signal due to the accumulation of measurement error over time (i.e., integration drift, see [404]). This is a well-known issue accompanying gait speed estimations on the basis of accelerometers/IMUs and presumably why the literature lacks successful validations of accelerometer derived speed measures. While filter algorithms exist to minimize this drift (e.g., [405]), the adequate application of these would have exceeded the scope of this study. An alternative feasible way to decrease the bias in the accelerometer data could be to use longer walkways, thereby reducing the number of steps exceeding the estimated walking distance during turns. The study presented in Chapter four used a walkway of ten meters (as opposed to

the five-meter-long walkway of this study), which across the identical walking time of 120 seconds would have resulted in approximately half the amount of turns as in the present study, thus likely resulting in increased accuracy of the accelerometer derived speed data.

In conclusion, the comparison to a pressure-sensing walkway system revealed a systematic bias of speed data calculated based on smart-phone inbuilt accelerometry if a fixed, predefined distance is used across which participants walk numerous laps. Future studies estimating gait kinematics with smartphone accelerometers in the laboratory should aim to minimize the discrepancy between actual distance walked and distance used for speed calculation. However, to be able to fully exploit the accessibility and portability of smartphone accelerometers in psychological research (e.g., through large-scale data collection of natural walking outside of the laboratory), future research would benefit from evaluating currently available filters (see [405]) for their aptitude to sufficiently minimize integration drift.

Chapter 6: General Discussion

6.1. Overview of findings

Overlapping atypicalities in social and motor function have been observed in a variety of clinical populations which have all been linked to a dopamine system dysfunction[50], however the nature of this three-way relationship is currently unclear. The present thesis examined the relationship between motor- and socio cognitive function in healthy individuals as well as the role of dopamine in this relationship, using a pharmacological model of dopamine disruption. One of the aims of this thesis was to investigate the hypothesis that dopamine modulates socio-cognitive functioning via affecting motor function and thereby altering internal action models. Throughout the presented studies we did not find any evidence for this. While we did find evidence for movement similarity as an important factor in mental state attribution, acute dopaminergic challenge likely does not alter the action models individuals use for interpreting others' actions.

Chapter two evaluated which stimulus characteristics individuals make use of when interpreting the movements of triangles in the animations task. We confirmed triangle jerk and other kinematics to be crucial for successful identification of animation identity and determined a variety of additional spatial stimulus features, such as certain trajectory components, as important for the accurate interpretation of animations. More intriguingly, the chapter demonstrates how similarity between an observer and the creator of an animation in a selection of those features facilitated mental state attribution. Chapter three discussed the contribution of dopaminergic disruptions to altered performance in the animations task and evaluated whether dopamine disruptions may lead to compromised mentalizing by decreasing movement

similarity between two counterparts. The study illustrated that dopamine disruption using a dopamine D2 receptor antagonist results in decreased accuracy in labelling both mental and non-mental state animations, supporting the idea that dopamine modulates mental state attribution in a domain general way. Furthermore, dopamine challenge affected participants' motor function, however drug effects on motor and socio-cognitive ability were not related. Thus, findings do not provide any evidence for a role of dopamine in affecting motor simulation processes by decreasing movement similarity between observer and animator. Instead, while it is still possible that dopamine affects internal action models via its long-term effects on movement, our results suggest that dopamine in part modulates mentalizing ability independently of its influence on motor function. Chapter four investigated the influence of aberrant dopamine signaling (using the same dopamine D2 antagonist as in Chapter three) on emotion perception from whole-body motion. Findings of this study implicate dopaminergic processes in emotion perception. Furthermore, in this study drug effects on social and motor function were related, however not in the selective way that would have been predicted if dopamine had affected motor simulation processes, thus again suggesting no influence of dopamine manipulation on internal action models. Rather, drug-related changes in motor function and the observed relationship to changes in emotion recognition performance may be reflective of effects of dopamine challenge on internal timing mechanisms. The fifth chapter of this thesis addressed a prevalent limitation of studies investigating emotion perception based on movement information, namely the fact that the majority of dynamic emotion stimuli are created using actors posing affective states. The hypothesis that genuinely felt whole-body expressions of emotional states do not show the same kinematic patterns as posed emotions was supported by our results and confirms previous observations in the facial emotion expression literature[355-357]. The chapter further showed that the extent to which an individual uses

kinematic information to infer emotions from others' movements depends on their own kinematic variability, suggesting that clinical populations which exhibit higher degrees of movement variability may to a lesser extent draw on their own motor experience when judging others' affective actions. Finally, the fifth chapter presents a short analysis of the concurrent validity of smartphone accelerometers for the assessment of walking kinematics, demonstrating a strong relationship between the smartphone data and gold-standard reference. However, the study also revealed a systematic bias in the smartphone recordings, the implications of which are further discussed in the following sections of this thesis.

In summary, this thesis demonstrated how dopaminergic processes are involved in socio-cognitive function, including both emotion perception and mental state attribution. Whilst dopamine disruption affected motor function in addition to socio-cognitive abilities, we did not find any evidence to support the hypothesis that dopamine may modulate social cognition via affecting motor function. Instead, our results suggest that dopamine regulates social and motor function independently.

Throughout the remainder of the discussion, I present a synthesis of all findings of this thesis and elaborate the potential alternative mechanisms via which dopamine may affect both social and motor function. Finally, I discuss implications for clinical populations and provide directions for future work.

6.2. The role of dopamine in the relationship between social and motor function

Individuals with movement disorders, such as patients with PD, HD and TS, as well as individuals who present with motor atypicalities in addition to other primary symptoms (e.g.,

ASD, schizophrenia) all show difficulties in the attribution of internal states to others. Overlapping motor and socio-cognitive symptoms in these conditions may be indicative of a causal relationship between social- and motor abilities in these individuals. Based on previous research suggesting that we use representations of visual and motor experiences with our own actions to interpret others' movements[1,2,110], the primary hypothesis of Chapter two was that movement similarity between observer and agent should foster an observer's accurate labelling of another agent's social movement cues. Presenting a novel adaptation of a classic task which utilizes movement cues to convey mental states, Chapter two confirmed this hypothesis, illustrating how similarity in several movement properties between an observer and the original animator of an animation facilitated the correct interpretation of that animation. These results suggest that individuals whose representations of mental states are associated with similar kinematics (and other movement features) are better able to interpret each other's depictions of those mental states. Given the involvement of dopamine in motor function, as well as the established link between all of the abovementioned clinical conditions and a dopamine system dysfunction, we hypothesized that dopamine may affect social perception by affecting individuals' internal action models.

6.2.1. Effects of acute dopamine challenge on putative motor simulation processes

As outlined in Chapters three and four, dopamine challenge did affect motor function in a subgroup of our participants in three different motor domains. The D2 antagonist haloperidol decreased movement speed in subjects with hypothesized high susceptibility to dopaminergic manipulation in the production part of the animations task, a shapes drawing task, and a walking task. Dopamine disruption further resulted in changes in social performance: Haloperidol affected mental state attribution (Chapter three) and emotion recognition (Chapter four).

Moreover, while effects of the drug on mental state attribution scores were independent of any drug related changes in motor function, drug effects on emotion recognition were statistically related to drug effects on motor function.

Yet, as indicated in Chapter four, effects of dopamine challenge on emotion recognition and walking speed were not related in the selective way that we predicted. Based on evidence of specific associations between gait speed and perceived affective state[75,78-80,82], and on suggestions that individuals may judge observed affective movements in relation to their own movement kinematics[2,110], we expected that drug induced motor slowing would be related to higher perceptual sensitivity for emotions which are generally associated with faster walking speeds. In other words, we predicted that (given individuals' moods remained unchanged by the pharmacological manipulation), by reducing participants' movement speed, haloperidol may have biased their internal representations associated with a slower walking speed towards a neutral mood state. As a consequence, we hypothesized that those individuals would show lower recognition rates for sad PLWs, because they perceived the speed of the sad (i.e., slowest) PLW stimulus to be most similar to their own, slower walking speed, which they did not associate with a sad mood. In contrast, the same participants might have perceived the angry PLWs' speeds as more dissimilar to their own current movement speed under haloperidol compared to placebo, and in result may have rated those stimuli as more intensely expressing an angry affective state. Contrary to our expectations, those individuals who exhibited motor slowing as a result of haloperidol showed increased emotion discrimination ability not only of angry, but all emotion stimuli. In conclusion, the observed non-selective relationship of drug induced movement slowing and increased emotion recognition performance contradicts the hypothesis that our dopamine manipulation affected emotion recognition by changing internal action models of angry, happy and sad emotions.

In combination with the lack of relationship between drug effects on mentalizing and motor function reported in Chapter three, the latter results suggest that acute haloperidol administration did not affect participants' perception of social cues via effects on existing motor representations. However, while the results presented in this thesis support the proposition that the dopamine system is involved in the direct modulation of socio-cognitive processes, they do not rule out the possibility that, *in addition* to direct, acute effects on social ability, long-term dopamine dysfunction (e.g., in clinical conditions) affects internal action models via long term effects on action production. Section 6.3. discusses possible implications of these results for individuals with early-stage and long-term disruptions of the dopamine system.

6.2.2. Evidence for domain-general contributions of dopamine signaling to social ability

Perhaps the oldest debate within the social cognitive neurosciences concerns the question of whether certain aspects of socio-cognitive abilities rely on domain-specific or domain-general processes. While proponents of the domain-specificity of social cognition have argued that social ability relies upon specialized neural and/or cognitive processes which solely serve social functions (e.g., [117,406,407]), opponents believe that current experimental evidence is not sufficient to support domain-specific accounts (e.g., [408,409]). Rather, they argue that aspects of social reasoning can be wholly attributed to domain-general mechanisms, which are responsible for a broad range of skills including, but not exclusive to, the social domain. More recently, this rather dichotomous view of brain-domain relationships has been challenged and conceptions have evolved to a more integrative picture, accepting that a combination of both domain-general and domain-specific processes may give rise to socio-cognitive abilities[410-413].

Within its role as a modulator of brain function, dopamine signaling may on the one hand modulate domain-specific processes by excitatory or inhibitory action on parts of the

hypothesized mentalizing system[414]. On the other hand, well-established links between dopamine and cognitive functions such as working memory (WM) may suggest that dopamine exerts influence on social ability by regulating domain-general processes. Determining the exact neuroanatomical actions of dopamine, and thus explicitly linking dopaminergic actions to structures proposed to underlie specialized or non-specialized mechanisms lies outside the scope of this thesis. Nonetheless, Chapters three and four provide some evidence which supports a domain-general contribution of dopaminergic processes to social functioning.

First, as outlined in Chapter three, dopamine manipulation in our sample of healthy participants resulted in an overall decrease in their ability to correctly identify both mental state and non-mental state animations. The non-mental state animations employed in this study were adopted from Abell et al.[42], who selected their original goal-directed (G-D) animations with the intention of evoking descriptions of interaction, but without the implication that one triangle was reading the other's mind. In their study, the younger autistic and control groups were better at identifying the G-D animations compared to the mentalistic ToM animations, a result which could be ascribed to the higher mentalizing demands present in the ToM animations, as animations were matched for overall difficulty and perceptual complexity. The meta-analysis[315] referenced in Chapter three confirms a conceptual difference between these animation types by reporting a general consensus of a subtle but evident performance difference between autistic and control groups in interpreting the ToM and G-D animations. Under the assumption that correctly interpreting the G-D animations does indeed not require the spontaneous attribution of mental states, our observation that dopamine disruption impaired performance for both animation types equally indicates that dopaminergic processes may play a more general role in modulating performance in the animations task. Furthermore, in the study discussed in Chapter three, although there were no group-level drug effects on working memory (WM) performance,

individual drug-related changes in WM scores were related to drug effects on both mental and non-mental state animation accuracy (see Appendix 2.3). This relationship, as well as a lack of relationship to other measures of ToM (i.e., cognitive and affective ToM as measured by the MASC task) suggests that the finding of reduced animations task accuracy after haloperidol does not reflect dopaminergic modulation of dedicated ToM processes, but rather may be a result of drug induced changes in more general cognitive abilities (such as working memory). Section 6.2.3. provides a detailed analysis of the potential domain-general mechanisms underlying the observed findings.

Second, we argue that the observed pattern of results presented in Chapter four, wherein haloperidol resulted in improved emotion recognition performance in subjects with low, and decreased emotion recognition abilities in individuals with high baseline dopamine levels, can be best explained by effects of dopamine challenge on domain-general mechanisms such as time estimation and working memory abilities. I reiterate the main points of this discussion in Section 6.2.3.

Collectively, I argue, the observed effects of dopamine challenge on performance in two tasks measuring mentalizing and emotion recognition are reflective of domain-general contributions of dopamine to social function. The following section elucidates three candidate mechanistic pathways via which dopaminergic processes may impact on social and motor ability.

6.2.3. Three possible mechanistic pathways of dopaminergic modulation of social function

The working memory hypothesis

Undeniably, successful social interaction requires the ability to access, maintain and manipulate oftentimes large amounts of information relating to others as well as oneself. Thus, the idea that executive functions (including abilities such as working memory, inhibitory control, and attention[415]) are recruited during the processing of social cues is perhaps unsurprising. Yet, amongst social cognition researchers it is highly debated whether socio-cognitive function at least in part relies on executive functioning. As already discussed in Chapter three, a variety of studies find no statistical relationships between measures of executive function and socio-cognitive performance, suggesting independence of socio-cognitive and executive function processes (e.g., [46,202,416,417]). Other studies, however, do provide evidence for an involvement of executive functions in socio-cognitive performance and include correlational studies which report statistical relationships between socio-cognitive ability and executive function[418,419], dual-task paradigms which show that mentalizing performance decreases with increasing cognitive load[420,421] and lesion studies demonstrating socio-cognitive impairments in patients with neuronal damage in brain regions specifically associated with general cognitive ability[422]. For example, investigating links between ToM performance, executive functions and ASD symptoms in a large sample of autistic adolescents, a recent study[419] found strong relationships between ToM responses (including in the animations task) and performance in tasks of executive function (including indices of working memory such as backwards digit span).

It is well-established that the dopaminergic system is implicated in cognitive processes and cognitive deficits have been linked to dopaminergic dysfunctions in both the PFC[423] and

striatum[135,295]. Intriguingly, evidence from animal and human studies has yielded contrasting findings with both decreased and enhanced cognitive performance after dopamine receptor stimulation[424,425] and administration of dopamine agonists[331,426] and antagonists[135,427]. Those seemingly paradoxical effects led researchers to theorize that the dopaminergic modulation of cognitive function follows an inverted U-shaped curve, where medium levels of dopamine are considered optimal for cognitive performance, and low and high dopamine concentrations are associated with cognitive impairments[428]. Accordingly, cognitive responses to pharmacological dopamine manipulation have been demonstrated to vary depending on baseline WM span, a proxy of striatal dopamine synthesis[295]. In fact, one of the cognitive functions which has consistently been associated with dopamine is WM, where dopamine agents improve performance in individuals with low baseline WM span (indexing low striatal dopamine availability) while subjects with high WM function at placebo (i.e., hypothesized high striatal dopamine availability) show detrimental or no effects of the drug (e.g., [135,330,336,429]).

A specific role in the dopaminergic modulation of WM function has been ascribed to the basal ganglia, where frontostriatal loops are believed to regulate the updating of WM representations in the PFC via two distinct pathways, which have previously primarily been associated with action control (see Frank & O'Reilly[135]): The *direct* (Go) pathway, where activity leads to the updating and maintaining of current sensory information, and the *indirect* (no-Go) pathway, where upon activation, the threshold for WM updating is raised (by suppressing activity in cortical regions), thereby enabling the maintenance of previously stored information. While dopamine signaling has excitatory effects with respect to the direct pathway via activating D1 receptors, the D2 receptors located in the indirect pathway are inhibitory by nature, thus dopamine release here exerts inhibitory control on the indirect pathway.

Consequently, dopaminergic activity in the striatum has excitatory effects on the frontal cortex via both pathways (see Fig. 6.1.A).

It is possible that the effects of dopamine challenge on social performance presented in this thesis (mental state attribution: Chapter three, emotion recognition: Chapter four) are indicative of dopaminergic modulation of working memory function. To understand how our observed drug effects on mental state attribution and emotion recognition may relate to dopaminergic modulation of working memory function, one needs to consider the specific actions of the selective D2 receptor antagonist haloperidol, as well as the abovementioned dependency of drug responses on individual baseline dopamine levels. As outlined in Chapter one, due to the relatively high ratio of D2 auto- to heteroreceptors in the striatum, low doses of D2 antagonists are expected to mainly block the former, leading to increased phasic release of dopamine (i.e., presynaptic effects). In contrast, high doses of the same antagonist will lead to blocking of both auto- and heteroreceptors, resulting in both increased phasic, and reduced tonic dopamine (i.e., postsynaptic effects) signaling[430]. With low striatal dopamine synthesis capacity potentially reflecting higher responsivity to dopaminergic drug effects (presumably through compensatory upregulation of either receptor density or sensitivity[295]), it should follow that the same dose of haloperidol (2.5 mg) results in both increased phasic and reduced tonic dopaminergic activity in our low WM span group, whereas we would expect only subtle phasic drug effects in high WM span individuals. Indeed, only our low WM group exhibited movement slowing, which is indicative of postsynaptic effects on the indirect pathway (see Chapter four). Moreover, because dopamine has inhibitory effects on the indirect pathway, thereby leading to *disinhibition* of cortical activity, tonic effects of a dopamine antagonist should revert these effects and ultimately lead to increased, by nature inhibitory, activity in the direct pathway, which is presumed to serve to suppress cortical activity. Frank et al[135] argue that this

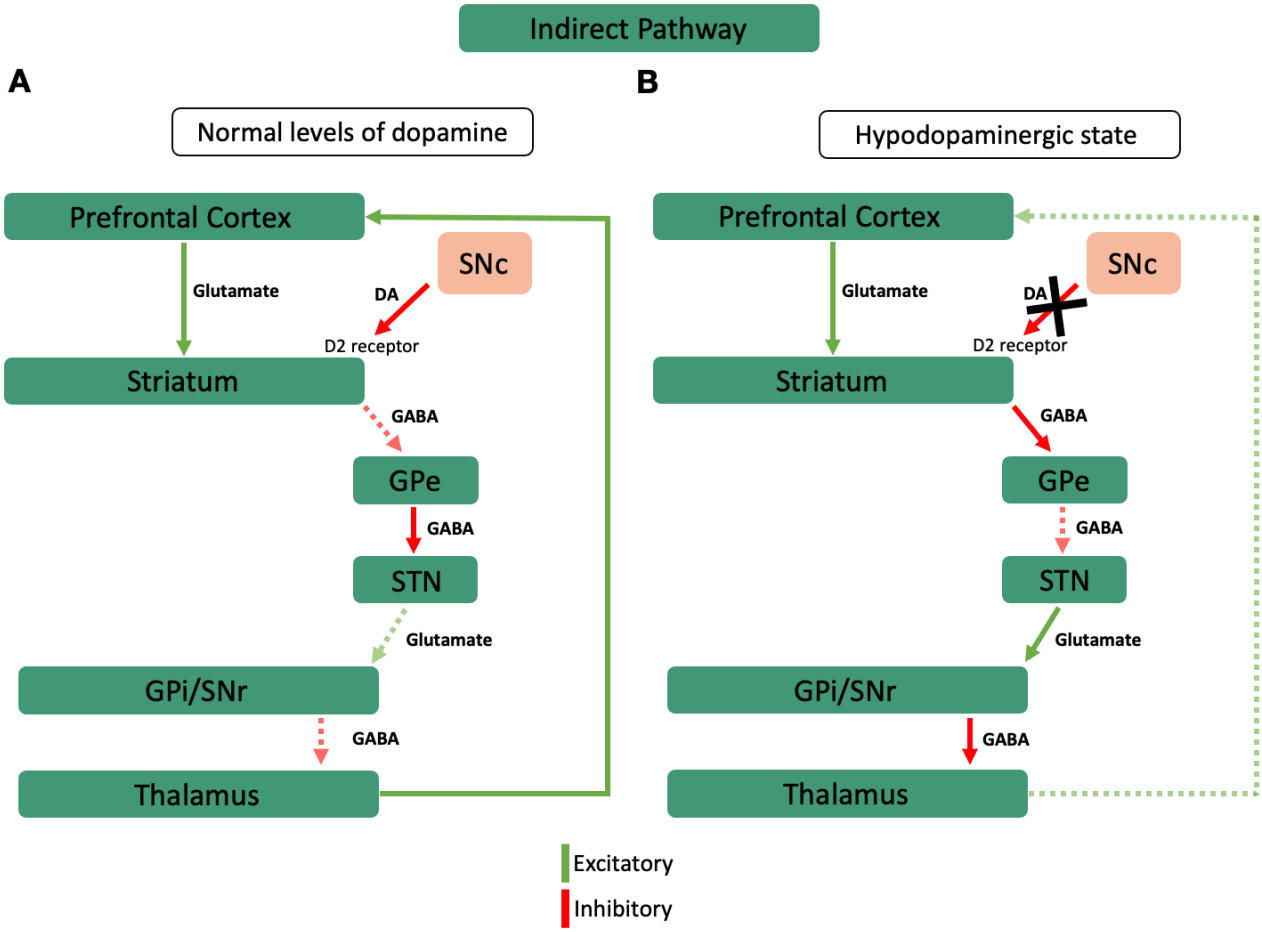

Figure 6.1. Schematic depiction of dopaminergic effects on the indirect pathway. SNc = substantia nigra pars compacta; GPe = globus pallidus external; STN = subthalamic nucleus; GPi = globus pallidus internal; SNr = substantia nigra pars reticularis. (A) Pale, dashed lines represent diminished activity compared to neural activity uninfluenced by dopamine. By activating inhibitory D2 receptors in the striatum, dopamine reduces the inhibitory effects the striatum has on the GPe, which in turn increases inhibitory action on the STN, thereby reducing the by nature excitatory action the STN has on the SNr, resulting in reduced inhibition of the thalamus, which has excitatory projections to the PFC. (B) Pale, dashed lines represent diminished activity compared to the direct pathway under dopaminergic influence. In the hypodopaminergic state, i.e., through tonic effects of a dopamine antagonist or in the parkinsonian state, reduced dopamine release results in less inhibition of the striatum and subsequently in increased inhibition of the GPe. Consequently, less inhibitory input into the STN leads to increased excitation of the SNr and in turn to increased inhibition of the Thalamus, finally resulting in suppression of prefrontal activity.

suppression of critical activity inhibits the updating of PFC representations, thus making the content of working memory stable and robust against distractors, but inflexible to new input (see Fig 6.1.B). With postsynaptic D2 receptors being predominantly located in the indirect

pathway[431], blockade of these postsynaptic receptors by the D2 selective antagonist haloperidol should lead to less facilitatory action of dopamine in this pathway and thus result in increased robustness of mental representations against interference[135]. While we would have expected tonic drug effects only in the low WM group, we predicted increased pre-synaptic action on the direct pathway in both WM groups, resulting in increased updating and maintaining of current, task-relevant information.

The animations and PLW tasks presented in this thesis are methodologically similar in that in both tasks, following stimulus presentation, target rating scales were presented on a new screen simultaneously with distractor rating scales. Thus, successful attribution of the adequate emotion or mental state label required the maintenance of stable representations of the stimulus and the associated internal state, as well as the inhibition of representations of the irrelevant distractor scales. Consequently, in both tasks enhanced performance would be consistent with the postsynaptic drug effects observed in our low WM group only. In other words, the increased emotion discrimination performance observed in the low WM group may be indicative of an enhanced ability to maintain stable representations of the PLW stimuli as a result of postsynaptic effects of haloperidol. In comparison, the pattern of emotion confusion demonstrated by the high WM group is congruent with potential pre-synaptic effects of more rapid updating of representations. While drug effects on mental state attribution accuracy were not dependent on individual WM span, they were strongly positively related to drug effects on the PLW task (see Appendix 2.3), indicating that those subjects who after drug ingestion showed increased emotion recognition performance also exhibited enhanced ability to attribute the correct label to animations in the animations task. Moreover, we observed a negative relationship between drug effects on animations task accuracy and individual drug induced changes in the WM task, indicating that increased WM function after haloperidol was

associated with decreased mental state attribution performance. In line with Frank and O'Reilly[135], enhanced WM function after haloperidol is likely to be representative of presynaptic drug effects, resulting in rapid updating of salient representations. Thus, the negative relationship between WM and animations task drug effects further supports our interpretation that phasic drug effects, while potentially beneficial for the fast-paced methodological demands of the WM task (see Chapter 4: Methods), may have given rise to higher confusion between emotion scales.

In conclusion, we propose that the observed contrasting pattern of drug effects on emotion recognition in individuals with low and high WM span and the associations with drug effects on mental state attribution are consistent with previous findings concerning the dopaminergic modulation of cognitive function. Our findings suggest that dopaminergic contributions to social cognition involve effects on WM functions such as the ability to maintain stable representations of internal states. While these conclusions highlight the possibility that social cognition inherently recruits WM processes (see also [421,432]), for instance when inhibiting distracting representations of one's own internal states while reasoning about others' minds, they also hint at potential methodological issues of commonly employed tasks measuring socio-cognitive ability. Section 6.3. discusses resulting implications for investigating social cognition in individuals who also display deficits in executive functions.

The internal timing hypothesis

As illustrated in Chapter one, temporal movement cues are rich in information relating to an agent's internal state. More specifically, in the previous literature, movement speed, as well as the subtle changes in speed (i.e., acceleration and jerk) have been shown to be indicative of affective states such as anger, happiness or sadness (e.g., [9,12,18,79,80]). The current thesis added

to existing evidence by demonstrating that movement kinematics (in particular jerk) are among the most important features for accurately inferring mental states from movements of interacting triangles (Chapter two), and that the extent to which an individual utilizes the emotion-specific kinematic information available to them predicts their success in recognizing certain emotions (Chapter five). If humans use temporal information to successfully infer emotions and mental states from body movements, it is conceivable that those internal state judgements are influenced by the accuracy with which an individual internally represents temporal cues.

A wealth of evidence from animal (e.g., [433,434]) and human studies (e.g., [337,338,435-437]) suggests an implication of the dopamine system in the regulation of temporal information processing. In human studies, pharmacological manipulation of dopamine has been shown to affect both sub-second timing (i.e., time *perception*), as well as the timing of supra-second intervals (i.e., time *estimation*). Importantly, however, D2 receptor activity in the striatum and the nigrostriatal pathway have been attributed a specific role in the processing of brief time intervals in the range of milliseconds[337,435-437]. For instance, the D2 receptor antagonist haloperidol reduced participants' ability to discriminate between two brief, sub-second time intervals, which has been proposed to reflect the slowing down of a hypothetical 'internal clock'[6,438]. This internal clock mechanism is hypothesized to track time by means of an intrinsic accumulator which counts the number of pulses emitted by a neural pacemaker within a certain interval (see Fig. 6.2).

In Chapter four we proposed that the observed relationship between drug induced movement slowing and emotion recognition performance may be reflective of haloperidol affecting timing mechanisms, which in turn may have mediated the temporal encoding of

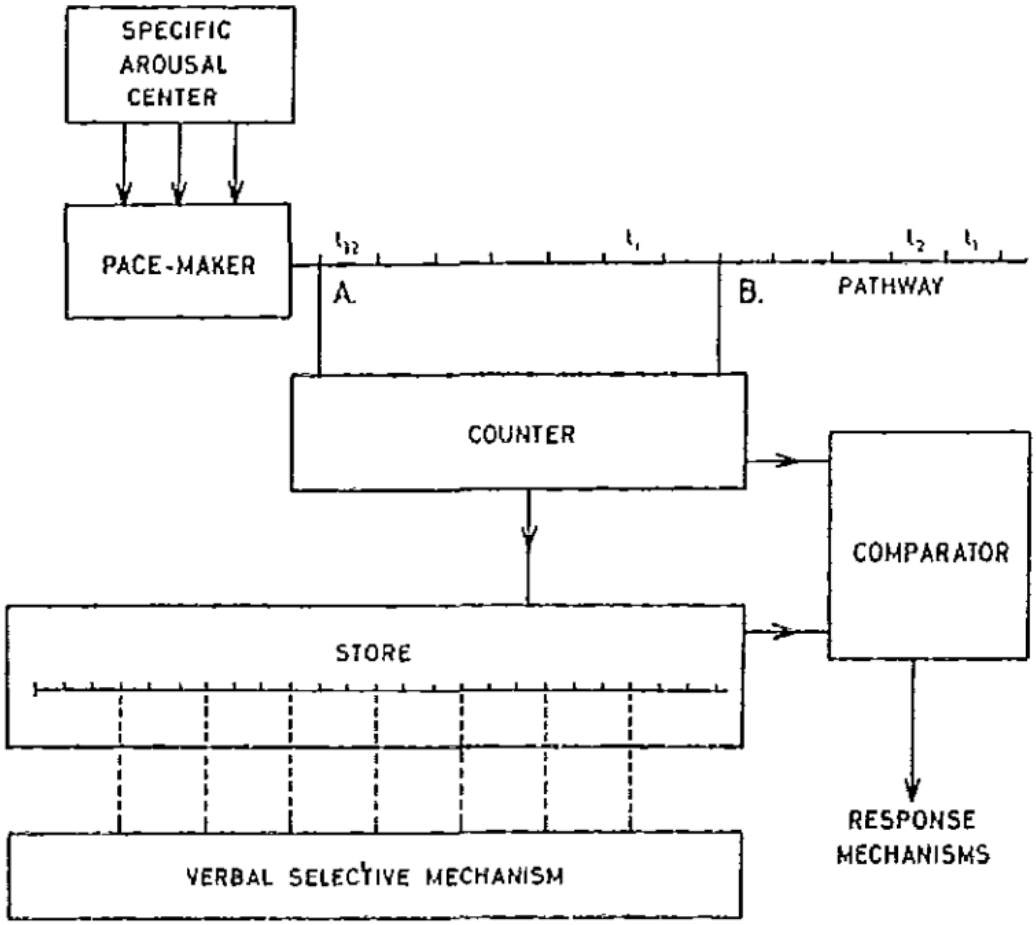

Figure 6.2. Internal clock model as proposed by Treisman[6]. A pacemaker produces a sequence of pulses which travel along a pathway. A counter records the number of pulses accumulated over a given interval and transfers this measure to the store. The comparator compares previously retrieved measures against current counts and selects appropriate response mechanisms. A specific arousal center additionally acts on the pacemaker and can thereby affect the rate at which pulses are produced. Image and description from Treisman.

dynamic emotion cues, and thus, emotion recognition accuracy. With respect to our supra-second time estimation task, we neither observed group-level effects of haloperidol on performance, nor did we find any statistical associations between individual drug-related changes in time estimation and drug effects on emotion recognition (see Chapter four). Both findings can be explained in line with the attentional gate model[439], which proposes that directing attention to passing time opens an attentional gate, allowing more pulses to be accumulated, which causes individuals to overestimate time periods. In our dedicated time

estimation task, the requirement for participants to pay explicit attention on the time period to be estimated may have led to biased estimates of the time intervals. It is possible that this bias exceeded any potential drug effects on supra-second time estimation, thus resulting in decreased sensitivity to detect any influence of haloperidol on temporal processing.

In contrast, recent theoretical work[341] provides support for the idea that our walking task may represent a more implicit and thus more accurate (i.e., less prone to attention-mediated biases) index of internal timing mechanisms which may be more sensitive to subtle effects of dopaminergic manipulation. In their article, De Kock et al. review evidence that suggests that movements are closely linked to timing processes: A number of studies show that movements concurrent with, as well as preceding or succeeding a time estimation trial can bias, or increase the precision of (i.e., increase sensitivity to time cues) time judgements. The authors explain the reviewed findings within a Bayesian cue combination framework, which postulates that movements are used in combination with other sensory information to make optimally precise predictions about perceived events (see Fig. 6.3C). Crucially, within this account, movements are seen as informative input to, rather than mere reflection of, timing processes, with presumably high precision weights relative to other input modalities due to inherent high temporal precision of motor outputs[341]. In line with this account, we propose that movement slowing under haloperidol in our studies may have biased timing judgements by pulling estimates towards longer durations. As pointed out in Chapter four, one could speculate that the hypothetical slowing of an internal timing mechanism may have resulted in higher sensitivity to temporal emotion-specific cues. Future studies could investigate the validity of this speculation by directly manipulating walking speed (e.g., using treadmills) and testing the effect of this manipulation on individual perceptual thresholds for kinematic emotion information using staircase paradigms.

Bayesian cue combination further serves to explain some of the findings presented in Chapter five: The observation that individuals exhibiting higher between trial variation in walking speed rely less on kinematic cues when judging dynamic emotion stimuli is in accordance with the prediction by Bayesian cue combination accounts that the weight given to a sensory input modality when making perceptual judgements is the inverse of its variance. In other words, if movements can be seen as sensory input to timing processes which inform temporal judgements, and given there are no alternative sensory cues to timing available, more variable walking speed may result in loss of precision of those timing estimates. Consequently, individuals with higher movement variability may rely less on the temporal movement cues present in emotion stimuli.

In summary, a growing body of work suggests that movements can alter our judgements of time. This evidence has been interpreted to reflect motor outputs providing relatively high-precision sensory information, which is used to form posterior estimates of a given time interval. In line with this, we speculate that the observed effects of dopamine challenge on emotion recognition in Chapter four may be mediated by dopaminergic modulation of an internal timing mechanism reflected by change in walking speed. Much future work is needed to evaluate whether this speculation proves true, and to address many open questions, some of which are discussed in Section 6.4.

The precision weighting hypothesis

Our social environment is inherently noisy with a richness of sensory cues which could potentially inform us about our interaction partners' internal worlds. For the sake of illustration, let us imagine we run into an old friend. In addition to the very complex auditory input we might receive from our friend's verbal account about how their day was, we are confronted

with a wealth of visual cues relayed primarily by their movements, such as facial expressions, gestures or body posture. While Bayesian theories of visual perception date back to 1962[440], in recent years, more and more researchers have turned to Bayesian frameworks to explain typical and atypical social behavior, including ToM[441] and emotion attribution[442], leading to the formulation of Bayesian accounts of autism[118] and schizophrenia[443] (amongst others). According to Bayesian inference theories (e.g., [444,445]), an agent builds models of their perceptual environment by integrating a multitude of sensory signals from various modalities (i.e., sensory evidence/likelihood) with top-down estimates about the likelihood of a particular event (i.e., prior probability/prior belief), formed based on previous experience. To form a maximally precise prediction, this evidence is not simply averaged, but weighted according to the noise ascribed to the different individual estimates, where precision is defined as the inverse of an estimate's variance (see Fig. 6.3). For instance, we might see our friend smile and hear them assuring us they are doing excellent, but given our knowledge about the likelihood of social platitudes implicitly might attribute more weight to the tone of their voice or the visual information of our counterpart's movements. Moreover, our perceptual system may ascribe higher weight to posture or movement kinematics relative to the inherently noisy and unreliable[446-448] facial expressions. In addition, we might draw on contextual information such as, for instance, our friend's fully black outfit, which may suggest they have just come from a funeral (based on our prior knowledge of how often in the past an all-black outfit was associated with a funeral). Finally, a combination of these differentially weighted cues leads us to make a best-estimate prediction about our friend's true internal state[449]. Throughout time, our brain learns about the stochastic probabilities of events through prediction errors, where large prediction errors reflect high discrepancy between predicted outcome and actual outcome.

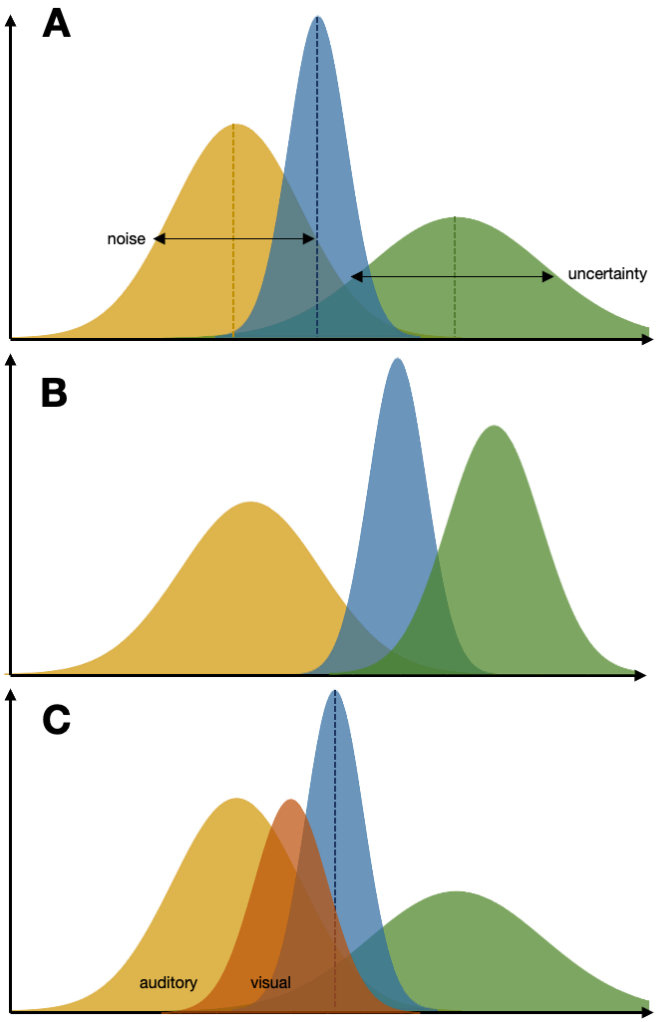

Figure 6.3. Diagram depicting Bayesian inference scenarios in form of gaussian probability distributions. Yellow = likelihood distribution (i.e., sensory evidence), Green = prior belief/expectation, Blue = posterior belief. Widths of distributions correspond to the individual estimate's variance, where its precision is the inverse of the variance. Posterior beliefs are biased towards either prior or likelihood according to their relative precision. (A) Higher precision in sensory evidence. (B) Higher precision in prior belief. (C) Bayesian cue combination frameworks propose that agents combine sensory estimates from multiple modalities by weighting individual estimates according to the precision (noise) associated with them.

According to Bayesian theories, our system seeks to minimize these prediction errors by changing internal models of the world (i.e., belief updating). Newer theories of 'active inference' have added to this stance by proposing that individuals additionally can minimize discrepancy between predictions and sensory outcomes by changing their actions (and thereby changing the sensory input itself)[249].

Up until recently, phasic dopamine has been primarily discussed in the context of reinforcement learning where phasic dopamine signals are believed to encode reward prediction errors, i.e., the discrepancy between expected and received reward (e.g., [450]). However, newer evidence suggests that the dopamine system is not only involved in evaluating outcomes against predictions, but may also play a role in increasing the precision of predictions by tracking the statistics of the likelihood of occurring events over time, as well as balancing prior beliefs against sensory information and coding for uncertainty relating to the sensory information[310,313,347,451,452]. In clinical conditions, aberrant dopamine signaling has been linked to overestimation of the precision of either prior beliefs or sensory information. For example, low striatal dopamine levels are believed to be responsible for PD patients showing an over-reliance on top-down information at the expense of updating their behavior to adapt to surprising sensory information[452]. A recent study[314] aimed to disentangle the specific contributions of dopamine to decision making under uncertainty by asking PD patients and controls to determine the position of a stimulus from noisy visual information and prior information about the possible locations of the stimulus. By varying uncertainty in both prior and sensory information, the authors observed that PD patients off dopaminergic medication showed decreased weighting of sensory information compared to the "on" state. In addition, PD patients on and off medication were less sensitive to changes in likelihood uncertainty compared to healthy participants. Thus, dopaminergic state appears to be directly related to the precision weights attributed to sensory, relative to top-down information.

Based on the assumption that the correct classification of internal states on the basis of motion cues requires the balanced integration of internal models of affective movements (i.e., motor representations with associated affective states) with sensory input, any bias in weighting of either prior or likelihood may result in aberrant inferences about those internal states. For

example, to recognize anger from fast gait speed, an individual needs to be relatively certain that fast gait speeds are associated with an angry affective state (prior precision), in addition to being able to rely on sensory input (likelihood precision) to successfully categorize the observed speed as 'fast'. In Chapter four, we observed contrasting effects of haloperidol depending on individual striatal baseline dopamine levels. In line with evidence for an overreliance on prior information evident in a dopamine depleted state[314], it is plausible that those of our participants hypothesized to have lower baseline dopamine (i.e., low WM span participants) showed an overreliance on prior information under placebo, which was shifted to an optimal balance between prior and sensory weights due to an increased phasic dopamine response to the drug, thus increasing emotion recognition performance in this group[135]. Likewise, the high WM span group may have exhibited dopamine levels associated with optimal precision weighting at placebo, which by phasic action of dopamine was shifted towards atypically high weights for sensory information. If a system for instance attributes high certainty to sensory information but fails to utilize top-down information (i.e., affective states associated with motor representations matching with the perceived input) to assign emotion labels to this input, the result may be confusion of emotion labels as observed in our high WM sample after administration of haloperidol. Correspondingly, in the animations task (Chapter three), a haloperidol-induced overreliance on an animation's motion information at the expense of certainty in prior beliefs of what movement patterns are associated with which (non-)mental state may have resulted in participants' relative inability to attribute correct animation labels. Such a relative decrease in prior precision has for instance been associated with elevated striatal dopamine levels in patients with schizophrenia[453], and linked to key features of autism[118], two populations which exhibit aberrant performance in the animations task[282,315] as well as impairments in emotion recognition[323,454].

In conclusion, our results suggest that dopamine did not affect the specific inference of emotions from body movement or mental states from object movements, rather, our findings might reflect more general effects of dopamine on perceptual inference. In particular, dopamine manipulation may have affected precision in higher-level representations (priors) which are necessary to adequately infer meaning from lower-level perceptions of motion patterns.

Yet, it should be noted that the exact picture of the dopaminergic modulation of precision weighting is far from clear, and there are findings that suggest the opposite relationship between baseline (i.e., tonic[430,455]) and/or phasic dopamine, and weighting of prior versus sensory information (e.g., Cassidy et al[456]. observed an increased bias towards top-down information alongside striatal dopamine release after amphetamine administration in schizophrenic patients). One major contributing factor to this current lack of clarity is perhaps that most of the few studies which so far investigated the role of dopamine in perceptual inference used patient samples, complicating conclusions due to high within- (e.g., disease progression) and across sample (e.g., underlying pathophysiological mechanisms) variance. To gain a more thorough understanding of the specific dopaminergic contributions to inference under uncertainty, future studies should employ highly selective dopamine agents (such as haloperidol which primarily targets D2 receptors in the striatum[457]) in healthy individuals in combination with manipulation of both sensory and to-down information.

An integrative perspective on the dopaminergic modulation of cognition and behavior

Importantly, the three mechanistic accounts of the drug effects on socio-cognitive performance outlined in this section are not to be viewed as competing, mutually exclusive hypotheses. Rather, they represent potential mechanisms which might be simultaneously at play. Indeed, with dopamine being a key player in a multiplicity of processes spanning from

learning to motor control, it should not be surprising that dopamine receptor antagonism may have a variety of concomitant effects on perception, cognition and behavior. In fact, the internal timing hypothesis is just an extension of the precision weighting hypothesis, where movement is viewed as one of many sensory input modalities informing a particular estimate of the perceived environment. Thus, in line with hierarchical Bayesian inference frameworks, dopamine may modulate the precision of sensory information relating to estimates of timing by altering movement speed, where the resulting timing estimates feed into higher-level perceptual inference processes as prior information. Furthermore, at this higher level, dopamine may encode the relative precision attributed to priors and new incoming sensory information. Lastly, it is conceivable that dopamine modulates WM function and perceptual inference in parallel, and that those two processes influence each other. For instance, if dopamine regulates our ability to maintain and update internal representations, aberrant dopamine signaling may disrupt this ability to manipulate information, rendering our prior estimates less precise, which in turn may result in higher reliance on sensory estimates. Such a relationship between WM capacity and individuals' ability to adjust to perceptual uncertainty has already been demonstrated for anger perception in a previous study[458]. Crucially, while each of these mechanistic avenues via which the dopamine system may be implicated in social function on their own is critically underexplored, an integrative view of potential interactions between these pathways may be necessary to fully understand the complex co-occurrence of social, cognitive, and motor symptoms within and between clinical populations such as PD or ASD.

6.3. Implications for populations with dopamine dysfunctions

One of the primary findings of this thesis was that we did not observe any effects of acute dopamine challenge on motor simulation processes. However, as discussed in Chapter four, this is perhaps unsurprising as motor representations of internal states are likely built over a lifetime of experiences with one's own movements, making them robust against temporary interferences such as short-term dopamine disruptions. Conceivably, it is adaptive that action models are robust against short-term changes in movement as otherwise our internal models would change every time some external influence prevents us from moving in our own, idiosyncratic patterns (such as a leg injury which forces us to walk slower than we normally do). Consequently, in disorders with dopamine dysfunction where motor symptoms only occur later in life, internal action models can be presumed to be largely unchanged at least in the early stages of the disease. It follows that any early-stage decline in socio-cognitive abilities in those late onset conditions is a result of direct dopaminergic modulation of socio-cognitive function independent of motor simulation processes. This is at odds with recent accounts emphasizing the role of hypomimia in emotion recognition impairments in PD (e.g., [195]). Two recent studies found relationships between reduced (relative to controls) facial EMG responses and emotion recognition abilities of PD patients, leading authors to hypothesize a causal role for facial mimicry in emotion recognition[459,460]. However, the observed relationship between reduced emotion recognition accuracy and reduced emotion-specific EMG responses could equally well reflect independent effects of low tonic dopamine on motor and cognitive function.

As outlined in Section 6.2.3, emotion recognition deficits in PD potentially arise from low tonic dopamine resulting in stable representations which in combination with an overreliance on prior estimates (presumably due to low phasic dopamine activity) may lead to reduced flexibility to adapt to a rapidly changing sensory environment. In line with this, in

cognitive tasks, PD patients have shown difficulties in adapting to unexpected events[452] and in task switching[461]. In tasks measuring mentalizing or emotion recognition, this reduced flexibility may be particularly evident for dynamic stimuli due to the inherent rapid change in sensory events. Surprisingly, despite the apparent higher ecological validity of dynamic emotion stimuli, few studies to date have employed dynamic stimuli to study emotion recognition in PD, which may be contributing to the mixed literature (see Chapter one). If PD patients do indeed show deficits in adapting to sensory change, commonly used static stimuli may heavily underestimate emotion recognition impairments in this population.

An alternative route via which dopamine dysfunctions may lead to atypical social responses in PD may be aberrant internal timing processes. Timing is known to be impaired in PD, with evidence suggesting underestimation of time intervals consistent with proposals of a slowed down internal clock (e.g., [462,463]), as well as increased timing variability (e.g., [464]). De Kock and colleagues[341] proposed that own movement presents a primary source of sensory information for timing estimates due to the low variance ascribed to human movement patterns. At first sight, this may seem in disagreement with our findings of Chapter four that reduced movement speed (as seen in low WM participants after haloperidol) was associated with *improved* emotion recognition. However, in comparison to our low WM participants, who did not show increased between- or within trial movement variability after haloperidol (see Appendix 3.3), PD patients exhibit high gait variability (indexed by measures such as step time variability[379] or stride variability[376]). Thus, in contrast to our healthy participants, in PD patients, highly variable gait kinematics may represent imprecise sensory information. High uncertainty in sensory input from movement information, in combination with an overall lower sensitivity to changes in the sensory environment may therefore in part be responsible for inaccurate timing processes in PD. Chapter five demonstrated how individuals with highly

variable walking speed relied less on dynamic emotion specific information when judging emotional PLW. It is plausible that accurate internal timing is crucial for the precise evaluation of temporal information, and that imprecise time estimates in participants exhibiting high movement variability may have prevented them from utilizing temporal emotion related cues. Consequently, it may be that PD patients show less sensitivity to dynamic emotion cues, as has been shown for autistic individuals[378]. Strikingly, while there is considerable research on the dilation effects of emotion perception on time estimation (e.g., [465,466]), to our knowledge no study to date has directly investigated potential influences of intrinsic timing on the perception of emotions or mental states. In addition to PD, timing has been found to be atypical in ASD[467], schizophrenia[468], and HD[469], which are all disorders presenting with increased movement variability (e.g., ASD[470], schizophrenia[471], HD[376]). Thus, as aberrant internal timing may play a role in socio-cognitive deficits in a wide range of conditions, future research should investigate a potential mediating role for timing mechanisms in the relationship between motor function and socio-cognitive abilities.

The same three mechanistic pathways elaborated in Section 6.2 serve to explain atypical social responses in ASD. WM function, timing processes and Bayesian inference have all independently been proposed to be aberrant in autistic individuals. For example, executive function impairments are remarkably prevalent in ASD, including impairments in working memory, response inhibition and planning[472]. A recent computational approach links cognitive inflexibility in ASD to aberrant dopamine signaling and proposes a role for dopamine as an 'adaptive gating mechanism' regulating the updating of representations in the PFC[473]. While this model has striking similarities with the direct/indirect pathways model of the basal ganglia detailed in Section 6.2.3, it needs to be confirmed whether either of these models can successfully predict autistic individuals' performance in tasks of socio-cognitive function.

Moreover, in recent years, Bayesian inference accounts have grown popular for their aptitude in explaining the heterogeneity of symptoms prevalent in autism. In direct contrast to PD, Bayesian theories of autism propose increased weighting of sensory signals, at the expense of reliance on priors, to be at the core of autistic symptomatology including sensory hyper- or hyposensitivity, stereotyped and repetitive behaviors, motor impairments, and social atypicalities (e.g., [118,122,474]). In relation to aberrant precision weighting in ASD, however, only a few studies have discussed links to dopamine, which is presumably due to the highly conflicting empirical evidence for dopamine dysfunctions in this condition (e.g., [475]; see Chapter one). According to an influential model by Friston et al.[310], a preference towards sensory signals relative to priors is reflective of high levels of tonic dopamine, which is in line with the low tonic dopamine levels in PD hypothesized to be related to an overreliance on priors. It is possible that the mixed results regarding aberrant dopamine signaling in ASD are owed to the high heterogeneity of the condition, and future studies are needed to evaluate the potential of dopaminergic treatment for social symptoms of ASD.

In addition to the acute influence of dopaminergic dysfunctions on mentalizing and emotion recognition, the findings presented in this thesis indicate that abnormalities in the dopamine system may also have long-term effects on social ability by changing individuals' movements. Chapter three and four illustrated that dopamine disruption by administration of a relatively low, acute dose of a dopamine antagonist can lead to broad effects on motor function: A reduction in movement speed after haloperidol was evident for arm movements (animations task, shapes drawing task) as well as gait. Accordingly, although there is currently little direct evidence for this, dopaminergic disruptions may be a causal factor in early onset motor abnormalities seen in conditions such as ASD[54]. Furthermore, Chapter two demonstrated how movement similarity between two agents facilitates mental state attribution. We hypothesized

that movement similarity was important for successful mentalizing because individuals use representations of associations between specific movement patterns and internal states to infer meaning from the movement cues provided by others. Thus, individuals who experience motor abnormalities from early childhood may build their internal action models based on atypical movements, and in turn may show difficulties in interpreting the internal states of interaction partners who display typical movement kinematics. Additionally, there are other cascading effects of motor disruptions on social interaction that should be considered, for example by limiting an individuals' potential to participate in social situations which require high levels of physical ability, which ultimately might result in social exclusion (e.g., see [476]).

In summary, the findings presented in this thesis suggest that dopaminergic disruptions in conditions such as PD or ASD may alter social cognition via two primary routes: First, dopamine dysfunctions may lead to atypical action models calibrated on a lifetime of atypical movements, thereby potentially resulting in compromised interaction with individuals who show typical movement patterns. Second, hypothesized aberrant tonic and phasic dopaminergic signaling may additionally lead to social impairments via short-term actions on working memory, timing and/or precision weighting processes. By unpacking the relative contributions of each of these dopamine-mediated processes to socio-cognitive function, future research could provide new directions for the development of therapeutical interventions, including behaviorally based training.

6.2. General limitations and future directions

There are several limitations of the research presented in this thesis one should take into account when considering our findings. First and foremost, whilst this thesis aimed to explore

the underlying mechanisms via which dopamine may modulate both motor and social function, no direct conclusions can be made about the precise neuroanatomical and neurophysiological actions of our dopamine manipulation. Such inferences require methods such as molecular imaging techniques (e.g., PET) or brain tissue analysis (e.g., fast-scan cyclic voltammetry), which are costly and require special expertise. Consequently, any conclusions drawn about the likely loci of actions (i.e., striatum vs. PFC) and neuronal activity patterns (i.e., tonic vs. phasic dopamine activity) are based on knowledge about the pharmacokinetic properties of haloperidol and previous literature. Yet, I argue that the behavioral analyses in combination with pharmacological manipulation of dopamine used in this thesis offer novel insights with important implications for future research. For example, while the dopaminergic regulation of cognitive processes has been well studied, very few studies to date have investigated the direct dopaminergic modulation of socio-cognitive function, despite various theoretical accounts suggesting a role for dopamine in social behavior. The present thesis is therefore one of the first pieces of work demonstrating a causal role for the dopamine system across mentalizing and emotion recognition. Future studies could follow on by studying the influences of dopaminergic activity on socio-cognitive ability on a neuro-anatomical and brain-functional level, for example by the combined use of brain imaging techniques (e.g., fMRI, PET) and pharmacological as well as experimental manipulations. For instance, by tracking changes in brain activity associated with dopaminergic manipulation, pharmacological fMRI could provide evidence for or against hypotheses about the domain-specificity of the dopaminergic modulation of socio-cognitive function (e.g., increased activity in hypothesized mentalizing system vs. only in the striatum).

A second limitation of this thesis is the examination of the neurotransmitter dopamine in isolation. A growing body of research suggests that several neuromodulators are involved in

regulating social function, such as serotonin, glutamate, noradrenaline, or oxytocin which for example have been implicated in addition to dopamine in the etiology of ASD[178,179,477], PD[478-480] and schizophrenia[481,482]. Specifically, serotonin has been hypothesized to modulate socio-cognitive processes in interaction with dopamine[212,483]. For instance, Nakamura et al.[484] found serotonin transporter binding to be significantly lower in autistic, relative to control, participants (across the brain) and this was inversely correlated with abnormally high levels of dopamine transporter binding in the orbitofrontal cortex. Moreover, the relative reduction in serotonin transporter binding was related to impaired performance in the faux-pas test in autistic subjects, suggesting a functional role for serotonin in ToM processes. As already noted in Chapter one, further support for the dopamine-serotonin hypothesis comes from observations that antipsychotic medication which binds to both serotonin and dopamine receptors (e.g., olanzapine, clozapine), rather than to dopamine receptors alone (e.g., haloperidol), was associated with improvements in social cognition in schizophrenic participants[286,287]. Furthermore, in addition to dopamine, very recent work[313] has linked serotonin to the encoding of perceptual uncertainty, indicating that dopamine and serotonin may in tandem modulate perceptual processes including the perception of social stimuli. In sum, there is ample evidence suggesting that in addition to dopamine, other neuromodulators may play a critical role in the regulation of social function and that our understanding of the neurochemical bases of social cognition would greatly benefit from investigating effects of several neuromodulators in conjunction.

Lastly, a third limitation of the present findings concerns the emotion/mental state stimuli that were used to approximate social understanding outside of the laboratory. To be able to investigate effects of movement kinematics and movement similarity, in Chapters two to four we used dynamic stimuli with limited capability to represent real-world situations of social

interaction. Furthermore, the present thesis focused on the understanding of the inference of internal states from movement kinematics, however real-life social interaction is undisputedly more complex. It is possible that dopaminergic or dopamine-mediated processes influence more than one aspect of social cognition. For example, conceivably, effective turn-taking during conversation requires precise timing, consequently inaccurate internal timing mechanisms arising from aberrant dopaminergic signaling could considerably impact an individuals' ability to engage in social interaction[485]. Future studies could therefore explore whether, and in what way, dopaminergic imbalances affect the perception and processing of socially relevant cues beyond movement kinematics.

In conclusion, this thesis demonstrated that movement similarity between observer and agent enhances mental state attribution, thereby adding to previous evidence suggesting that we use models of our own movements to infer internal states from others' motion cues[2,110]. While it is possible that dopaminergic effects on movement affect our internal action models on a long-term basis, our findings indicate that acute dopamine disruptions do not impede putative motor simulation processes. Rather, they suggest that the dopamine system is directly involved in the modulation of socio-cognitive processes, bearing important implications for our understanding of the dopaminergic contribution to social impairments in clinical populations. By elucidating three candidate mechanistic pathways via which dopaminergic signaling potentially influences socio-cognitive function, the present work paves the way for future research to investigate the various avenues via which dopamine and other neuromodulators may impact upon social cognition.

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Appendix 1

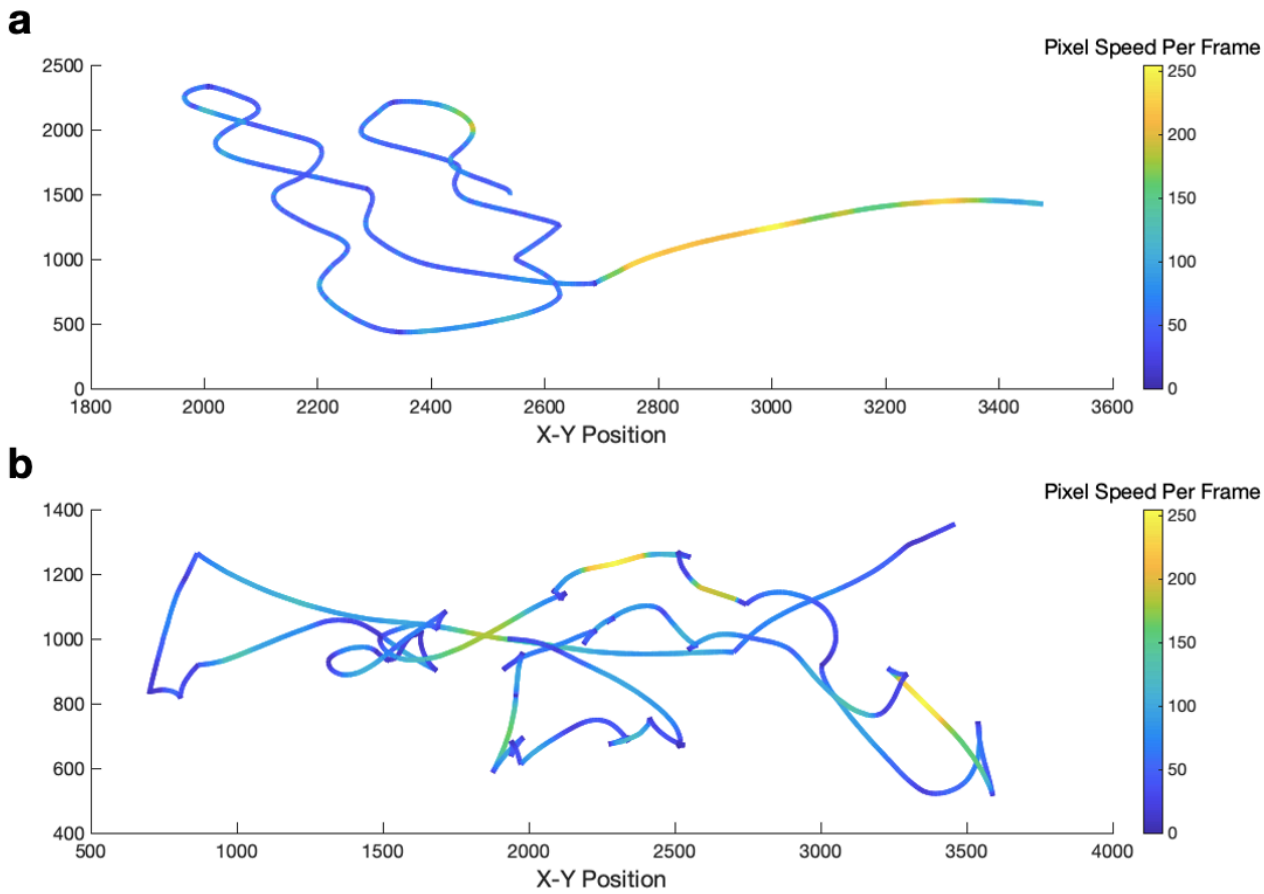
Supplementary Information for the publication

Kinematics and observer-animator kinematic similarity predict mental state attribution from Heider-Simmel style animations

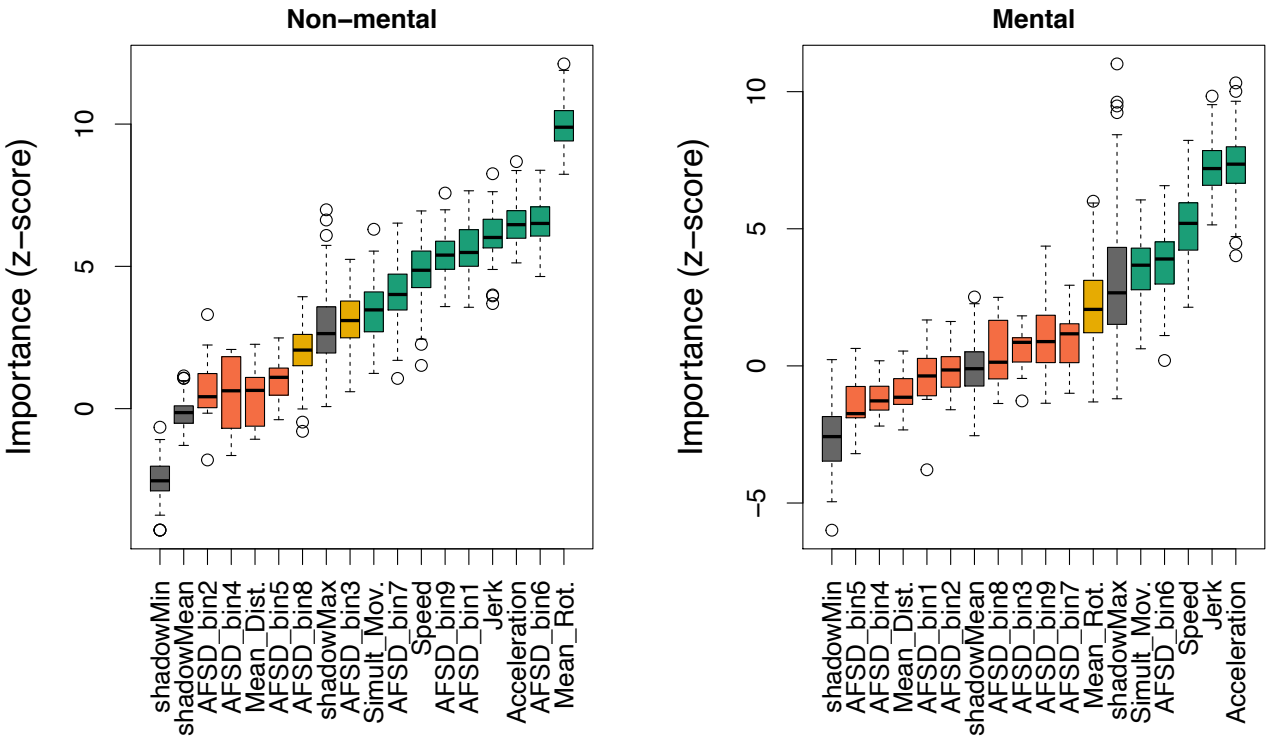
(Chapter 2)

1.1. Creation of triangle trajectories

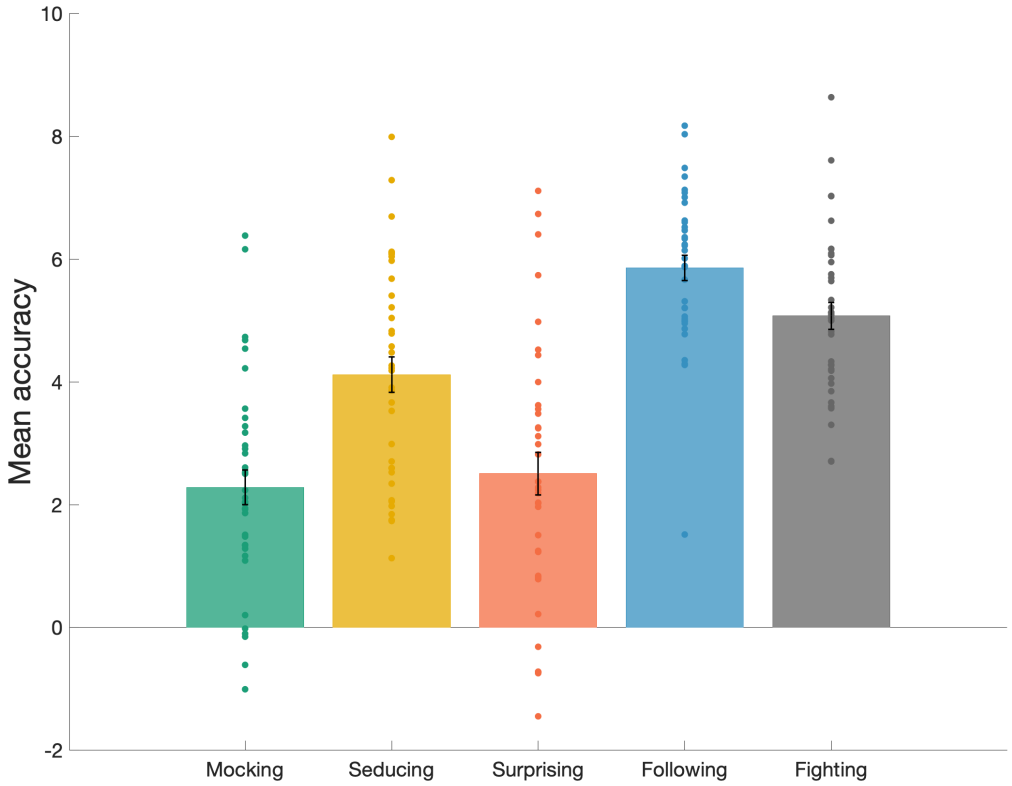
Participants created their own animations by using their index fingers of both hands to move two triangles and open/close a 'door' of an enclosure (see Supplementary Figure S1.5). With the intention to constrain the animation creation process as little as possible, individuals were free to move in and out of contact with the triangles/door throughout the 45 seconds time window for an animation. Periods of no movement were disregarded in the calculation of triangle kinematics. Accordingly, zero movement frames were removed from triangle trajectories, thus trajectories may not represent continuous movements. Furthermore, as noted in 2.4 Methods: Building the Animotions database, to suppress unvoluntary rotations of the triangles, object motion is suppressed until the pointer is dragged sufficiently far away from the center point. This entails that triangles can never be rotated around their own axis and that rotation is always determined by the motion direction.



Supplementary Figure S1.1. Example trajectories of one triangle's path for a seducing (a) and a fighting (b) animation.

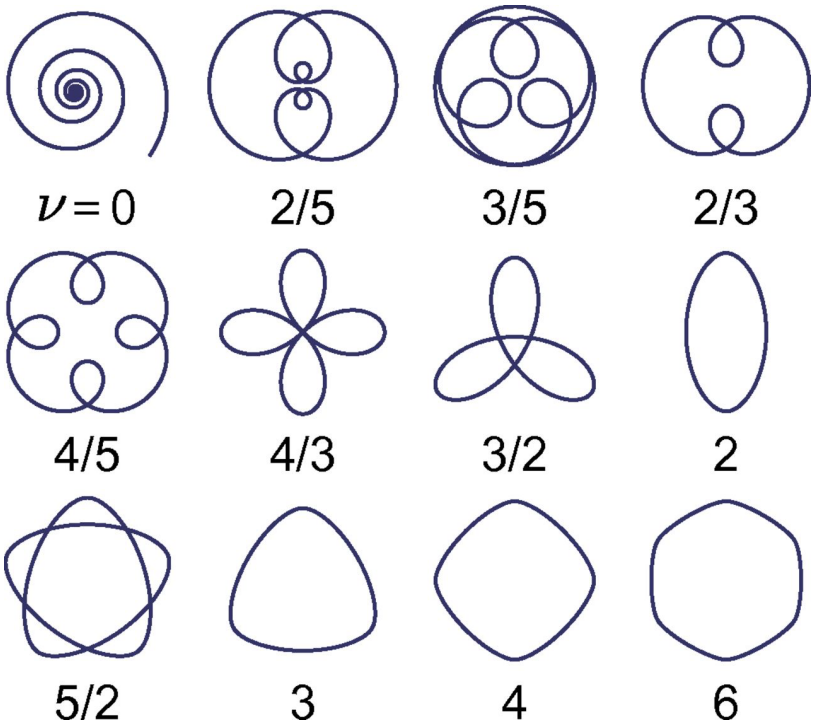


Supplementary Figure S1.2. Mean Accuracy Ratings for the Five Word Categories. Error bars represent 1 standard error of the mean (SEM).

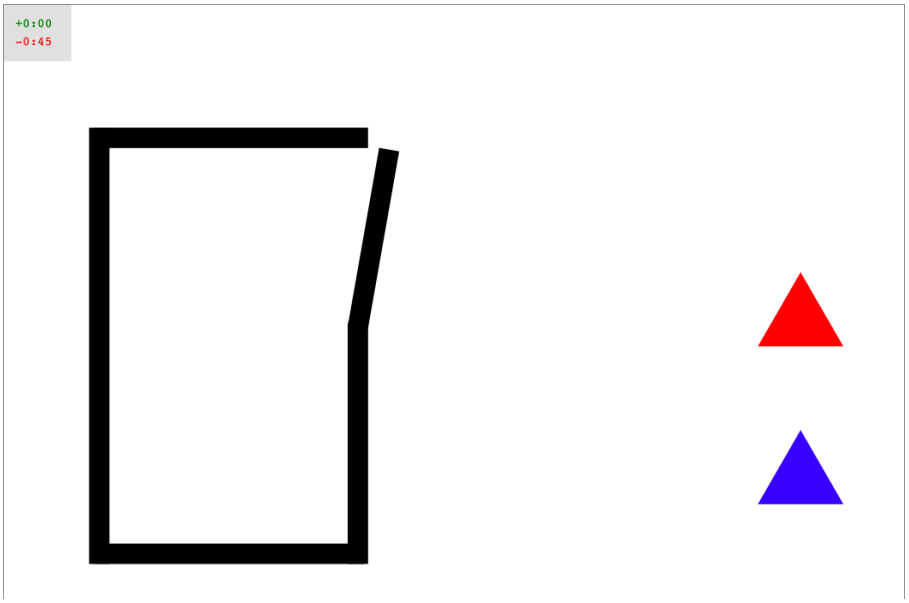


Supplementary Figure S1.3. Post-hoc random forest models. Box edges denote the interquartile range (IQR) between first and third quartile; whiskers denote 1.5 * IQR distance from box edges; circles represent outliers outside of 1.5 * IQR above and below box edges. Box color denotes decision: Green = confirmed, yellow = tentative, red = rejected; grey = meta- attributes shadowMin, shadowMax and shadowMean (minimum,

maximum and mean variable importance attained by a shadow feature).



Supplementary Figure S1.4. Examples of pure frequency shapes shown with their characteristic frequencies. Figure taken with permission from Huh & Sejnowski (2015). See https://www.youtube.com/watch?v=waXWOv0YqFE for a movie showing how the shape of the curve varies with continuously changing angular frequency.



Supplementary Figure S1.5. Animotions task starting screen.

1.2. Further analysis of accuracy scores

A one-way analysis of variance (ANOVA) comparing rating accuracy in the five word categories showed a main effect of word category, indicating that the five types of animations differed with respect to how accurately they were rated ($F(4,175) = 31.03$, $p < .001$). Separate Bonferroni-corrected post-hoc t-tests (using the MATLAB *multcompare* function with Bonferroni correction) revealed that while there was no difference in accuracy between the words following and fighting (following mean (M) = 5.86, standard error of the mean (SEM) = 0.28, fighting M = 5.07, SEM = 0.22, $p = .507$), both words were rated with higher accuracy than mocking (mocking M = 2.28, SEM = 0.28, both $p < .001$), and surprising (surprising M = 2.51, SEM = 0.35, both $p < .001$) and following was rated more accurately than seducing (seducing M = 4.12, SEM = 0.29, $p < .001$). Furthermore, seducing animations exhibited higher accuracy than both mocking and surprising videos (both comparisons $p < .001$), whereas there was no difference in accuracy between mocking and surprising ($p = 1.000$).

1.3. Task instructions

Production task

In the following task you will be asked to use your fingers to move two triangles around the screen in order to depict various words. Both triangles can be moved at the same time using both of your index fingers. After you press continue you will have a chance to practice moving the triangles around.

Perception task

The main task will now begin. On the screen you will be presented with a word. Please move the triangles around to represent the word on the screen. You will be presented with five words in total, one after the other. You can move the triangles around in any way you want, as long as you think their movements represent the word. Remember that you can move both triangles at once!

After you press 'continue', the first word will appear on the screen, along with a timer. You will have 30 seconds to plan how you are going to move the triangles to depict the word. You will not be able to move the triangles during the 30 second

thinking time. If you don't know the meaning of a word, you can look it up in the dictionary during this time.

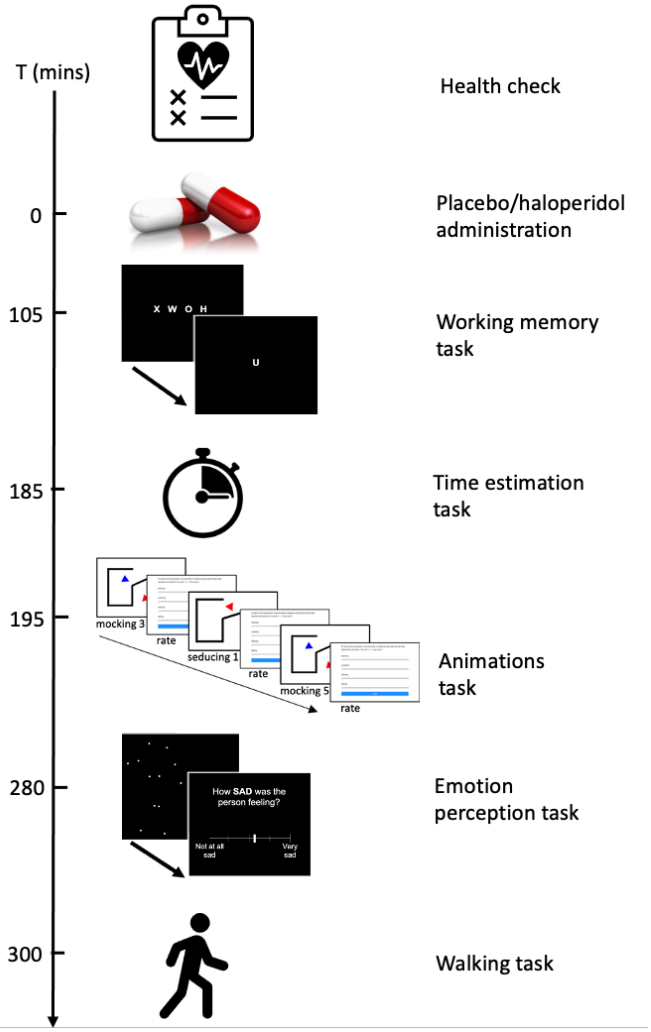
When the thinking time is up, you will have 45 seconds to create your animation. Please try and use all of that time to create your story. If you are happy with your animation, press 'submit' and you will be presented with the next word. If for any reason you are not happy with your animation, you can press 'start over' and restart that word as many times as you like.

Appendix 2

Supplementary Information for Chapter three

2.1. Drug study supplemental information

As experiments presented in Chapters three and four were both part of the same drug study, all information under 2.1 is applicable to both chapters.



Supplementary Figure S2.1. Drug study tasks and timing.

2.1.1. Drug study eligibility criteria

Inclusion criteria

- Participant is willing and able to give informed consent for participation in the study
- Sufficient English to be able to consent and understand study instructions

- Aged 18-45
- BMI in range of 18.5 – 29.5

Exclusion criteria

- Participated in another drug study within last 3 weeks
- Primary sensory impairment (e.g., uncorrected visual or hearing impairment)
- Personal or first-degree relative history of: cardiovascular disease (specifically hypotension, arrhythmias or valvular disease, stroke)
- Personal history of: any neurological abnormalities or past traumas, kidney disease or liver disease, stomach ulcers, skin conditions, endocrine conditions,
- Inherited blood conditions
- Psychiatric or psychological disorder (e.g., depression, anxiety)
- Known learning disability
- Elongated Q-T interval identified during the health screening using single-lead ECG (heart rate corrected): > 500 ms
- Low heart rate
- Low or high blood pressure (outside of lower bound 90/60 – upper bound 140/90)
- Blood oxygenation below 95%
- Any regular medication (excluding oral contraceptive pill)
- Recent recreational drug use or alcohol and/or drug dependency
- Known allergy to any medication or lactose sensitivity
- Current pregnancy or breastfeeding

Eligibiltiy as confirmed by medic during health screening

During the health screening, participant and medic discussed the participant's medical history by going through a health check questionnaire which participants filled out beforehand. Subsequently, a number of physiological measures were taken to confirm eligibility (e.g., cardiovascular and respiratory assessments, BMI, blood oxygenation %, resting blood pressure, resting heart rate ECG QT-interval).

2.1.2. Baseline measures

1. Autism Spectrum Quotient (AQ) [486]

2. Toronto Alexithymia Scale (TAS-20) [487]
3. BIS-BAS (Behavioural Inhibition Scale – Behavioural Activation Scale) [488]
4. The Depression, Anxiety and Stress Scale - 21 Items (DASS-21) [489]
5. Interpersonal Reactivity Index (IRI) [490]
6. Positive Affect Negative Affect Scale (PANAS) [491]
7. Beck Depression Inventory (BDI) [492]

2.2. Task battery

Tasks in order of completion. Participants had regular breaks and the opportunity to eat between tasks with a maximum period of 60 minutes between breaks.

1. **Go-NoGo learning task**
   An adapted version of a probabilistic Go/No-Go Task[135].

2. **Visual working memory task** (for description see Chapter four)

3. **Point Light Faces dynamic facial emotion perception task**
   Emotion perception task using dynamic point light face stimuli. Task design equivalent to Point Light Walker emotion perception task (Chapter four).

4. **Social learning task**
   A modified version of a probabilistic learning task[493] first developed by Behrens et al[494].

5. **Time estimation task** (Chapter four)

6. **Animations task** (Chapter two)

7. **Shapes drawing task** (Chapter three)

8. **Point Light Walker dynamic whole-body emotion perception task** (Chapter four)

9. **Walking task** (Chapter four)

10. Movie for the Assessment of Social Cognition (MASC) task [146]

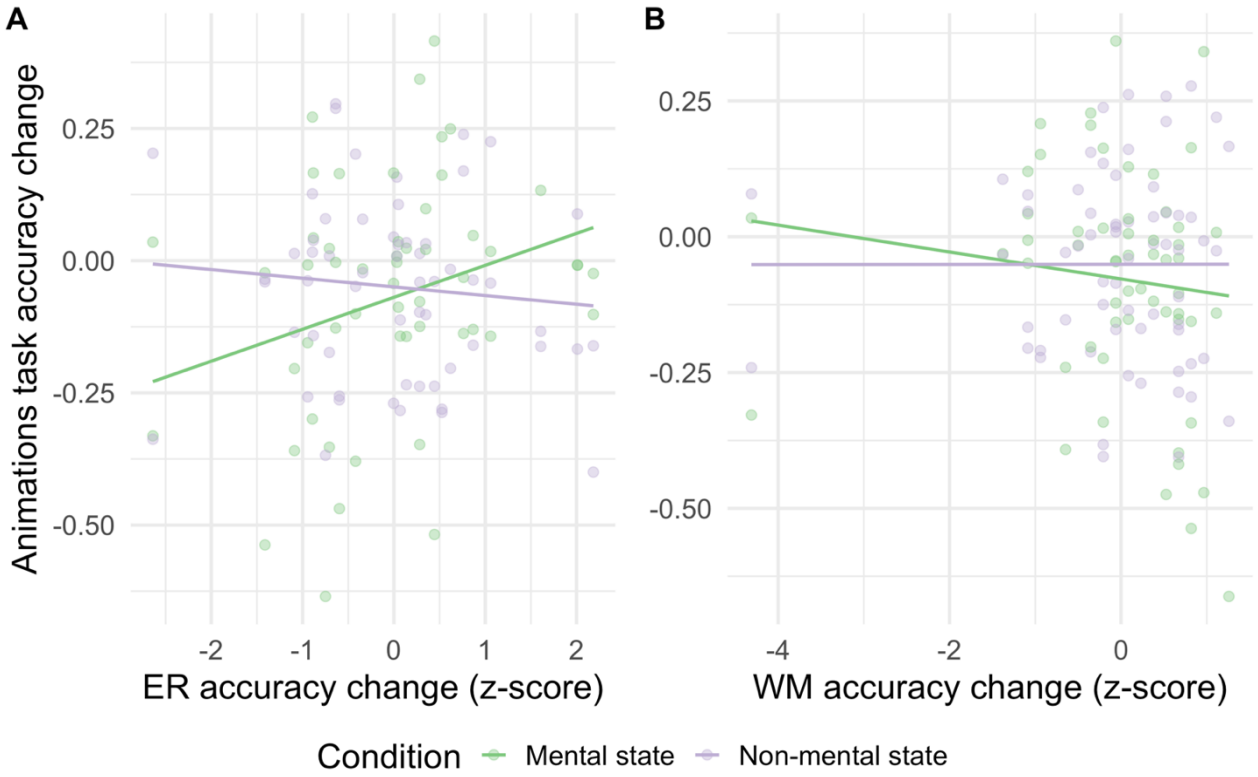
Participants viewed short video clips of social interactions and were subsequently asked to answer questions referring to the protagonists' mental states, emotions and intentions.

2.3. Exploratory analysis: what other factors predict drug effects on mentalizing?

To shed light on other possible underlying mechanisms of the observed drug effects on animations task accuracy, we calculated indices of drug effects on tasks measuring WM function (for task description see Chapter four), cognitive and affective ToM performance (as measured with the MASC task, see 2.2), and emotion recognition performance (see Chapter four). For all tasks, change scores were calculated by subtracting scores of PLA trials from scores of HAL trials, with positive change scores indicating increased performance under HAL compared to PLA trials, and negative change scores reflecting a decrease in performance under the drug.

A Bayesian mixed effects model (with random intercept for subject ID) was fit *to WM change scores*, *cognitive ToM change scores*, *affective ToM change scores*, and *emotion recognition (ER) change scores*, as well as the dummy-coded factor mental state, predicting animations task accuracy change scores. The model showed an interaction between ER change scores and mental state, where ER change scores were positively related to animations task accuracy change scores for mental state animations ($E\mu_{mental,ERchange}$ = 0.05, CrI = [-0.01, 0.11], P($E\mu_{mental,ERchange}$ > 0) = 0.96) and more negatively related to accuracy change scores for non-mental state animations (in comparison to mental state animations; $E\mu_{mentalVSnon-mental,ERchange}$ = -0.06, CrI = [-0.14, 0.01], P($E\mu_{mentalVSnon-mental,ERChange}$ < 0) = 0.95). Thus, a decrease of 1 SD in emotion recognition performance after taking the drug was associated with a decrease in accuracy in identifying mental state animations by 0.05

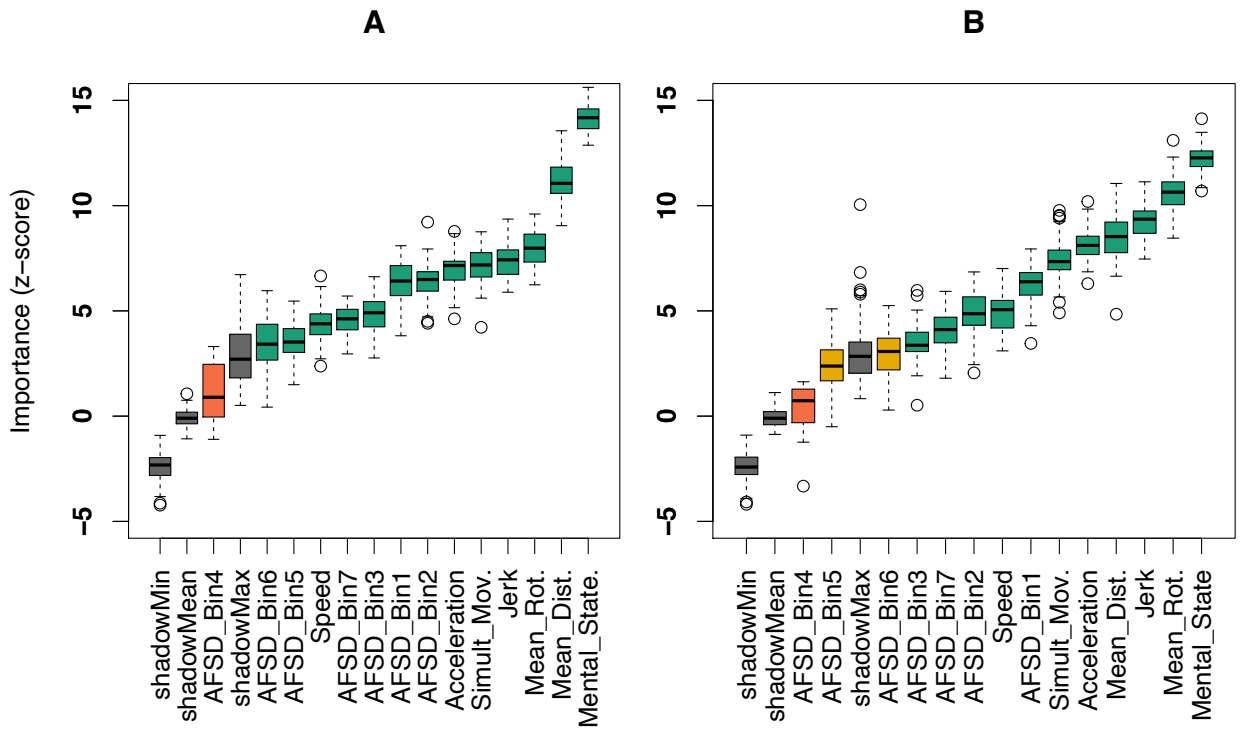
percent. In contrast, the same drug induced decrease in emotion recognition performance was associated with a 1 percent increase in accuracy in labelling non-mental state animations ($E\mu_{non-mental,ERchange} = E\mu_{mental,ERchange} + E\mu_{mentalVSnon-mental,ERchange}$ = 0.05 – 0.06 = -0.01; see Fig 3.4A). The model further revealed an effect of WM change on accuracy in mental state animations, suggesting that here, accuracy was negatively correlated with WM change ($E\mu_{mental,WMchange}$ = -0.06, CrI = [-0.12, 0.01], P($E\mu_{mental,WMchange} < 0$) = 0.98). In comparison, the relationship between WM change and non-mental state animations accuracy was close to zero with a coefficient of -0.03 ($E\mu_{mentalVSnon-mental,WMchange}$ = 0.06, CrI = [-0.05, 0.18]; $E\mu_{non-mental,WMchange} = E\mu_{mental,WMchange} + E\mu_{mentalVSnon-mental,WMchange}$ = -0.09 + 0.06 = -0.03; see Fig 3.4B). Consequently, for every 1 SD decrease in WM accuracy after haloperidol, individuals increased their accuracy in identifying mental state animations by percent. There was no effect of cognitive or affective ToM change scores on either mental state nor non-mental state animation accuracy ($E\mu_{mental,cogToM}$ = 0.03, CrI = [-0.47, 0.53]; $E\mu_{mentalVSnon-mental,cogToM}$ = 0.01, CrI = [-0.65, 0.66]; $E\mu_{mental,affToM}$ = 0.07, CrI = [-0.19, 0.34]; $E\mu_{mentalVSnon-mental,affToM}$ = -0.22, CrI = [-0.57, 0.12]). A post-hoc model of ER change and WM change predicting mental state animations revealed a larger, negative effect for WM change ($E\mu_{WMchange}$ = -0.10, CrI = [-0.19, -0.01]) and a smaller, positive effect for ER change ($E\mu_{ERchange}$ = 0.05, CrI = [-0.00, -0.11]). In summary, drug effects on emotion recognition and drug effects on WM performance together explained R^2 = 0.22 of variance in drug effects on mental state attribution accuracy.



Supplementary figure S2.2. Relationships between drug effects on animations task and control tasks.

2.4. Exploratory analysis: Do participants use different stimulus properties to infer animation identities under haloperidol compared to placebo?

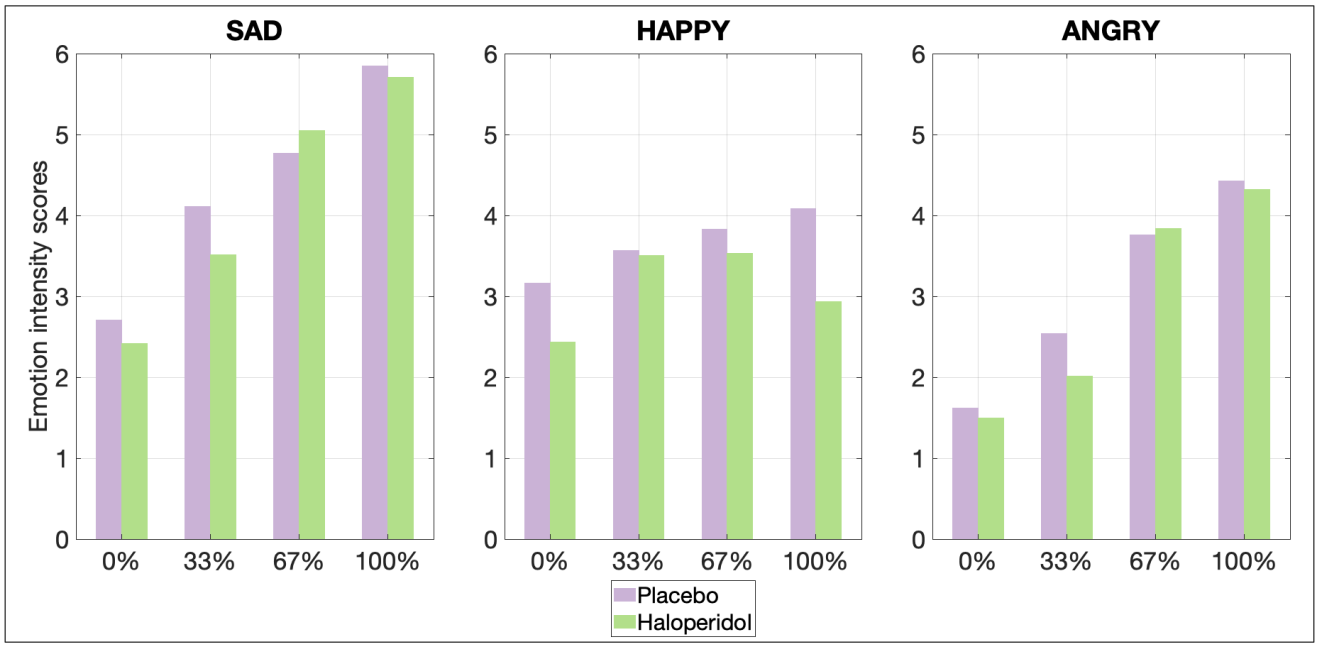
Two independent random forests were conducted to evaluate the relative importance of animation stimulus properties under placebo and haloperidol, respectively. As can be seen in Supplementary Figure S2.3., the same stimulus features are ranked among the top five variable importances (excluding the dummy variable mental state) for haloperidol and placebo: Mean distance, mean rotation, jerk, acceleration and simultaneous movement.



Supplementary figure S2.3. Random forest variable importances for placebo (A) and haloperidol (B) trials. Box edges denote the interquartile range (IQR) between first and third quartile; whiskers denote 1.5 * IQR distance from box edges; circles represent outliers outside of 1.5 * IQR above and below box edges. Box color denotes decision: Green = confirmed, yellow = tentative, red = rejected; grey = meta- attributes shadowMin, shadowMax and shadowMean (minimum, maximum and mean variable importance attained by a shadow feature)

Appendix 3

Supplementary Information for Chapter four



Supplementary Figure S3.1. Emotion intensity scores per stimulus speed level for placebo and haloperidol trials.

3.1. Model 1

Population-level effects	**Estimate**	**Error**	**95% CrI (lower)**	**95% CrI (upper)**
Intercept	3.71	0.23	3.26	4.17
HAL-PLA	-0.06	0.14	-0.32	0.21
Sad	0.64	0.13	0.39	0.89
Happy	-0.05	0.12	-0.29	0.19
Angry	-0.59	0.13	-0.84	-0.34
Speed level linear	1.68	0.18	1.33	2.03
Speed level quadratic	-0.12	0.18	-0.47	0.23
Speed level cubic	0.02	0.18	-0.33	0.36
Low WM	-0.00	0.23	-0.44	0.45
High WM	0.00	0.23	-0.44	0.46
HAL-PLA, sad	0.18	0.18	-0.18	0.54
HAL-PLA, happy	-0.23	0.18	-0.59	0.12

HAL-PLA, angry	0.05	0.18	-0.31	0.41
HAL-PLA, speed level linear	0.01	0.26	-0.50	0.53
HAL-PLA, speed level quadratic	-0.23	0.26	-0.74	0.28
HAL-PLA, speed level cubic	-0.20	0.26	-0.72	0.30
Sad, speed level linear	0.57	0.25	0.07	1.06
Happy, speed level linear	-1.00	0.25	-1.49	-0.51
Angry, speed level linear	0.43	0.25	-0.06	0.93
Sad, speed level quadratic	-0.04	0.25	-0.53	0.46
Happy, speed level quadratic	0.05	0.25	-0.44	0.55
Angry, speed level quadratic	-0.02	0.25	-0.51	0.47
Sad, speed level cubic	0.23	0.25	-0.26	0.72
Happy, speed level cubic	-0.02	0.25	-0.51	0.48
Angry, speed level cubic	-0.21	0.25	-0.70	0.27
HAL-PLA, low WM	0.47	0.14	0.21	0.75
HAL-PLA, high WM	-0.47	0.14	-0.74	-0.20
Sad, low WM	0.15	0.13	-0.10	0.39
Happy, low WM	0.26	0.13	0.01	0.50
Angry, low WM	-0.40	0.12	-0.64	-0.16
Sad, high WM	-0.15	0.13	-0.39	0.10
Happy, high WM	-0.26	0.13	-0.50	-0.01
Angry, high WM	0.40	0.12	0.16	0.64
Low WM, speed level linear	0.24	0.18	-0.11	0.59
High WM, speed level linear	-0.24	0.18	-0.59	0.11
Low WM, speed level quadratic	-0.09	0.18	-0.44	0.26
High WM, speed level quadratic	0.09	0.18	-0.26	0.44
Low WM, speed level cubic	0.18	0.18	-0.16	0.53
High WM, speed level cubic	-0.18	0.18	-0.53	0.16
HAL-PLA, sad, speed level linear	0.31	0.37	-0.40	1.03
HAL-PLA, happy, speed level linear	-0.40	0.37	-1.12	0.33
HAL-PLA, angry, speed level linear	0.09	0.37	-0.63	0.82
HAL-PLA, sad, speed level quadratic	0.26	0.37	-0.48	0.99
HAL-PLA, happy, speed level quadratic	-0.62	0.37	-1.35	0.11
HAL-PLA, angry, speed level quadratic	0.36	0.37	-0.36	1.10
HAL-PLA, sad, speed level cubic	-0.25	0.37	-0.97	0.46
HAL-PLA, happy, speed level cubic	0.35	0.37	-0.38	1.08
HAL-PLA, angry, speed level cubic	-0.10	0.37	-0.81	0.63
HAL-PLA, sad, low WM	-0.15	0.18	-0.52	0.21
HAL-PLA, sad, high WM	0.15	0.18	-0.21	0.52
HAL-PLA, happy, low WM	-0.29	0.18	-0.65	0.07
HAL-PLA, happy, high WM	0.29	0.18	-0.07	0.65
HAL-PLA, angry, low WM	0.44	0.18	0.08	0.80

HAL-PLA, angry, high WM	-0.44	0.18	-0.80	-0.08
HAL-PLA, speed level linear, low WM	-0.10	0.26	-0.62	0.40
HAL-PLA, speed level linear, high WM	0.10	0.26	-0.40	0.62
HAL-PLA, speed level quadratic, low WM	0.15	0.26	-0.36	0.66
HAL-PLA, speed level quadratic, high WM	-0.15	0.26	-0.66	0.36
HAL-PLA, speed level cubic, low WM	-0.08	0.26	-0.59	0.43
HAL-PLA, speed level cubic, high WM	0.08	0.26	-0.43	0.59
Sad, speed level linear, low WM	-0.13	0.25	-0.63	0.35
Sad, speed level linear, high WM	0.13	0.25	-0.35	0.63
Sad, speed level quadratic, low WM	-0.04	0.25	-0.53	0.45
Sad, speed level quadratic, high WM	0.04	0.25	-0.45	0.53
Sad, speed level cubic, low WM	0.03	0.25	-0.46	0.52
Sad, speed level cubic, high WM	-0.03	0.25	-0.52	0.46
Happy, speed level linear, low WM	-0.29	0.25	-0.77	0.20
Happy, speed level linear, high WM	0.29	0.25	-0.20	0.77
Happy, speed level quadratic, low WM	-0.15	0.25	-0.64	0.34
Happy, speed level quadratic, high WM	0.15	0.25	-0.34	0.64
Happy, speed level cubic, low WM	0.20	0.25	-0.30	0.69
Happy, speed level cubic, high WM	-0.20	0.25	-0.69	0.30
Angry, speed level linear, low WM	0.42	0.25	-0.08	0.91
Angry, speed level linear, high WM	-0.42	0.25	-0.91	0.08
Angry, speed level quadratic, low WM	0.19	0.25	-0.31	0.68
Angry, speed level quadratic, high WM	-0.19	0.25	-0.68	0.31
Angry, speed level cubic, low WM	-0.23	0.25	-0.73	0.26
Angry, speed level cubic, high WM	0.23	0.25	-0.26	0.73
HAL-PLA, sad, speed level linear, low WM	0.23	0.37	-0.48	0.95
HAL-PLA, sad, speed level linear, high WM	-0.23	0.37	-0.95	0.48
HAL-PLA, sad, speed level quadratic, low WM	0.13	0.37	-0.59	0.86
HAL-PLA, sad, speed level quadratic, high WM	-0.13	0.37	-0.86	0.59
HAL-PLA, sad, speed level cubic, low WM	-0.03	0.37	-0.74	0.69
HAL-PLA, sad, speed level cubic, high WM	0.03	0.37	-0.69	0.74
HAL-PLA, happy, speed level linear, low WM	-0.02	0.37	-0.72	0.70
HAL-PLA, happy, speed level linear, high WM	0.02	0.37	-0.70	0.72
HAL-PLA, happy, speed level quadratic, low WM	-0.22	0.37	-0.95	0.50
HAL-PLA, happy, speed level quadratic, high WM	0.22	0.37	-0.50	0.95

HAL-PLA, happy, speed level cubic, low WM	-0.35	0.37	-1.08	0.37
HAL-PLA, happy, speed level cubic, high WM	0.35	0.37	-0.37	1.08
HAL-PLA, angry, speed level linear, low WM	-0.21	0.37	-0.94	0.51
HAL-PLA, angry, speed level linear, high WM	0.21	0.37	-0.51	0.94
HAL-PLA, angry, speed level quadratic, low WM	0.09	0.37	-0.62	0.81
HAL-PLA, angry, speed level quadratic, high WM	-0.09	0.37	-0.81	0.62
HAL-PLA, angry, speed level cubic, low WM	0.38	0.37	-0.33	1.10
HAL-PLA, angry, speed level cubic, high WM	-0.38	0.37	-1.10	0.34

Group-level effects	**Estimate (SD)**	**Error**	**95% CrI (lower)**	**95% CrI (upper)**
Subject ID (intercept)	1.29	0.18	0.99	1.68

Supplementary Table S3.1. Model parameters for model 1. Model formula: Emotion recognition scores ~ drug * emotion * speed level * WM group + (1 | subject ID).

3.2. Individual ratings analysis

Under haloperidol, low WM individuals were better at discriminating angry, happy and sad PLWs from the distractor emotion scales.

To gain insight whether increased in emotion recognition scores in the low WM group after haloperidol were a result of HAL increasing the ratings for the correct emotion, decreasing ratings for the non-modelled emotions, or a combination, we explored effects of HAL on the individual (angry, happy, sad) ratings. We therefore subtracted PLA emotion ratings from HAL emotion ratings. Higher rating difference scores reflect an increase in emotion intensity ratings under HAL, with difference scores below zero representing decreased emotion ratings under HAL.

A Bayesian mixed effects model was fit to rating difference scores, with the factors emotion (angry PLW, happy PLW, sad PLW), *rating* (angry rating, happy rating, sad rating) and WM group (low, high), as well as all possible two- and three-way interactions (all factors

deviation coded). The model showed an interaction between emotion, rating and WM group ($E\mu_{sad,sadRating,lowWM}$ = 0.30, CrI = [0.07, 0.54]; $E\mu_{happy,happyRating,lowWM}$ = 0.33, CrI = [0.10, 0.57]), which was confirmed using Bayesian model comparisons with cross-validation (using the loo package [495]). To further unpack this interaction, two separate models were conducted for the high and low WM groups. This model comparison revealed a meaningful interaction between emotion and rating for the low, but not the high WM group. As can be inferred from Table S3.2, under haloperidol, low WM individuals gave 0.40 points higher angry ratings (i.e., intercept + angry + angry rating + angry : angry rating = -0.02 + 0.05 - 0.07 + 0.44 = 0.40) and 0.30 points less high sad ratings (-0.02 + 0.05 - 0.00 - 0.33 = -0.30) to angry PLWs (see Fig. 3). They also gave 0.16 points higher sad ratings to sad PLWs (- 0.02 - 0.14 - 0.00 + 0.32 = 0.16). Furthermore, low WM participants tended to increase their happy ratings to happy PLWs by 0.44 points (-0.02 + 0.09 + 0.07 + 0.30 = 0.44) and decreased their angry ratings to the same PLWs by 31 (-0.02 + 0.09 - 0.07 - 0.31 = -0.31) points after having taken the drug.

In sum, in our low WM group, responses under haloperidol were characterized by increased emotion discrimination: high target ratings and low non-target ratings.

	Low WM			
Population-level effects	**Estimate**	**Error**	**95% CrI (lower)**	**95% CrI (upper)**
Intercept	-0.02	0.19	-0.39	0.34
Sad	-0.14	0.12	-0.37	0.09
Happy	0.09	0.12	-0.15	0.32
Angry	0.05	0.12	-0.19	0.28
Sad rating	-0.00	0.12	-0.24	0.23
Happy rating	0.07	0.12	-0.17	0.30
Angry rating	-0.07	0.12	-0.31	0.17
Sad - sad rating	0.32	0.17	-0.01	0.66
Happy - sad rating	0.00	0.17	-0.33	0.34
Angry - sad rating	-0.33	0.17	-0.66	0.01
Sad – happy rating	-0.20	0.17	-0.53	0.13
Happy – happy rating	0.30	0.17	-0.03	0.63
Angry – happy rating	-0.10	0.17	-0.45	0.23
Sad – angry rating	-0.13	0.17	-0.46	0.21
Happy – angry rating	-0.31	0.17	-0.65	0.02
Angry – angry rating	0.44	0.17	0.10	0.77

Group-level effects	Estimate (SD)	Error	95% CrI (lower)	95% CrI (upper)
Subject ID (intercept)	0.59	0.17	0.33	0.98

Supplementary Table S3.2. Post-hoc mixed model of rating difference scores. Model formula: rating difference scores ~ emotion * rating + (1 | subject ID).

3.3. Comparison of between- and within trial walking speed variability between placebo and haloperidol trials

To investigate whether dopamine challenge affected movement variability, two separate dependent t-tests were carried out, once using a proxy of within-trial variability (coefficient of variation, i.e., SD divided by the mean), and once using an index of between-trial variability (speed difference scores calculated by subtracting speeds of walk one from speeds of walk 2). There was no difference between placebo and haloperidol conditions for either of the two measures of movement variability (within-trial: $t(31) = -1.76$, $p = .088$; between-trial: $t(31) = -0.003$, $p = .997$).

Appendix 4

Supplementary Information for Chapter five

4.1. Analysis of emotion induction success

The online rating task consisted of a total of 15 videos (average length: 2.5 minutes), 5 of each were selected to assess for successful induction of one of the three target emotions anger, happiness and sadness. Videos were presented in a pseudo-random order which resulted in 6 possible combinations. After each video, participants were required to rate, in a random order, how happy, angry, surprised, disgusted and neutral they felt. Participants also rated valence (positive/negative) and arousal levels following each video. Ratings were made on a 10-point likert scale, whereby 1 indicated 'not at all' and 10 indicated 'very'. For valence ratings, 1 indicated 'highly negative' and 10 indicated 'highly positive'.

Mean valence ratings

Discreteness scores were calculated as the target emotion rating minus the mean rating of all non-target emotions. The video that provided the highest discreteness score for each emotion was selected for the main Point Light Walker (PLW) task, resulting in three target videos (angry, happy, sad). A neutral film clip with similar length as the target videos was added to the battery to control for any emotion unrelated speed effects as a result of watching video stimuli. In addition, two short informational film clips (average length: 1.1 minutes) were selected as 'neutral filler videos' with the intention to reverse any emotion induction effects.

Emotion induction successfully changed participants' mood.

Due to data loss, all questionnaire data is based on a sample of 28 participants. Participants on average were in a positive mood at baseline as indicated by valence- (mean [M](standard error of the mean [SEM]) = 6.39(.45)) and happy ratings (M(SEM) = 5.96(.43)) which were significantly higher than the mid-point (= 5) of the scale (valence: $t(27) = 3.06$, $p < .01$; happy: $t(27) = 2.27$, $p < .05$), whereas ratings for all other emotions (anger, sadness, disgust and surprise) and arousal were significantly lower than the mid-point of the scale.

For all target emotions, discreteness scores were calculated by subtracting the mean ratings of the 4 non-target emotions from the mean rating of the target emotion. All three emotional films successfully elicited the target emotion as shown by the fact that all target ratings are significantly higher (happy) or lower (angry, sad) than the corresponding rating at baseline (Table S4.1). In addition, all target emotions were elicited discretely as indicated by all three discreteness scores being significantly different from zero.

Video	**Target rating M(SEM)**	**Valence rating M(SEM)**	**Arousal rating M(SEM)**	**Discreteness M(SEM)**
Baseline	-	6.39(.45)**	3.50(.46)**	-
Angry	8.11(.38)***	2.46(.24)***	7.50(.44)***	3.24(.25)***
Happy	7.32(.47)**	7.61(.43)*	4.82(.49)	4.94(.55)***
Sad	8.61(.45)***	2.11(.18)***	5.54(.42)**	5.32(.40)***
Neutral	7.89(.55)**	5.18(.26)**	2.75(.40)	5.85(.66)***

Supplementary table S4.1. Mean ratings for target emotion, valence and arousal and mean discreteness scores at baseline and for each of the emotion elicitation videos. Asterisks indicate significant differences from the corresponding rating at baseline (target, valence and arousal ratings for the four emotional videos), from the scale mid-point 5 (baseline ratings for valence and arousal) and from zero (discreteness scores) at p values of .05 (*), .01 (**) and .001 (***).