
UNIVERSITÀ DEGLI STUDI DI TORINO

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TITOLO DELLA TESI:

# The Role of Individual Motor Variability in Motor Learning


Tesi Presentata da: Enrico Zingarelli

Tutor: Prof. Cristina Becchio

Coordinatore del Dottorato: Prof. Andrea Calvo



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4. ACTION PREDICTION IN PSYCHOSIS

## Summary

This dissertation is organized into five chapters. Chapter 1 and Chapter 2 examine the role of individual motor variability in motor learning processes. The aim of these two first chapters is to identify how motor variability measured at baseline can influence the speed at which a motor task involving movements in multiple directions is learned. To this end, I present a theoretical overview of motor learning and motor variability (Chapter 1) and an experimental study designed to investigate the role of motor variability in motor learning processes (Chapter 2). Using a robotic manipulandum, we first quantified the individual motor variability of each participant at baseline and then we instructed them to complete a motor learning task. Analyses focused on the relationship between the amount of variability at baseline and the rate of learning. The results of the experimental study show that individual baseline motor variability does not predict faster learning rates in motor adaptation task with multiple directions.

Chapter 3 and 4 examine the ability to predict actions based on observations of arm movements. The aim of this research project is to determine the ability of patients with psychosis to predict the size of a to-be-grasped object. An introduction to the clinical picture of schizophrenia and, in particular, to the impairment of schizophrenic patients in action prediction is provided in Chapter 3. I then describe an experimental study whose primary goal is to determine whether there are differences between psychotic patients and healthy controls in discriminating the outcome of an observed action (Chapter 4). Using a progressive temporal occlusion paradigm with the kinematic coding framework, we quantify the ability of observers with psychosis and healthy controls to predict the size of a to-be-grasped object over progressive temporal occlusion intervals, from 10% up to 80% of movement duration. Our results show an overall reduced and discontinuous integration pattern associated with psychosis. Indeed, observers with psychosis are able to discriminate object size from 30% of the movement whereas healthy controls do so from only 10% of the movement observed. A further interesting result is that, contrary to predictions, observers with psychosis are overconfident compared to controls in the initial integration period (up to 20% of movement duration), but not at later intervals (30-80%).

# Chapter 1 – Motor Learning and Individual Motor Variability

## 1.1 Motor Learning

Motor learning is a complex process that involves changes in the nervous system as the brain acquire new motor skills or improves existing ones. It involves the integration of sensory information from the environment with the brain's internal representations of movement, leading to changes in neural pathways and the development of new motor programs. Motor skills are movements that involve the use of muscles to produce a specific action or behavior, such as throwing a ball, typing on a keyboard, or riding a bike.

Motor learning has important implications for a variety of fields, including education, sports, and rehabilitation. In education, an understanding of motor learning can help teachers design effective learning experiences that promote the acquisition and improvement of motor skills (Coker, 2017). In sports, motor learning principles can be used to design training programs that help athletes improve their performance (Raiola, 2017). In rehabilitation, motor learning principles can be used to design rehabilitation programs that help individuals with disabilities or injuries regain their motor skills (Levin & Demers, 2021).

One characteristic that is always present in the execution of actions and movements is motor variability. Motor variability refers to the inherent fluctuations in movement that occur during the performance of a motor task. It is a normal aspect of movement and is influenced by a variety of factors, including the complexity of the task, the individual's skill level, and the conditions of the environment. Motor variability can be beneficial for motor learning, as it allows the brain to explore a range of possible solutions to a motor task and identify the most efficient ones (Wu et al., 2014). However, excessive motor variability can hinder motor learning, as it may prevent the brain from accurately identifying the most efficient movements and consolidating them into a stable motor memory (Faisal et al., 2008; Smits-Engelsman & Wilson, 2013).

This first section of the dissertation focuses on the relationship between a specific motor learning paradigm (i.e., motor adaptation) and the individual motor variability: can individual baseline motor variability predict the motor learning rate in a motor adaptation task?

In this first chapter of the thesis I provide an overview of motor learning paradigms, focusing on those that were most relevant to this PhD project, and I present the neural basis and tasks of a particular motor learning process, namely motor adaptation. Finally, I describe the current state of research in the field of motor variability. The second chapter consists of the experimental study investigating the role of motor variability in motor learning rate in a motor adaptation task.

## 1.2 Motor learning paradigms

Motor learning paradigms are experimental protocols designed to investigate the neural and behavioral changes that occur during the acquisition of new motor skills. These paradigms include different tasks and methods to probe the changes that take place. For instance, adaptation tasks provide insight into how the nervous system adjusts to changes in the environment and learns new motor programs. We focus on those motor learning paradigms that use information content as a learning signal.

### 1.2.1 Error-based Learning

Error-based learning is a type of learning that occurs when individuals make an error or deviate from a desired movement or action and then adjusts their behavior based on the feedback provided by the error. It is a form of feedback-based learning that is thought to play a crucial role in the acquisition of motor skills (Diedrichsen et al., 2010; Izawa & Shadmehr, 2011; van Vugt & Tillmann, 2015). Specifically, error-based learning involves the modification of neural pathways in the brain based on the feedback provided by errors, leading to the development of new motor programs. For example, this type of learning is thought to be an important factor in

the acquisition of many everyday skills, such as writing, playing a musical instrument, or driving a car. It is also a key component of rehabilitation programs for individuals who have lost motor skills due to injury or illness.

There are several factors that can influence the effectiveness of error-based learning, including the complexity of the task, the individual's skill level, and the type and frequency of feedback provided. Studies have shown that providing frequent and timely feedback can be more effective for improving performance than infrequent or delayed feedback (Galea et al., 2015; Nikooyan & Ahmed, 2015; Seidler et al., 2013).

### 1.2.2 Reinforcement Learning

Reinforcement learning refers to a type of learning that occurs when an individual's behavior is modified by the consequences of that behavior. It can be used to shape and modify behavior by providing rewards or punishments in response to specific actions.

Reinforcement learning is based on two interacting processes to achieve learning: exploration and exploitation (Niv, 2009). Exploration consists of trying new options and gathering information about their potential rewards. It is crucial for discovering new solutions but also it carries the risk of trying options that may not be as rewarding as expected, leading to a temporary decrease in reward. Exploitation refers to the process of choosing the strategy with the highest reward on the basis of the current knowledge. On the other hand, exploitation could miss out on better options that may be discovered through exploration (Sutton, 2018). It is thought that the occurrence of reinforcement learning is based on the function of the basal ganglia (Schultz et al., 1997).

## 1.3 Motor Adaptation

Motor adaptation is the process by which the nervous system learns by adjusting to changes in the environment or task demands. It is an important aspect of motor learning, and it allows us to perform movements more efficiently and effectively in different contexts. Motor adaptation can involve changes at multiple levels of nervous system, including the muscles, the brain, and the spinal cord (J. W. Krakauer et al., 2019).

There are many factors that can influence motor adaptation, including the nature of the task, the individual's characteristics and abilities, and the environment in which learning occurs. Studies have identified a number of principles of motor adaptation that can help to optimize the learning process and improve performance. For example, it is generally accepted that practice that is varied, challenging, and consistent with the task goals leads to better learning outcomes (Galea et al., 2015; Gonzalez Castro et al., 2014; Malone et al., 2011). There are several types of motor adaptation, including error-based learning and reinforcement learning. Each of these types of motor adaptation involves different mechanism and can be more or less effective depending on the task and the individual.

### 1.3.1 Neural Basis of Motor Adaptation

The neural basis of motor adaptation refers to the changes that occur in the nervous system as a result of practice and experience. There is a large body of research on the neural basis of motor learning, and our understanding of this process has increased significantly in recent years. It is now widely accepted that motor learning involves changes in the way the brain process sensory information, as well as changes in the strength of connections between neurons. These changes can be observed using a variety of techniques, including neuroimaging, electrophysiology, and computational modeling (Aliakbaryhosseinabadi et al., 2021; Hardwick et al., 2013; Ostry & Gribble, 2016).

*Cerebellum*. The cerebellum plays a vital role in motor learning and is essential for the proper coordination of voluntary movements (Itō, 2008). Multiple studies have demonstrated the

important role of the cerebellum in motor learning. For example, a meta-analysis by Johnson et al. (J. F. Johnson et al., 2019) showed that cerebellum is involved in the process of adapting movements to changing environments, allowing us to adjust our movements and maintain coordination in new situations. Using a noninvasive brain stimulation technique, Wessel and colleagues (2016) showed that the cerebellar stimulation enhanced the consolidation of the new motor skill, retesting participants 24 h after training.

When we perform a motor task, the cerebellum is actively involved in the learning process. It receives input from various sources, including sensory receptors in the muscle and joints, as well from the eyes and ears (Raymond et al., 1996). The input is used to make adjustments to muscles output, allowing us to perform the task more accurately and efficiently. When learning to ride a bike, the cerebellum receives input from sensors in the muscles and joint, as well as visual and auditory input, and uses this information to make fine adjustments to the output of the muscles (Itō, 2008).

Many research studies involving individuals with cerebellar degeneration have found significant impairments in visuomotor adaptation (Rabe et al., 2009; Schlerf et al., 2013), force-field adaptation (Criscimagna-Hemminger et al., 2010a; Smith & Shadmehr, 2005), saccadic adaptation (Golla et al., 2008; Xu-Wilson et al., 2009), locomotor adaptation (Morton & Bastian, 2006), and speech adaptation (Parrell et al., 2017). Patients with cerebellar damage are more able to adapt to a change in their environment if it is introduced gradually, compared to if it is introduced suddenly. In fact, Criscimagna-Hemminger and colleagues (2010b) investigated motor learning processes in patients with cerebellar degeneration, with a task in which two groups of participants had to adapt their reaching movements in response to large perturbations. One group experienced the perturbations suddenly, while for the second group the perturbations were imposed gradually. The second group demonstrated significant improvement, compared to the first group, suggesting that, despite cerebellar damage, they maintained the ability to learn from small errors and show strong resistance to change.

*Primary Motor Cortex*. Using non-invasive brain stimulation techniques, the role of the primary motor cortex in motor learning, particularly in the acquisition and retention phases of information, has been investigated and deepened. Galea and colleagues (2011) found that, by

applying transcranial direct current stimulation (tDCS) on the primary motor cortex, retention in a visuomotor adaptation task improved, while it did not affect adaptation. This result showed a dissociation in the processes of acquisition and retention during motor learning in the primary motor cortex.

Supporting these findings, Richardson et al. (2006) used repetitive transcranial magnetic stimulation (rTMS) to induce a disruption on the primary motor cortex immediately before participants performed a viscous force-field adaptation. Subjects who received the brain stimulation performed significantly worse than control subjects in the retest task, despite they performed identically to control subjects in the adaptation task. Given these findings, the primary motor cortex seems to be involved in initiating the formation of long-term motor memories, but it is not essential in the process of motor adaptation.

*Basal Ganglia*. The basal ganglia are composed of multiple nuclei, including the striatum, globus pallidus, and substantia nigra, and are interconnected with the cerebral cortex, cerebellum, and brainstem. These nuclei are involved in a wide range of functions, including motor control, cognitive control, reward processing, and emotional regulation (Groenewegen, 2003). It has been suggested that patients with basal ganglia disease generally find intact adaptation but reduced long-term memory. For example, Huntington's and Parkinson's disease patients exhibited no deficits in adapting to a force field, but still showed smaller aftereffects in tasks of force-field adaptation, visuomotor adaptation, and prism adaptation (Bédard & Sanes, 2011; Gutierrez-Garralda et al., 2013; Leow et al., 2012; Smith & Shadmehr, 2005).

### 1.3.2 Motor Adaptation Tasks

*Force-field adaptation task.* One of the several paradigms used to study motor learning is the force-field adaptation paradigm. Force-field adaptation task is an exercise designed to improve an individual's ability to perform movements in a new dynamic environment (Bays et al., 2005; Scheidt et al., 2000).

In a force-field adaptation task, an external force, such as a mechanical or electromechanical device, is applied to the subjects' limbs to alter the way they move. The subject grasps the handle of a robotic manipulandum and perform arm movements, while forces are applied to the robot causing deviations during the movement. They must then adapt their movements in order to complete the task, which helps them to develop better control and learn how to move in a novel force environment (Gandolfo et al., 1996; Shadmehr & Mussa-ivaldi, 1994; Smith et al., 2006).

For example, when a subjects make reaching arm movements by holding the robotic manipulandum, the planned movement will be perturbed by the forces applied, creating an error between the predicted and the observed movement. This requires to process sensory information about the force field, make adjustment to the movement and execute again the task. The goal of the subject is to counteract the forces applied to the robotic arm, generating equal forces but in the opposite direction (Fig. 1). Additionally, force-field tasks can be modified to increase or decrease the level of difficulty, which allows the subject to progress at their own pace and improve themselves.

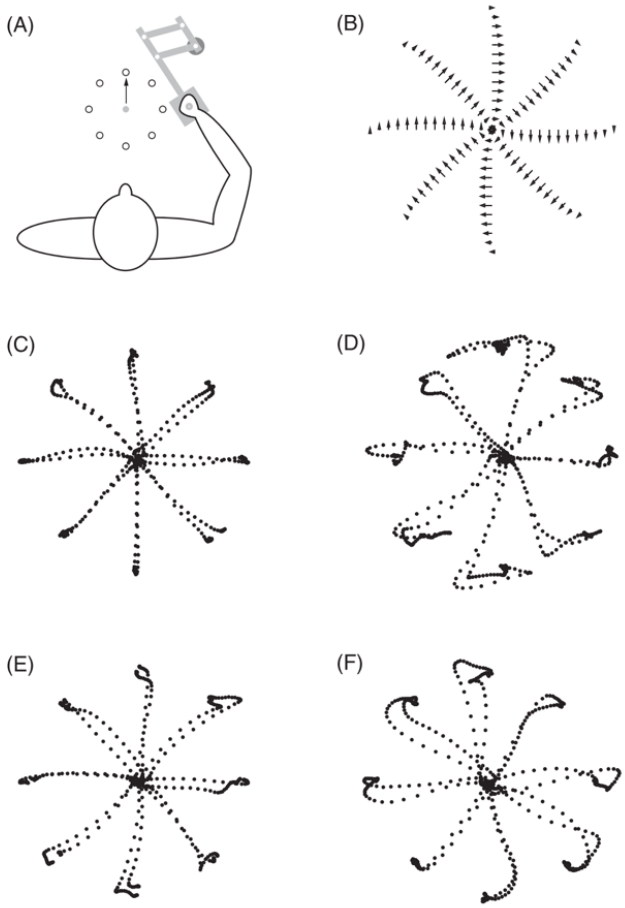


*Figure 1. Force-field adaptation and aftereffects. This figure (from Krakauer et al., 2019) illustrates behavior in a typical force-field adaptation task. In this study participants, holding a robotic manipulandum(A), perform a force-field (B) task adaptation. After a baseline, in which no force field was applied and movements were relatively straight (C), a clock-wise force-field was applied resulting in movement errors in the direction of the force field (D). After training, participants learned how to move in the force field, making straight trajectories to reach the targets (E). Removing again the force-field, the aftereffects of adaptation are revealed. Indeed, movements errors are in the opposite direction to the perturbation (F), because participants learned to counteract the force-field.*

*Visuomotor rotation adaptation.* The visuomotor rotation task is another commonly used paradigm to study motor adaptation process. In this task, the vision of the hand is obscured, while a cursor representing the hand's position is displayed on a screen. Subjects are instructed to make reaching movement by controlling the cursor on the screen. A visual perturbation is applied on the cursor with a rotation around the starting position, in such a way that the cursor no longer reflects the hand's position. Subjects need to adapt by adjusting their hand movements

with a deviated angle, in order to successfully move the cursor to the target in a straight line. This task causes a conflict between the visual error and the unchanged proprioceptive information, because the imposed perturbation is purely visual. But despite the discrepancy, participants show to be able to modify their movements following deviations, possibly indicating a prevalence of visual information over proprioceptive information (Fig. 2) (Huang et al., 2011; J. Krakauer et al., 2000; J. W. Krakauer, 2009; Wang & Sainburg, 2005).

An interesting study by Mazzoni and Krakauer (2006) showed that adaptation to a visuomotor rotation occurs through an implicit learning process, despite being given explicit instructions to complete the task perfectly. The authors informed the participants about the specific rotation and gave instructions on how to counteract it. However, it was surprising that they started to complete the task successfully with this strategy but then gradually could no longer maintain explicit control and made errors.

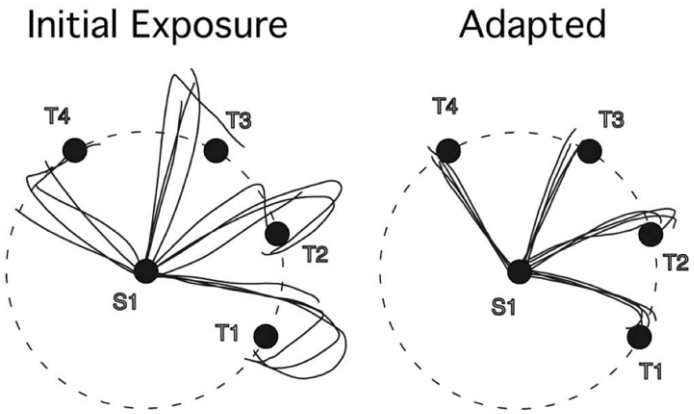


*Figure 2. The figure (from Wang & Sainburg) shows the visuomotor adaptation hand paths. On the initial exposure, hand paths are deviated from the target, because the position of the cursor was rotated 30° counterclockwise (left). After adaptation, when participants learn how to counteract the visual rotation, hand paths are relatively straight and significantly more accurate (right).*

They adapted unconsciously and failed to follow the cognitive strategy, indicating that the motor planning system overrides explicit strategies and cannot be replaced by them in adapting to the visuomotor rotation task.

## 1.4 Motor Variability

Motor variability refers to the inherent variability present to some degree in all movements of a human being (Stergiou, 2018). An expression used to describe motor variability is *'repetition without repetition*', alluding to the fact that the same motor act or motor task, no matter how many times we repeat it, will always be unique (Bernstein, 1966). Motor variability is the worst enemy of athletes and musicians who, in order to improve their performance on the field or on stage, practice hard to reduce it as much as possible. Reducing motor variability also often leads to improved performance because of the constant search for movement perfection. In fact, studies suggested that motor variability interferes with the goal to be achieved through motor control and therefore had to be counteracted (Harris & Wolpert, 1998; Todorov & Jordan, 2002). But is that true? Is motor variability just a 'noise' of the movement to be eliminated? And why is it so difficult to eliminate it completely, or at least tame it?

One reason why motor variability is difficult to eliminate is that there is not just one source of variability (Faisal et al., 2008). The sources of individual motor variability have been analyzed using multiple experimental and computational methods, finding variability at various levels, from movement planning in central nervous circuits to force production in muscles (Dhawale et al., 2017). Variability was shown at the cellular level in various processes, such as spike initiation (van Rossum et al., 2003; White et al., 2000), propagation (A. A. Faisal & Laughlin, 2007), synaptic transmission (Calvin & Stevens, 1968; Katz, B., & Miledi, 1970), and muscle activation (Hamilton et al., 2004; Jones et al., 2002).

As mentioned before, motor variability plays a decisive role in motor learning. It is thought to play a role in the exploration and adaptation of movements during learning, and in the ability to adapt to new or changing environments. Indeed, new research has helped change the classical

view of motor variability from being 'noise' of movement to an advantageous feature (Cowin et al., 2022; Stergiou & Decker, 2011). Evidence suggests that movement variability may have functional benefits in specific contexts, such as in tasks requiring the ability to adapt to changing conditions or to perform a range of tasks. For example, research has shown that individuals can control and modify their movement variability to adapt to new or changing environments and are more efficient at switching between different tasks (Pekny et al., 2015; Trommershäuser et al., 2005).

Wu and colleagues (2014) explored the hypothesis that there was a relationship between learning rates and baseline task-relevant variability. The authors instructed healthy participants to complete reaching movements in a single direction, by using a robotic manipulandum. They measure the variability of movements in a baseline session and then predict how fast each subject could learn to complete a force-field motor adaptation task by stratifying participants based on their individual variability. They found that higher task-relevant variability predicts faster learning rates, in other words, the more variable the movements, the faster the learning.

In view of these results, motor variability can no longer be considered only as a negative aspect of the human nervous system, but rather as a crucial tool for motor learning. In the context of the exploration-exploitation dilemma (Sutton & Barto, 2018; Kaelbling, 1996), individual motor variability appears to be a key characteristic of the exploration phase (Dhawale et al., 2017). In short, the dilemma is whether to continue exploring new options or to exploit the knowledge already acquired to complete a task. Thus, the individual motor variability could be modulated according to the exploration needed to find better solutions.

There are also many examples in the field of sports research where the motor variability of athletes becomes a critical element that plays a role in performance. Increasingly, studying motor variability is crucial to provide more detailed and reliable data to coaches and athletes who want to improve performance (Barris et al., 2014; Bartlett, 2008; Busquets et al., 2016).

## Aim of the study

Many research has shown that motor variability plays an important role in motor learning processes. It has been demonstrated that participants who exhibit higher baseline motor variability show faster learning rates in a motor adaptation task in which they complete reaching movements in one direction.

The aim of this study is to explore if higher individual baseline motor variability promotes motor learning in multiple directions. If motor variability could predict the rate of learning also in multiple directions, this would provide support for the general importance of variability in motor learning processes. To explore this hypothesis, in the current research was utilized a force-field motor adaptation task in which participants have to perform reaching movements towards eight targets. This approach will reinforce our knowledge about the relationship between motor variability and motor learning.

# Chapter 2 - The role of Individual Motor Variability in Motor Learning

## 2.1 Introduction

From the way we write to the way we throw a ball, our movements are not always the same (Djioua & Plamondon, 2009). Even people, who have a high level of skill and consistently achieve the same result, show variations in their movements during the execution of a goal-oriented action or task (H. W. Johnson, 1961). No matter how long one practices, there is an ever-present variability in motor execution that makes it virtually impossible to exactly repeat actions. This is particularly evident in the performance of individuals with high levels of motor expertise. In fact, motor variability has been shown and studied even in elite athletes and dancer (Hopper et al., 2018; Truong et al., 2023). It was commonly believed that variability of movement is caused by a noisy nervous system that impedes peak performance (Cohen & Sternad, 2009; A. Faisal et al., 2008; Renart & Machens, 2014).

Subsequent studies have shifted the perspective on variability from a negative aspect to be minimized to an advantageous feature (Cowin et al., 2022; Stergiou & Decker, 2011). Studies in songbird have shown that variability in motor performance can be used as a support for motor learning (Kao et al., 2005; Ölveczky et al., 2005; Tumer & Brainard, 2007). Adult birds show variations in intonation in the sounds they emit. If some variations are followed by negative reinforcement, then the birds make sounds with intonations gradually further away from these. These results show that motor learning and performance optimization are also facilitated by variability. Something similar was also observed in humans. Indeed, Wu and colleagues (2014) demonstrate a correlation between variability and motor learning. They instructed participants to make reaching movements in a single direction, completing a force-field adaptation task. The results showed that higher baseline task-relevant variability predicted faster learning rates in the very early stages of the learning session (i.e., the first ten trials).

What is still unknown is whether higher individual baseline motor variability promotes motor learning also in multiple directions. It has been shown that training a larger portion of the workspace during a motor learning task leads to a broader generalization of learning. Neva and Henriques (2013) investigated the effects of repeated and varied training on visuomotor

adaptation and generalization, by training a group of participants in a visuomotor rotation task under different training conditions. Participants were divided into two groups: one group received repeated training on a single rotation (i.e., trained on 4 targets 18 times), the other group received varied training on multiple rotations (i.e., trained on 18 targets only once). The kinematics of the reaching movements were recorded and analyzed to assess the changes in movement patterns over the course of the training. The results showed that the group that received repeated training showed better adaptation to the specific rotation for which they were trained on, but poor generalization to other rotations. The group that received varied training showed better generalization to other rotations. These findings suggest that repeated training on a single rotation improves adaptation to that specific rotation but does not promote generalization to other rotations. On the other hand, varied training promotes generalization to other rotations.

To investigate whether individual baseline variability facilitates motor learning in an environment not restricted to one reaching direction, we used a force-field adaptation task with eight targets in four different directions. We used the experimental task from the study by Mattar and Gribble (2005). In this study, participants were instructed to make reaching movements by holding the handle of a robotic manipulandum device. They used the robotic arm to guide a cursor presented on a screen in front of them. The task was to perform point-to-point reaching movements, reaching 8 different targets from a central starting position. Participants were asked to guide the cursor to the targets, while the robot was applying a clockwise force-field. At the start of the session, trajectories of the movements show the typical right hook in proximity to the target, due to the clockwise force-field. At the end of the session, participants were able to make straight movements towards the targets showing they learned how to move in the force-field environment.

Here, we explore if higher individual baseline motor variability promotes motor learning in multiple directions. To test this hypothesis, we measured baseline motor variability before participants performed an eight-target motor adaptation task and examined whether individual baseline variability could predict the rate at which participants learned.

## 2.2 Methods and Materials

### 2.2.1 Participants

Forty-one right-handed adults (mean age 25,2 ± 2,5, 24 females) were recruited for the study. Participants had no neurological or musculoskeletal impairments and they had normal or corrected-to-normal vision. The study received approval by the ethical committee of Liguria Region and was carried out complying with the principles expressed in the revised Helsinki Declaration (World, 2013). Participants provided written informed consent. The sample size for the experiment was determined based on previous similar experiment (Wu et al., 2014).

### 2.2.2 Experimental design and procedure

Subjects sat in a comfortable chair in front of a custom robotic manipulandum (Casadio et al., 2006; Lombardi et al., 2021; Marini et al., 2019), grasping the handle with the right hand that allows for arms movements along the transversal plane. The position of the seat was regulated facing the computer monitor. The 24.5” LCD screen was set to a spatial resolution of 1920 x 1200 pixels and 100 Hz refresh rate. To set the distance between the seat and monitor, participants were asked to reached the extreme point of the workspace with the arm fully extended, and a reference position 10 cm below the center of the workspace, keeping the elbow flexed approximately 45° (Fig. 3). The adjustment of the chair on the axis parallel to the monitor was set by aligning the participant's shoulder with the workspace midline. The torso was strapped to the seat with belts to prevent the subject from compensating and moving the torso. The robotic manipulandum used for the study is based on a planar haptic manipulator with 2 degrees of freedom. It has a workspace area of 80 x 40 cm, which is limited by a virtual wall that subjects cannot overstep.

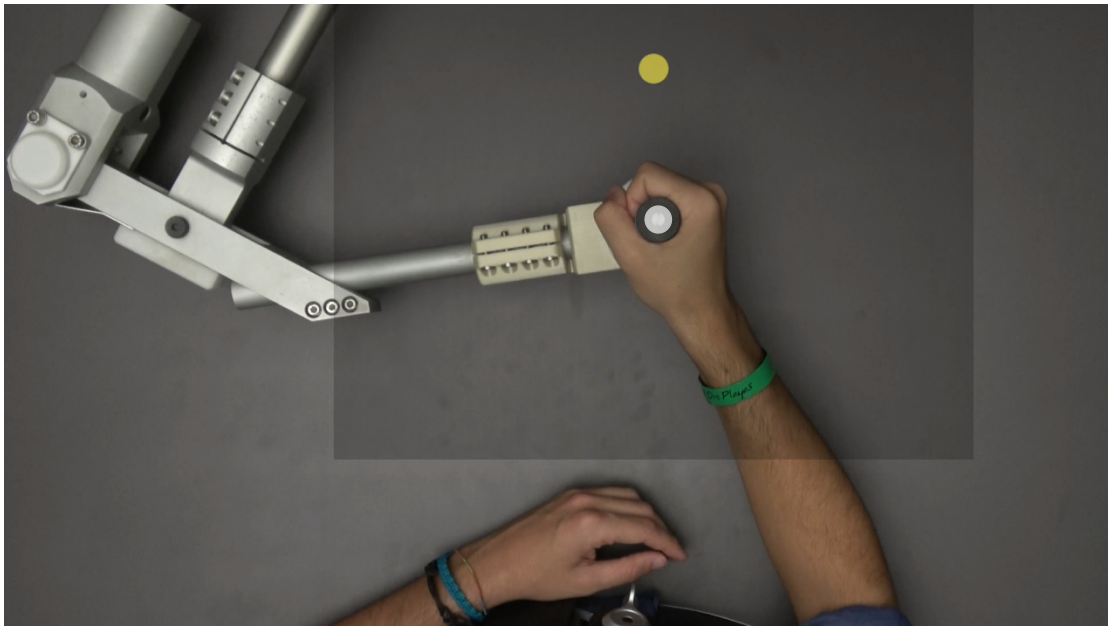

*Figure 3. The picture depicts a subject holding the robotic manipulandum in the process of reaching the target in the vertical direction (90°), starting from the central position. We superimposed on the picture what the subject could see on the monitor in front of him to make the image easier to understand.*

The manipulandum is able to measure the trajectory of the hand at the resolution of 0.1 mm, it records lateral force profiles of the movements and gives us the possibility to apply force field environment at a sampling rate of 200 Hz. The control architecture is based on the RT-LabH real-time operating system.

*Procedure*. To accurately measure baseline variability, we included a prolonged baseline period in the study that consisted of two phases of 400 trials. We considered the first phase of the baseline period as a *familiarization period*, while with the second we would measure individual baseline motor variability. After the prolonged baseline period, subjects performed a learning phase of 200 trials, in which they were exposed to a velocity-dependent force-field environment. Participants were instructed to make point-to-point reaching arm movements (10 cm length), while grasping the handle of the robotic manipulandum. Starting from the central starting position, the task was to reach one of the eight peripheral targets that appeared on the

screen monitor (Fig. 4). Each trial started from the central position to reach one of eight peripheral targets.

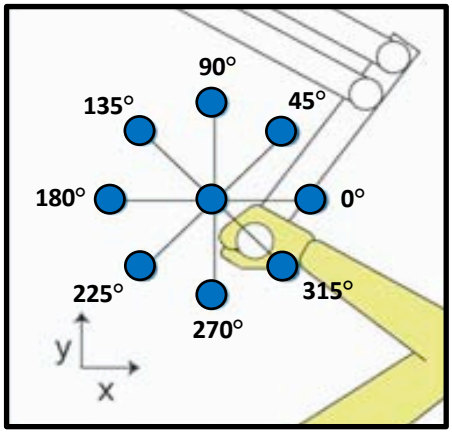


*Figure 4. Experimental Task. Subjects hold a custom robotic manipulandum, which they used to guide a cursor on the monitor screen to reach the eight targets. (modified from Mattar & Gribble, 2005)*

Once the target was reached, it would disappear, and the target indicating the initial starting position would reappear. The targets were 24 mm in diameter, located 10 cm away from a central starting position and could appear in eight different positions. The instruction given was to reach the peripheral target quickly and accurately, possibly in one movement. The participants received feedback on the speed of the movement for each trial. The desired movement duration was in the range of [175 - 275] ms. At the conclusion of each reaching movement, the color of the target was changed according to whether the movement was too fast (red target), too slow (blue target) or the correct speed (yellow target).

The experimental protocol was divided in two experimental phases: a first phase, the baseline phase, in which no force field was applied to the robotic manipulandum, in order to quantify individual baseline motor variability, then the learning phase, in which a clockwise force field was applied to the manipulandum, so they could learn how to move in a new force environment. The force-field environment applied to the manipulandum for the learning phase was velocity dependent and with a clockwise direction according to the following equation:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & dk \\ -dk & 0 \end{bmatrix} \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix}$$

where $F_x$ and $F_y$ are robot-generated forces in the left/right and forward/backward direction, $\dot{x}$ and $\dot{y}$ are hand velocities, $k = 20\ Ns/m$ and $d = +1.0$.

*Error-clamp trials*. In both baseline and learning sessions, a particular kind of trial, called *error-clamp trials*, was interspersed at 20% of total trials (80 error-clamp trials in each baseline phase and 40 error-clamp trials in the learning phase). Error-clamp trials are used to measure the feedforward motor output that is produced during a movement. Reaching movements are controlled by feedforward motor output, which is based on pre-planned information, and online feedback error correction, which adjusts the movement based on any errors that are detected. In error-clamp trials, the lateral deviations during movements are limited to below 1 mm, eliminating the lateral error signal and allowing for the isolation of feedforward motor output. Error-clamp trials involve the application of damped high-stiffness elastic force to restrict the subjects' lateral forces to a straight channel towards the target. This effectively "clamps" the movements within a narrow path. To ensure that we captured the entire movement, we examined the force output generated over an 860 ms window centered at the peak speed point, even though the movement duration was generally between 500 and 600 ms. This allowed us to study the lateral force output generated during the reaching movement in greater detail. To remove high-frequency noise we applied a second-order Butterworth filter with a cutoff frequency of 10 Hz to the force data. This smoothing process helped to improve the signal-to-noise ratio and enhance the accuracy of the force measurements. Data analysis were performed using custom Matlab software (MathWorks, Natick, MA).

*Individual baseline variability estimation*. We calculated the amount of the individual task-relevant variability by considering movement variability recorded during baseline error-clamp trials. We first computed a variability index by projecting the lateral forces onto the ideal lateral forces (ideal velocity-dependent force patterns), using the following formula:

$$F_{proj} = \frac{dot(F_{lat},\ vel)}{dot(vel, vel)} .* vel$$

where $F_{lat}$ is the time dependent force profile in a single trial, *vel* is the velocity profile in a single trial, *dot* represents the scalar product between two vectors, $F_{proj}$ is the projections of lateral force profiles onto its corresponding velocity profile. Then, the variability is the standard deviation over time points of the $F_{proj}$ projection vector. This variability index is a single-trial index. To obtain a single value for each subject, we averaged this single-trial index across baseline error clamp trials.

*Initial learning rate estimation*. We followed the method used in previous studies and performed a baseline subtraction per participant (Wu et al., 2014), using the last eight error clamps during the baseline as a reference for the changes in force output measurements during error-clamp trials in the training period. Then, we computed the multiple linear regression with position, velocity, and acceleration as the independent variables as follows:

$$F_{lat} = \beta_0 + \beta_{pos\_lat} * p_{lat} + \beta_{vel\_lat} * v_{lat} + \beta_{acc\_lat} * a_{lat}$$

Then we determined the learning level by first extracting the velocity regression coefficient of ideal force and finally by normalizing the velocity regression coefficient so that a value of 1 indicated full learning:

$$F_{ideal} = \beta_0 + \beta_{vel\_ide} * v_{lat}$$

$$Learning\ Level\ = \frac{\beta_{vel\_lat}}{\beta_{vel\_ide}}$$

For each participant an initial learning rate was determined by calculating the average rate of increase in learning level during the first ten trials of the training period, which included two error-clamp trials:

$$Initial\ learning\ rate = \frac{EC_1 + EC_2}{10}$$

where $EC_1$ is the learning level in the first error-clamp trial and $EC_2$ is the learning level in the second error-clamp trial.

## 2.3 Results

Participants completed two experimental sessions in which they were instructed to perform reaching movements using a robotic manipulandum. They performed the baseline session without any perturbations applied to arm movements. They were then asked to complete a force-field adaptation task in which a clockwise force field was applied to the robot. The task was to learn how to move in a force field environment without receiving explicit instructions. In other words, participants had to learn how to move precisely to targets in a single motion while applying perturbing forces to the arm.

To replicate the results obtained by Wu and colleagues (2014) on the positive relationship between individual variability and learning rate, we focused on the very first phase of the learning session, the initial learning rate. We found no significant correlation between individual task-relevant variability and the initial learning rate, over first two error-clamp trials, across subjects (Fig. 5; r = +0.02, P = 0.90, $t_{(39)}$ = 0.12).

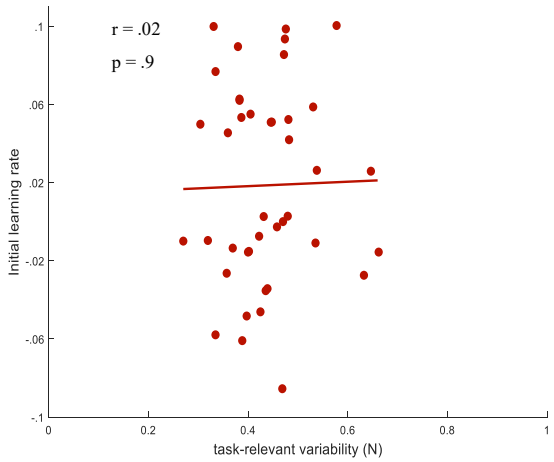


*Figure 5. Comparison of task-relevant variability with the initial learning over the first two error-clamp trials.*

The pseudorandomisation of the trials permitted participants to experience targets in cycles of eight. Similarly, they experienced the error-clamp trial with the same scheme. This allowed us to extend the computation of initial learning over the first eight error-clamps, considering that participants had experienced all the eight targets. Consistently, calculating the initial learning over the first eight trials (i.e., the first error-clamp trial for each target direction) we do not find a significant correlation (Fig. 6; r = -.075, P = 0.63, $t_{(39)}$ = -0.47).

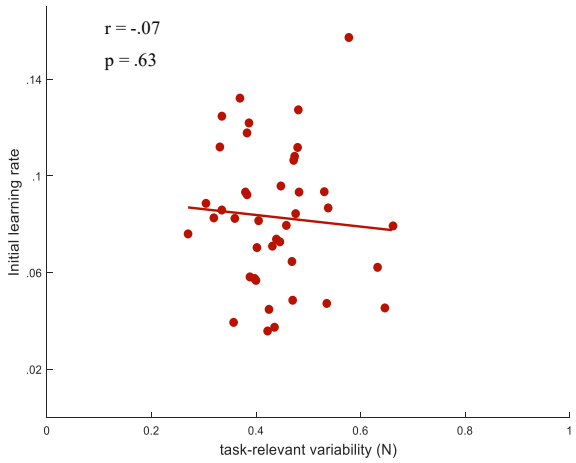


*Figure 6. Comparison of task-relevant variability with the initial learning over the first eight error-clamp trials.*

By stratifying participants according to their individual variability, replicating the analysis from Wu and colleagues (2014), we can form four subgroups, from participants with above-average variability to those with below-average variability. We had subjects (n = 6) with variability that was at least one standard deviation below average, subjects (n = 22) with variability that was below average, subjects (n = 19) with variability that was above average, and subjects (n = 7) with variability that was at least one standard deviation above average. We compared the individual variability with the average learning rate over the first two trials (Fig. 7) and the first eight trials (Fig. 8). Consistent with previous results, there is no positive correlation between initial learning rate and task-relevant variability (Suppl Fig. S1-S2).

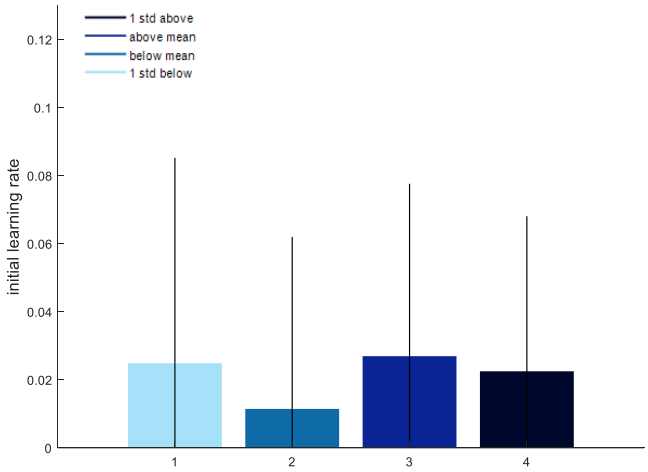


*Figure 7. Comparisons between average learning rate, over first two error-clamp trials, and individual task-relevant variability. Four subgroups are shown from least to most variable (from 1 to 4). Bars error show standard deviation.*

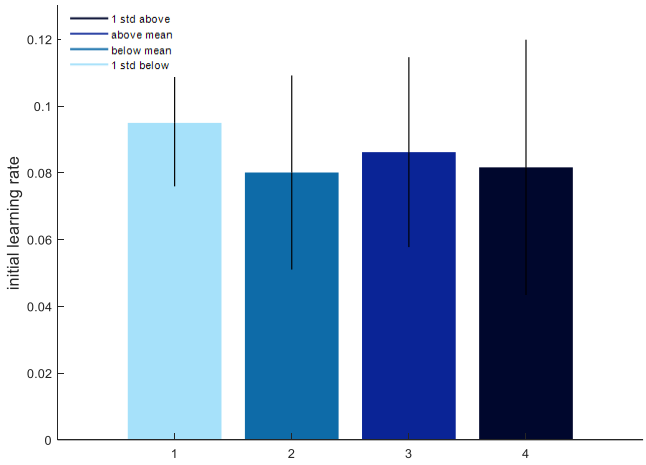


*Figure 8. Comparisons between average learning rate, over first eight error-clamp trials, and individual task-relevant variability. Four subgroups are shown from least to most variable (from 1 to 4). Bars error show standard deviation.*

These findings are corroborated by further analysis in which we investigated the relationship between variability and learning by calculating initial learning differently. To our knowledge, this is the first study to investigate the role of variability on motor learning with a force-field

adaptation task with eight targets, we explored the possibility of computing initial learning in a different way compared to the one described by Wu and colleagues. The initial learning was also computed: - over the first error-clamp (Suppl Fig. S3A, in Appendix A), considering an even earlier phase of the learning session than the one already analyzed, - over the first sixteen error-clamp trials (i.e., the first two error-clamp trials for each target direction) (Suppl Fig. S3B, in Appendix A), over the first two error-clamp trials of a specific target (Suppl Fig. S4, in Appendix A), - over the first two error-clamp trials of a specific direction (i.e., four directions: 0°-180°, 45°-225°, 90°-270°, 135°-315°) (Suppl Fig. S5, in Appendix A).

## 2.4 Discussion

Previous work has shown that subjects who had more task-relevant variability at baseline learned faster than those who had lower variability (Wu et al., 2014). The crucial difference with our study is the extent of workspace used for the motor adaptation task, as our study used a larger surface using a task with more targets. By using one of the most common motor adaptation tasks, i.e. a velocity dependent force-field design with eight targets (Bays et al., 2005; Mattar & Gribble, 2005; Miyamoto et al., 2019), we were able to both quantify the amount of individual motor variability and to make participants complete a motor learning task.

Here we have shown that individual baseline motor variability does not predict faster learning rates in motor adaptation task with multiple directions. Indeed, we found that individuals undergoing a force-field adaptation task with multiple directions show that motor learning rate is not predicted by their individual motor variability. The correlation between individual motor variability and initial learning rate was not significant. Interestingly, even when exploring new ways of interpreting the computation of initial learning, the results remain consistent.

To our knowledge, no study has previously investigated the role of motor variability in motor learning processes over a larger workspace than a single direction. Indeed, Wu and colleagues demonstrated that higher task-relevant variability predicts faster learning rates in the very early stages of the learning session. They calculated the initial learning rate as a measure of learning

in early phases and showed that this effect occurs in the window encompassing the first two error-clamp trials and disappears soon after. In our study, we show that there is no such window in which higher baseline variability accelerates learning in the adaptation task.

The number of targets played a role in these results, as it undoubtedly made the task more difficult, in terms of the number of trials required, and thus the cognitive and physical effort involved. It has been shown that fatigue can affect movement variability differently, leading to both an increase and a decrease in variability depending on the specific variable being considered (Cortes et al., 2014). Our results can outline that motor variability overall, rather than in reaching movements directed at specific targets, is not predictive of motor learning. The task with eight different target positions introduces an additional factor that might have influenced the results, namely the anisotropy of the movement. Anisotropy of limb movements refers to the fact that the inertial resistance of the arm depends on hand movement direction (Flanagan & Lolley, 2001), thus certain movements are easier to perform in certain directions or orientations than in others. It has been shown that trajectory kinematics of reaching movements are significantly different as the direction changes, and this is due to limb inertia (Gordon et al., 1994). The properties of the arm affect the way the target is reached, depending on its position. We could hypothesize that part of the variability that participants show in reaching targets is the inevitable variability that arises from reaching a specific target due to the properties of the arm. To account for this when calculating motor variability, future studies could consider this property of arm movement in reaching different targets. Moreover, in this study, the amount of motor variability at baseline of each individual was computed based only on the lateral forces applied in the error-clamp trials. It should also be considered that the individual motor variability has been quantified based on several variables such as the maximum curvature of the trajectory, the angle and velocity of the movement, or the amplitude of the movement (Cohen & Sternad, 2009; Torres, 2013; Wulf & Schmidt, 1997).

In summary, our current findings do not support the view that motor variability could be a predictor of faster learning in a motor adaptation task. There is no significant correlation between individual baseline variability and learning rate in performing a motor adaptation task with multiple targets. Further studies will be necessary to reinforce knowledge of the role of

motor variability in motor learning processes and to determine how generalizable the *positive effect* of motor variability is in a broader workspace.

# Chapter 3 - Introduction to Schizophrenia and Prediction Abnormalities

This second section of the thesis aims to investigate the alterations in the action prediction in subjects suffering from psychotic disorders. The primary goal is to detect whether there are differences between patients with psychotic disorders and healthy controls in discriminating the outcome of an observed action (i.e., the size of an object from movement kinematics). Indeed, a previous study found that healthy subjects were able to predict the size of an object just by observing grasping movements using a progressive temporal occlusion task (Ansuini et al., 2016). Secondly, different cognitive areas, such as functioning, psychopathological symptoms, cognition and neurological signs, were tested in order to investigate if the severity of positive and negative symptoms influences the ability to predict object size.

## 3.1 Schizophrenia

*Schizophrenia* is a severe neuropsychiatric disorder that affects approximately 1% of the world's population. The age of onset in males is from 20 to 24 years and slightly later in females (Jablensky & Kalaydjieva, 2003). Less than 50% of patients acquire long-term recovery (Tandon et al., 2010), which leaves many patients disabled and disadvantaged. The impact of the disease is further highlighted by the Global Burden of Disease study ranking schizophrenia as the seventh leading cause of years of life lived with disability (YLD) in all age groups and third in the 15 – 44 years old (World Medical, 2013). In general, patients with schizophrenia present deficits in several areas, such as distortions in thinking, perception and behavior that lead to severe impairments in cognition, clinical outcomes, social status and quality of life (Green et al., 2000; Harvey et al., 2012; Hofer et al., 2005).

The various areas in which these patients have been shown to exhibit deficits are executive functioning, attention (Orellana & Slachevsky, 2013), language processing (Crow, 1998), working and episodic memory (Barch & Ceaser, 2012). Regarding the onset of these deficits, evidence says that they may be present before the onset of the disorder (Lencz et al., 2006), stable during its course (Heilbronner et al., 2016) and associated with abnormalities in prefrontal and temporal brain structures (Antonova et al., 2004).

In the DSM-V, two significant changes were made to the diagnosis and classification of schizophrenia. Firstly, the diagnostic criteria for schizophrenia were revised, and the disorder's name was changed from *schizophrenia-to-schizophrenia spectrum disorder*. This allows specialists to diagnose the condition based on the severity of symptoms. Secondly, the subtypes of schizophrenia (paranoid, disorganized, catatonic, undifferentiated, and residual) were removed. The reason for eliminating the previous subtypes is that they are not stable conditions and have not afforded significant clinical utility nor scientific validity and reliability.

**Table 1. DSM-V TR – diagnostic criteria for schizophrenia**

| Disorder Class: Schizophrenia Spectrum and Other Psychotic Disorders |
|---|
| A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2) or (3):<br>1. delusions<br>2. hallucinations<br>3. disorganized speech (e.g., frequent derailment or incoherence)<br>4. grossly disorganized or catatonic behavior<br>5. negative symptoms (i.e., diminished emotional expression or avolition) |
| B. *Social/occupational dysfunction*: For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning). |

C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully

treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic feature have been ruled out because either (1) no major depressive or maniac episodes have occurred concurrently with the active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

(DSM-V, 2013, American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.))

## 3.2 Symptoms

Schizophrenia involves a range of issues with thinking (cognition), behavior, and emotions. Patients with schizophrenia often present with a range of symptoms that can be divided into three major categories: positive symptoms, negative symptoms, and cognitive symptoms.

### 3.2.1 Positive symptoms

*Positive symptoms*, generally known as *psychotic symptoms*, include delusions and hallucinations, and indicate a disturbance in a person's ability to distinguish between reality and fantasy. These symptoms can manifest in various ways and may involve different sensory modalities. Delusions of persecution and auditory hallucinations are two examples of positive symptoms that are commonly experienced by individuals with schizophrenia. These symptoms may suggest that a person has difficulty determining what is real and what is not (Tandon et al., 2009).

*Hallucinations*. Hallucinations occur when seeing, hearing, smelling, tasting, or feeling things that do not actually exist outside our minds. Hallucinations are experiences that seem real to the person having them, but are not based in reality. They can involve any of the senses and are often distressing for the person because others around them cannot hear or see the same things. Hearing voices is the most common type of hallucination reported by people with schizophrenia. Brain imaging studies have shown that people with schizophrenia experiencing persistent hallucinations have a reduction in the volume of several brain areas (e.g., insular cortex, superior temporal gyrus and fusiform gyrus) (O'Daly et al., 2007). Hallucinations can involve voices that are perceived as friendly or hostile, pleasant or unpleasant. The content of these voices may include instructions, commentary on the person's thoughts or behavior, or other messages. The source of the voices may be attributed to an internal or external origin, and may appear to come from one or multiple locations (Plaze et al., 2011; F. Waters et al., 2012; F. A. V. Waters et al., 2006).

*Delusions*. A delusion is a belief that is not based in reality and is held firmly despite evidence to the contrary. It can be a symptom of various mental health conditions, such as schizophrenia,

schizoaffective disorder, and delusional disorder. Delusions may also be a symptom of other conditions, such as dementia or brain injury (Coltheart et al., 2007; Feyaerts et al., 2021; Langdon et al., 2010).

Delusions can take many forms and can be based on a wide range of topics. Some common types of delusions include:

- Persecutory delusions: these involve the belief that one is being persecuted, watched, or plotted against by others
- Grandiose delusions: these involve the belief that one has exceptional abilities, wealth or power
- Erotomaniac delusions: these involve the belief that someone is in love with the person experiencing the delusion
- Nihilistic delusions: these involve the belief that the world is about to end, or that one's body or self does not exist

It is important to note that what may seem like a delusion to one person may be a sincerely held belief to another. Moreover, not all false beliefs are delusions. In order for a belief to be considered a delusion, it must be fixed and resistant to change despite evidence to the contrary.

### 3.2.2 Negative symptoms

Negative symptoms of schizophrenia refer to a lack or absence of certain behaviors or emotions. Negative symptoms include:

- Alogia, reduction in speech, including a lack of fluency, a decrease in the amount of speech, and a lack of content in conversation
- Anhedonia, lack of pleasure or enjoyment in activities that used to be enjoyable
- Asociality, lack of interest in social interaction or decrease in social functioning
- Avolition, lack of motivation or a difficulty initiating and completing tasks
- Flat affect: lack of emotional expression, such as a lack of facial or vocal changes in response to emotional stimuli

Negative symptoms can have a significant impact on a person's daily life, and it can be difficult for patients to care about themselves and their personal hygiene.

It can be difficult to tell whether the symptoms are part of the development of schizophrenia or caused by something else. Relationships with friends and family can become problematic as these symptoms can be mistaken for deliberate laziness or rudeness. (Buchanan, 2007; Mäkinen et al., 2008; Rector et al., 2005).

### 3.2.3 Cognitive symptoms

Cognitive symptoms are a prominent and consistent feature of schizophrenia. These symptoms may involve various types of impairments, and can often be detected before other symptoms appear. They tend to persist over time and are a core part of the disorder (Bora & Murray, 2014; Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009). Cognitive symptoms, especially impairment in social cognition, predict poor social and vocational outcomes (Bowie et al., 2008). Patients with schizophrenia may experience disorganized thoughts and behavior, as well as problems with working memory, such as difficulty holding onto multiple pieces of information at once. They may also have difficulty paying attention and may struggle to organize their thoughts and make decisions. These cognitive symptoms can significantly impact their daily functioning (Forbes et al., 2009).

## 3.3 Action Prediction in Schizophrenia

Planning and executing actions are a crucial aspect of human life that enables us to influence and shape our environment. Underlying these capabilities of human beings are specific neural circuits (Haggard, 2008), and they also allow for a unique subjective experience, which has been called '*sense of agency*' (Gallagher, 2000). Predicting events in time is a significant aspect of the temporal structure of consciousness, and it plays a role in shaping a person's mental life. The impairment of this ability in patients with schizophrenia (Fuchs, 2007; Vogeley & Kupke, 2007) seems to be related with self-disorders (Martin et al., 2014; Mishara et al., 2016), which are disturbances of the "basic-self" that affect individual's sense of self and inner experiences. Self-disorders are a common feature of schizophrenia. This dysfunction can manifest in a variety of ways, including self-awareness, self-regulation, and self-esteem. These difficulties may contribute to social impairments, as patients may have trouble making valid predictions

about expected sensations and experiences. Indeed, many studies have suggested that some of the social difficulties experienced by people with schizophrenia may be due to a deficit in mentalization, which is the cognitive ability to understand and interpret the mental states (e.g., intentions) to others, and to predict their behavior (Sprong et al., 2007; Harrington et al., 2005; Frith, 2004).

There is substantial evidence in the literature indicating that people with schizophrenia have difficulties making predictions. Early research on motor control suggested that problems with agency, or the sense of control over one's own actions, may be caused by impairments in the processes involved in predicting the sensory consequences of an action (Blakemore et al., 1998; Franck et al., 2001; Frith et al., 2000; Jeannerod, 2009; Shergill et al., 2005). Several studies have suggested that a key feature of psychosis is difficulty in attributing experiences to oneself and a significant change in fundamental aspects of the self (Sass & Parnas, 1998). In addition, it has been shown that deficits related to disorders of self-agency might be due to an inability to predict future events (Fourneret et al., 2002; Franck et al., 2001; Frith et al., 2000; Lindner et al., 2005; Shergill et al., 2005). Patients who have schizophrenia, therefore, seem to rely more on sensory afferent information to compensate for this deficit (Chambon et al., 2011a; Synofzik et al., 2010; Voss et al., 2010).

### 3.3.1 Linking positive symptoms and error predictions

A framework of the motor control system depicts the components that can be related to the subjective experience of motor control (Blakemore et al., 2002). According to this model, a copy of the motor commands is sent to an internal predictor, which estimates the likely outcome of the motor command. These predictions can be made about both one's own actions and those of external agents. A comparator node then compares sensory input to these predictions, generating a prediction error. When afferent sensory inputs and predictions cancel each other out, and there is no prediction error at the comparator node, it is thought that a sense of agency is experienced. The comparison between the efferent signal (indicating that a particular action will occur) and the reafference signal (resulting from the completed action) occurs at the comparator node.

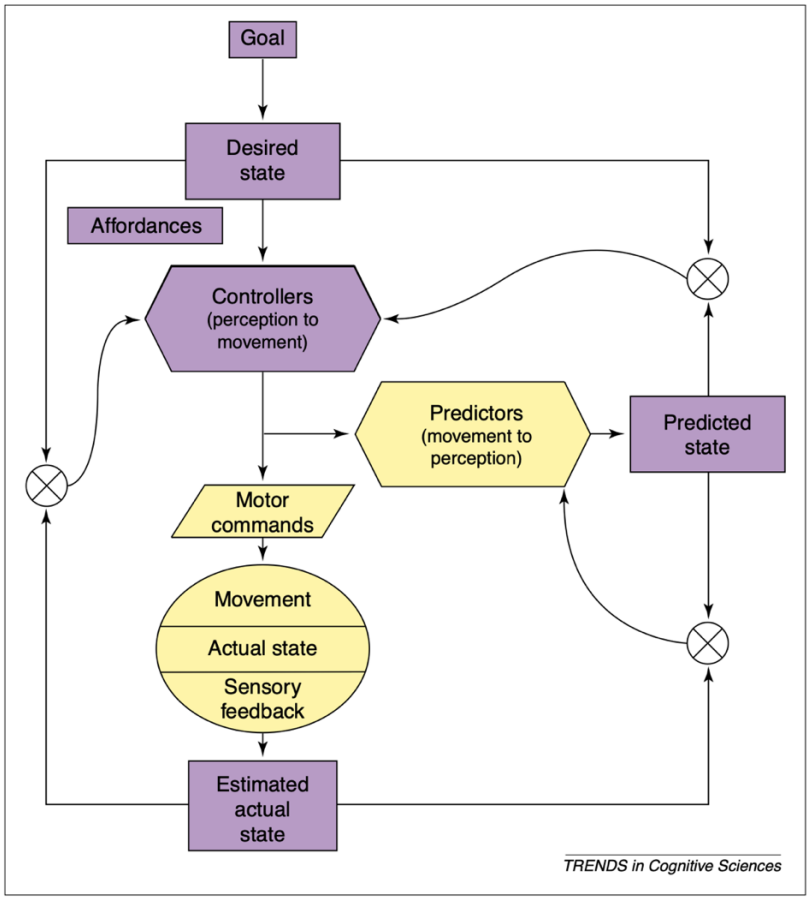


*Figure 9. Internal models of the motor system (from Blakemore et al., 2002)*

In schizophrenia disorder, the ability to predict based on an efferent copy would be impaired (Frith, 1992; Lindner et al., 2005). From this perspective, positive symptoms might occur when there is a lack of predictive input at the comparator (e.g., in delusions of control). The misattributions can also occur for internally generated thoughts and intentions, which are perceived as coming from outside.

It has been suggested that brain functions may be based on a hierarchical Bayesian system (Friston et al., 2006; Lee & Mumford, 2003; Summerfield & Koechlin, 2008). A Bayesian mechanism refers to the process by which the brain uses prior knowledge and expectations to make predictions about incoming sensory information (Bayes, 1763). In healthy individuals,

the brain constantly updates its predictions based on new sensory information, allowing for the efficient processing of information. A prediction error generated by a lower-level system is used as input for a higher-level system, while simultaneously, feedback from the higher-level system provides the prior beliefs for the lower-level system. Fletcher and Frith (2009) suggested that, in patients with schizophrenia, there may be a dysfunction in the hierarchical Bayesian framework, leading to positive symptoms, both hallucinations and delusions. In terms of this framework, the source of the positive symptoms of schizophrenia is the propagation of false prediction errors up the hierarchy. The more severe the damage to the Bayesian system, the higher in the hierarchy will be the prediction error.

Chambon et al. (2011) showed that psychotic patients have specific difficulties in predicting intentions achieved by a sequence of motor acts. They found that patients with schizophrenia performed poorly on an action discrimination task because they were excessively confident in their prior expectations. Indeed, a positive relationship was found between the severity of positive symptoms and the tendency of patients to rely too heavily on previous expectations when making decisions: the more patients relied on their previous expectations, the more severe their symptoms were. Only a few studies have attempted to investigate the nature and extent of action prediction deficits in schizophrenia. One study found that individuals with schizophrenia were less able to anticipate the actions of others in a virtual reality task, suggesting that the impairment is specific to action prediction and not general social cognition deficits (Freeman, 2008). Another study found that patients with schizophrenia struggle to predict the actions of others in a simulated grocery store task, suggesting that impairment may also affect more complex social situations (Aubin et al., 2018).

## Aim of the study

It has been shown that humans can predict the result of an action, such as the size of an object being grasped, using a progressive temporal occlusion paradigm, in which participants observe reach-to-grasp video (Ansuini et al., 2016). As the occlusion intervals progress, the accuracy of predictions quickly improves and reaches almost perfect accuracy at around 60% of the movement's duration. Earlier temporal occlusions of action predictions have not been investigated in patients with schizophrenia, but only actions occluded at 79%, 83%, 87% and 100% of the entire movement (Chambon et al., 2011a).

It is currently unknown whether, in psychosis, this predictive ability is still intact even at earlier time occlusions and whether there are any differences between individuals with psychosis and a control group in this regard. To investigate this hypothesis, we asked two groups of participants, patients and healthy subjects, to complete the same object size prediction task from Ansuini et al. (2016). The assessment of patients' symptomatology and functioning was evaluated using neuropsychological scales and allowed us to explore whether the severity of positive and negative symptoms affects the ability to predict object size.

# Chapter 4 – Action Prediction in Psychosis

## 4.1 Introduction

Complex, high-level dysfunctions are often grounded in subtle abnormalities in low-level processes. Theoretical considerations and empirical findings suggest that psychotic symptoms such as diminished demarcation of self-other boundaries and misattributions of self-generated actions arise from abnormal motor-sensory predictions (Fletcher & Frith, 2008).

In motor control the brain relies on internal forward models to predict the outcome of a motor command and attenuate the predicted sensory feedback of the generated action (Gallivan et al., 2018; Wolpert et al., 2003). Mechanistically, when the predicted and the generated outcome match, the sensory feedback is attenuated, and the action is labeled as self-generated. When they do not match, the sensory feedback is not attenuated, and the action is labeled as externally generated. Increasing evidence suggests that a disturbance in this self-monitoring mechanism may underlie both reduced suppression for self-generated actions and altered self-monitoring in psychosis (Ford et al., 2001, 2014; Perez et al., 2012; Salomon et al., 2020, 2022; Shergill et al., 2014).

What remains unclear is whether prediction deficits generalize to other-generated actions (Sokolov et al., 2017). That is, do patients with psychosis also exhibit deficits in predicting the actions of others? This hypothesis is motivated by the computational parallels between the processing of self- and other-actions (Wolpert et al., 2003) and, more specifically, by the view that action prediction engages neural pathways associated with internal forward models (Hommel et al., 2001). This hypothesis makes the distinctive prediction that observers with psychosis, with aberrant internal models, should also show abnormal predictions of the actions of others.

At present, psychosis has been associated with abnormalities in intention understanding (inferring the intention of a manipulative action sequence), but not in action prediction (discriminating the outcomes of two manipulative actions) (Chambon et al., 2011). However, abnormalities in action prediction may be masked by the rapidity with which action-related

information is integrated. Using a progressive temporal occlusion paradigm, we have previously demonstrated that human perceivers can predict the outcome of an observed action (i.e., the size of the to-be-grasped object) as early as 80 ms after movement onset (10% of movement duration) (Ansuini et al., 2016). Prediction accuracy rapidly increases from the earlier to the later occlusion intervals, culminating in near perfect accuracy at about 60% of movement duration, well before the hand reaches the target (Ansuini et al., 2016). Previous work tested action predictions from late sequences (actions occluded at 79%, 83%, 87% and 100% of movement duration) (Chambon et al., 2011b). Therefore, it is unknown whether early integration processes required for rapid other-action predictions are preserved in psychosis.

Here, we address this gap and investigate the ability of observers with psychosis to predict the size of a to-be-grasped object over progressive temporal occlusion intervals, from 10% up to 80% of movement duration. Using a novel analytic approach to examine information encoding and readout with single-trial resolution (Montobbio et al., 2022; Patri et al., 2020), we demonstrate that whilst observers with psychosis use the same sources of advance information as controls, they require more information to reliably predict object size and specifically lack the capability to extract information from earlier time periods.

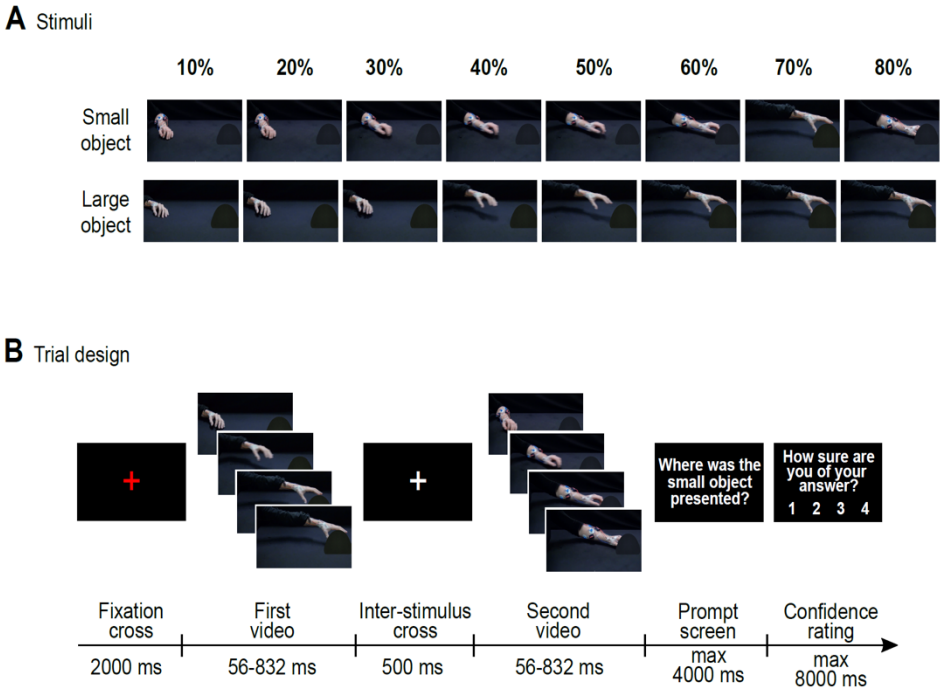


*Figure 10. Experimental design. (A) Example video frames of reach-to-grasp actions towards a small or large object presented under eight level of temporal occlusion. (B) Trial design of the action prediction task.*

## 4.2 Methods

### 4.2.1 Participants

Sixteen outpatients (8 females) diagnosed with non-affective psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorder, and brief psychotic disorder) and 16 control participants (11 females) participated in the study. Groups were matched for age (healthy mean ± SD = 26.9 ± 4.6 y; patients mean ± SD = 30 ± 4.5 y; $t_{(30)} = -1.83$, P = 0.077). Outpatients were recruited from the Community Mental Health Services in Ferrara and had previously been diagnosed by an experienced psychiatrists according to ICD-9 CM criteria. Patients with neurological disorders, comorbid major depression and/or substance abuse according to ICD-9 CM criteria were excluded. Psychiatric, neurological and substance-use disorder were exclusion criteria for controls. All participants had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the University of Ferrara and complied with the principles of the revised Helsinki Declaration (World Medical, 2013). All

participants received information about the content of the study and provided written informed consent prior to participation in the study.

### 4.2.2 Assessment of symptomatology and functioning

Symptom severity and classification were assessed in the patient group using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1990), the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011), the Trail Making Test (TMT B-A) (Partington & Leiter, 1949), and the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989). To measure real-world functioning, patients also complete the Specific Levels of Functioning Scale (SLOF) (Schneider & Struening, 1983).

### 4.2.3 Experimental design and procedures

*Action stimuli.* Stimuli were selected from a dataset of 900 reach-to-grasp movements obtained by recording 15 agents reaching, grasping, lifting and moving a hazelnut (diameter = ~1.5 cm; weight = ~2 g) or a grapefruit (diameter = ~10 cm; weight = ~354 g). Each agent performed a total of 60 action sequences (30 actions for each object size). Detailed procedures and apparatus are described in (Ansuini et al., 2015). Briefly, actions were tracked using a near-infrared camera motion capture system (frame rate = 100 Hz; Vicon System) and simultaneously filmed from a lateral viewpoint using a digital video camera (Canon Alegria, 25 frames/s). The agent's right hand was outfitted with 11 retroreflective hemispheric markers to compute the following variables of interest:

- wrist velocity, defined as the module of the three-dimensional velocity vector of the wrist marker (in mm/s);
- wrist height, defined as the z-component of the wrist marker (in mm);
- grip aperture, defined as the Euclidean distance between the tip of the thumb and the tip of the index finger;
- x-, y-, and z-index, defined as the x-, y-, and z-coordinates of the tip of the index finger (in mm);
- x-, y-, and z-thumb, defined as the x-, y-, and z-coordinates of the tip of the thumb (in mm);

- x-, y-, and z-dorsum plane, defined as the x-, y-, and z-components of the radius-phalanx plane. This plane provides information about the abduction, adduction, and rotation of the hand dorsum independent of the rotation of the wrist.

Custom software (MATLAB, MathWorks Inc.) was used to extract the selected variables. Each variable was calculated at intervals of 10% of the movement duration from reach onset to reach offset.

*Selection of action stimuli and video editing.* For each agent and each object size, we selected the two reaching acts that minimized the Euclidean distance with the average kinematics (computed across all agents and trials) (Ansuini et al., 2016). The final set of stimuli consisted of 60 reaching acts (2 reaching acts x 15 agents x 2 object sizes). Digital video editing (Adobe Premiere Pro; .avi format, disabled audio, 25 frames/s) was used to occlude the to-be-grasped object. Each movie started at reach onset and ended at reach offset.

*Procedure.* Participants were seated in front of a 17-inch computer monitor (resolution 1280 x 800, refresh rate 75 Hz, response rate 8 ms) at a viewing distance of 50 cm. The task structure conformed to a two-alternative forced-choice (2AFC) task. In each trial, participants observed two reaching acts in two consecutive temporal intervals: one interval displayed a hand a reaching for a hazelnut (small object), the other a hand reaching for a grapefruit (large object). The task was to predict the size (small, large) of the occluded to-be-grasped object (see "Selection of action stimuli and video editing"). To define the timing of information integration, reaching acts in each trial were presented under one of eight levels of temporal occlusion, from 10% up to 80% of movement duration.

Each trial started with the presentation of white fixation cross against a black screen for 2000 ms. Then, the first reaching act was presented, followed by an interstimulus interval of 500 ms (white fixation cross), after which the second reaching act was presented. After the second interval, the screen prompted participants to indicate the interval (first or second) containing the small (large) object by pressing a key. The prompt screen was displayed until response or for maximum of 4,000 ms. After response, participants were asked to rate the confidence of their choice on a four-level scale (from 1 = least confident, to 4 = most confident). Participants

were encouraged to use the full range of the confidence scale. The experiment consisted of 240 trials split in eight blocks of 30 trials each. Participants were instructed to indicate the interval containing the small (large) object in the first four blocks and the interval containing the large (small) objects in the last four blocks, counterbalanced across participants. Levels of occlusion were pseudorandomized and balanced across blocks so that each block contained at least one presentation of each of the eight levels of occlusion. Feedback was provided at the end of each block. To familiarize participants with the task, we administered 10 practice trials. The practice trials were randomly selected from the main experimental videos. Stimuli, timing, and randomization procedures were controlled using a PsychToolbox script running in MATLAB R2014a (MathWorks, Inc.).

### 4.2.4 Quantification and statistical analysis

*Psychometric curves.* We re-coded participants' choices in the 2AFC task as "small first" and "large first" choices, and computed, separately for each group, the psychometric curve of the probability of choosing "small first" as a function of the level of occlusion (Figure 11A). Positive and negative occlusion values in the x-axis indicate "small first" and "large first" trials, respectively. We used Logistic Mixed Effects Models to assess the significance of the effect of temporal occlusion on the interval choice probability *P*(small first) across groups. This allowed us to fit population-level psychometric curves while controlling for inter-subject variability (Moscatelli et al., 2012). We considered interval choice in each trial as dependent variable, group, occlusion level, and their interaction, as fixed effects, and subject (random intercept, and random slope of occlusion level) and block (random intercept) as random effects (Supplementary Table 1, in Appendix B). We used piecewise models with symmetrical change points to test for different integration rates as a function of occlusion level (as suggested by Figure 11A). The symmetrical change points could be set at -10% and +10%, -20% and +20%, or -30% and +30%. We compared these three piecewise models with a non-piecewise model and verified that the piecewise model with symmetrical change points at ± 20% yielded the best performance as measured by Bayesian Information Criterion (BIC) (Schwarz, 1978). We thus defined two integration periods determined by these change points – up to 20% of movement duration and from 30% to 80% of movement duration – and we used them as a factor in subsequent analyses.

*Confidence-accuracy calibration.* To measure the relationship between confidence and accuracy at different occlusion levels, we computed the ratio between the single-trial confidence rating and the prediction accuracy of a given observer at a given occlusion level. Next, we created a calibration curve by plotting confidence-accuracy calibration values as a function of occlusion level (Figure 11E). We used Gamma Mixed Effects Models to assess the significance of the difference in confidence-accuracy calibration between groups over the two integration periods. We chose a Gamma distribution because the confidence-accuracy data were non-negative and positively skewed (Ng & Cribbie, 2017). We compared gamma distributions with other distributions which allow for skewness (inverse gaussian, lognormal) and verified that models with gamma distributions performed better in terms of log-likelihood. We considered confidence-accuracy calibration as dependent variable, group and integration period, as well as their interaction, as fixed effects and subject (random intercept, and random slope of integration period) and session block (random intercept) as random effects (Supplementary Table 1, in Appendix B).

*Selection of random and fixed effects structure.* As in (Montobbio et al., 2022), we applied a backward model selection procedure, starting from the model with the most complex structure to arrive at a model that included only the significant predictors. We first selected the random effect structure of the model by keeping the full fixed effect structure and using the BIC. The BIC rewards model fit and penalizes model complexity. We then retained the optimal random effect structure and selected the best fixed effect structure by conducting likelihood-ratio tests (LRT) between models differing only by the presence or absence of one predictor (Alan Agresti, 2007). Model selection results are reported in Supplementary Table 1. We performed model fitting using the R package *lme4* (https://CRAN.R-project.org/package=lme4). We performed comparisons against chance and across levels of the selected models using the R package *emmeans* (https://CRAN.R-project.org/package=emmeans). The *emmeans* package estimates the marginal means and standard errors over combinations of predictors, from which *z*-values (to calculate two-sided *p*-values) are computed. Statistical comparisons for the effects are reported in Supplementary Table 1 (Appendix B).

*Logistic regression models of encoding and readout.* To model single-trial kinematics, we averaged the 12 kinematic variables of interest over 10 epochs of 10% of the normalized movement duration. For each occlusion level (from 10% to 80% of movement duration), we created an n-dimensional vector, with dimensions ranging from 12 features (12 kinematic variables over 1 time epoch) for the 10% occlusion level to 96 features (12 kinematic variables over 8 time epochs) for the 80% occlusion level. Next, based on (Patri et al., 2020), we computed the difference between the kinematics of two reaching acts in each trial as:

$$\vec{K} = \overrightarrow{K_1} - \overrightarrow{K_2}$$

where $\overrightarrow{K_1}$ and $\overrightarrow{K_2}$ are the kinematic vectors associated with reaching acts displayed in the first and second interval. To quantify the encoding of size information, for each occlusion level, we trained a logistic regression model to predict the single-trial probability that the small object was presented in the first interval $Y$ as a linear combination of the components of the single-trial kinematic vector $\vec{K}$. The equation was as follows:

$$P\left(Y = \text{"}small\ first\text{"} \mid \vec{K}\right) = \sigma\left(\vec{K} \cdot \overrightarrow{\beta} + \beta_0\right);$$
$$P\left(Y = \text{"}large\ first\text{"} \mid \vec{K}\right) = 1 - P\left(Y = \text{"}small\ first\text{"} \mid \vec{K}\right)$$

where $\sigma$ is the sigmoid function, $\overrightarrow{\beta}$ is the vector containing the values of the regression coefficients of each kinematic feature, and $\beta_0$ is the kinematic-independent bias term. The length of the weight vector $\overrightarrow{\beta}$ matched the dimension of the kinematic vector $\vec{K}$ for the considered temporal occlusion.

We used a similar set of logistic regression models to analyze how size information was read out by individual observers in each group. For each participant and each occlusion level, we trained a logistic regression model to predict the single-trial probability that the observer reported the small object to be in the first interval $Y$ as a sigmoidal function of a linear combination of the components of the single-trial kinematic vector $\vec{K}$. Kinematic readout

models were defined as in the above equation, but with the binary stochastic variable $Y$ representing the interval chosen by the participant (Figure 12A).

*Training and evaluation of logistic regression models.* Training and evaluation were performed similarly for both sets of models. All models were trained on all trials, separately for each level of occlusion, so that the dimension of the vector $\vec{K}$ was constant over the whole training set. To avoid penalizing predictors with larger ranges of values, we z-scored single-trial kinematic vectors within each model. Models were trained using $L^2$ regularization. The parameter $\lambda$, which controls the strength of the regularization term, was estimated for each model using leave-one-out cross-validation. We retained for each model the value $\lambda_{min}$ associated with the minimum mean cross-validated error. Models were trained on all trials with the retained regularization term. Logistic regression was implemented using the *pyglmnet* Python library (Jas et al., 2020).

We evaluated the performance of the encoding and readout models by repeated 5-fold cross-validation (50 random splits) (Kim, 2009), on top of the cross-validation used for the determination of the $\lambda$ parameter. We computed the most likely value of $Y$ for each trial by taking the argmax over $Y$ of $P(\vec{K})$. Model performance was quantified as the fraction of correct predictions averaged over folds and random splits. For each level of occlusion, we created a chance-level null-hypothesis distribution of model performance by fitting the models after randomly permuting across trials the binary variable $Y$. To quantify the effect of occlusion level on model performance, as well as differences between groups and against chance-level performances, we used Linear Mixed Effects Models with the normalized fraction of correct model predictions of each video across cross-validation repetitions as dependent variable (see Supplementary Methods, in Appendix B).

*Action prediction performance and confidence predicted by the readout model.* In Figure 13C, we used kinematic readout models to estimate the action prediction performance and confidence ratings of individual participants in each group. Using Eq. 1, we computed the interval choice predicted as most likely by the readout model for each trial and compared it to the actual order of the presented stimuli. Predicted action prediction performance was obtained by averaging

the probability of correct interval choice across all trials for a given participant. The resulting value was then compared to the observed discrimination accuracy of the participant. By the same logic, we computed the confidence of single-trial model predictions as deviations of the estimated probability of reporting "small first" from chance (0.5) and compared them with the confidence ratings reported by participants (Figure 13C).

*Contribution of individual kinematic features to encoding and readout.* We computed the contribution of each kinematic feature to kinematic encoding (readout) as the feature regression coefficient in the encoding (readout) logistic regression model. A positive (negative) sign is assigned to a feature distributed across trials with higher (lower) values for "small first" compared to "large first".

*Single-feature alignment between encoding and readout.* We quantified, separately for each observer and each level of occlusion, the alignment of readout coefficients relative to encoding coefficients at the single feature level. This was computed as the dot product between the encoding and readout weights of that feature, weighted by the norm of the whole encoding and readout vectors and adjusted by number of time epochs to make its values comparable across different occlusion levels:

$$alignment\ [i]\ (\vec{\beta}_{enc}\ ,\vec{\beta}_{read}) = \frac{{\beta^i}_{enc}\cdot {\beta^i}_{read}}{\left|\left|\vec{\beta}_{enc}\right|\right|\left|\left|\vec{\beta}_{read}\right|\right|}\cdot t,$$

where $t \in (1,\ldots,8)$ t is the number of time epochs; ${\beta^i}_{enc}$ and ${\beta^i}_{read}$ are the regression weights of the $i$-th kinematic feature in the encoding and readout model, respectively; $\vec{\beta}_{enc}$ and $\vec{\beta}_{read}$ denote the whole encoding and readout coefficient vectors. High positive values indicate that a feature is highly informative (large encoding weights) and is correctly readout with large readout weights; high negative values indicate that a feature is highly informative and is incorrectly readout with large readout weights. Alignment values close to zero indicate that a feature is either weakly informative, or weakly read-out, or both.

*Conventions for p-values.* Supplementary Tables 1-4 (Appendix B) report details of Generalized Mixed Effects Models statistical tests and non-parametric permutation tests. Reported *p*-values are two-sided and Holm-Bonferroni corrected for the number of comparisons listed for each entry. In all figures, * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$, *ns* indicates $p \geq 0.05$. Following standard notation, asterisk(s) above bars indicate significance of difference from chance of an individual quantity, asterisk(s) above brackets indicate significance of difference between two quantities.

*Statistical significance of correlations.* The significance of Pearson's correlation values in Figure 13C and in Supplementary Figure S7 (Appendix B), was assessed using the *stats* module from Python package *SciPy* (Virtanen et al., 2020) with two-sided parametric Student statistics.

## 4.3 Results

Participants completed a two-alternative size discrimination task under eight levels of temporal occlusion, from 10% to 80% of movement duration. Each trial displayed two reaching acts: one reaching act towards a small object and the other reaching act towards a large object. The task was to predict the size (small, large) of the to-be-grasped object. Full statistics of all comparisons are reported in Supplementary Tables (Appendix B).

Results using Logistic Mixed Effects Models revealed a significant interaction between observer group (psychotic, control) and occlusion level on psychometric curves (Supplementary Table 1, in Appendix B), reflecting group differences in the rate of information integration across occlusion levels (Supplementary Table 3, in Appendix B). As shown in Figure 11A, psychophysical performance in both groups increased as a function of occlusion level, indicating that observers in both groups integrated prospective size information over time. However, compared with controls, observers with psychosis showed an overall reduced and discontinuous integration rate, with a pronounced central plateau (Figure 11A). Fitting a piecewise-sigmoidal model, we identified two statistically significant change points at ± 20%, demarcating the boundaries of two integration periods, an initial period, from reach onset up to

20% of movement duration, and a second period from 30% to 80% of movement duration (Supplementary Table 1, in Appendix B). While the performance of the clinical group was lower in both periods, the offset between the two groups was more than twice as large in the initial up-to-20% period (Figure 11A). In this period, the slope of the psychometric curve of patients was not significantly different from 0 ($p=0.057$), indicating that psychotic observers failed to integrate size information (Figure 11B; Supplementary Table 3, in Appendix B). This was also reflected in prediction accuracy, computed as the fraction of correct interval choices (Figure 11C). While the control group performed above chance for all occlusion levels, the clinical group did not surpass chance-level performance up until presentation of 30% of the movement (Supplementary Table 3, in Appendix B).

### 4.3.1 Confidence-Accuracy relationship across integration periods

The above results identify two periods corresponding to different integration regimes. To assess whether the relationship between confidence ratings (Figure 11D) and discrimination accuracy (Figure 11C) differed between these integration periods, we defined a simple measure of calibration between confidence and accuracy (see Methods) and used Gamma Mixed Effects Models to statistically test the difference in confidence-accuracy calibration between groups and integration periods. As illustrated in Figure 11E, results revealed a significant interaction between group and integration period (Supplementary Table 1, in Appendix B), reflecting a higher confidence-accuracy calibration in the clinical group relative to the control group in the 0-20% period, but not in the 30-80% period (Supplementary Table 3, in Appendix B).

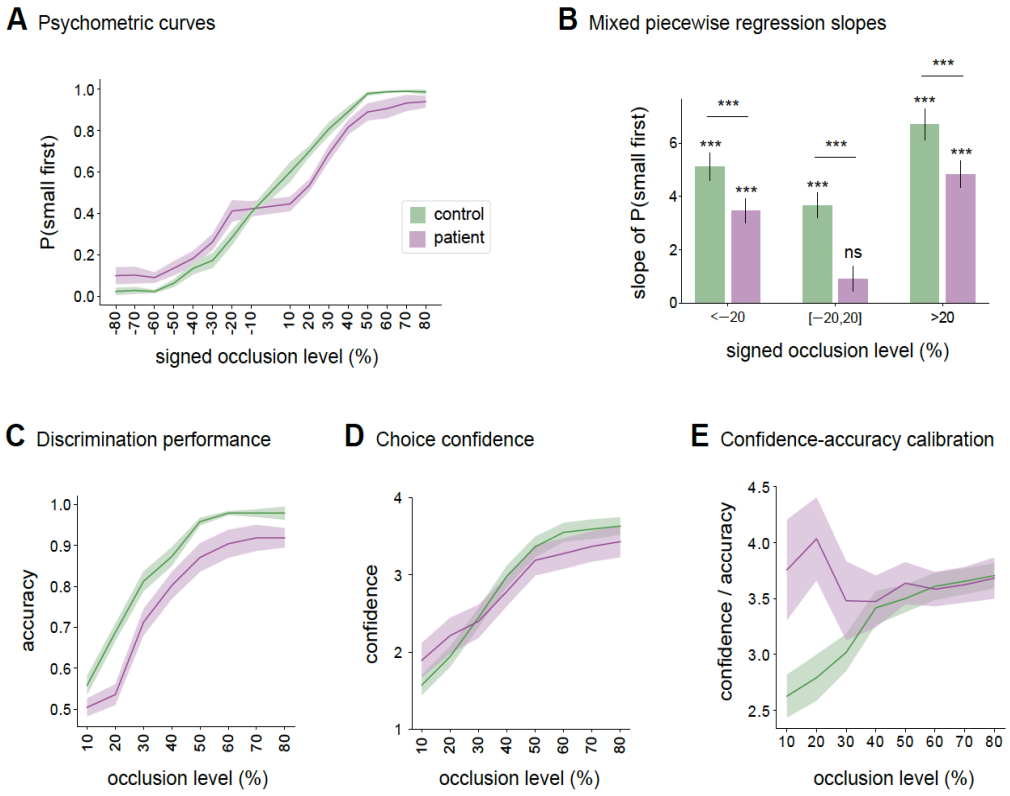


Figure 11. Results of action prediction. (A) Empirical psychometric curves of P(*small first*) as a function of signed occlusion level in observers with psychosis relative control observers. (B) Piecewise regression slopes of the psychometric curves as estimated by Logistic Mixed Effects Models with change points at ±20% in observers with psychosis relative to control observers. Error bars represent standard errors. (C) Trial-averaged action prediction performance (fraction of correct responses) as a function of occlusion level in observers with psychosis relative to control observers. (D) Trial-averaged reported confidence ratings as a function of occlusion level in observers with psychosis relative to control observers. (E) Trial-averaged ratio between confidence ratings and action prediction accuracy as a function of occlusion level in observers with psychosis relative to control observers. Solid lines and shaded areas represent mean ± SEM across participants.

### 4.3.2 Variability of prediction accuracy in the 0-20% period

The above results suggest an overall reduced sensitivity to size information in psychosis, characterized by an almost flat integration regime in the up-to-20% period. To better understand the origin of this plateau and to rule out a general latency in information processing at shorter viewing durations, we examined the across-trial variability of prediction accuracy in this period. Information encoding varies across actions, as does information readout (Montobbio et al., 2022; Patri et al., 2020). We have previously demonstrated that, across observers, prediction accuracy is consistently higher for some stimuli compared with others (Scaliti et al. submitted).

This effect was replicated for the 10% and 20% occlusion stimuli in the present study. As shown in Supplementary Figure S7 (Appendix B), plotting prediction accuracies at the single-stimulus level revealed a distribution that was both consistent across occlusion levels and groups and differed across stimuli. This observation, corroborated by a moderate intergroup correlation in single-movement prediction accuracy (Supplementary Figure S7, in Appendix B), suggest that observers with psychosis, whilst at chance across the entire stimulus set, were able to pick up some information from the most predictable stimuli in the initial period.

### 4.3.3 Kinematic encoding and readout of object size information

Our results so far reveal differences in information integration between observers with psychosis and control observers. However, they do not identify the specific features read out across temporal occlusion conditions, whether observers in two groups read informative or non-informative features, and how well they read the encoded information. To directly address these questions, we extended our kinematic coding framework. We developed this framework to quantify how information encoded in movement kinematics is read out by individual observers with single-trial resolution (Becchio, 2021; Montobbio et al., 2022; Patri et al., 2020). Here, we extended it to measure how size information encoded in single-trial kinematics was read out by individual observers in each group across progressive levels of occlusion.

As a first step, we developed an encoding model (Figure 12A; see Methods) to determine the availability of size information in single-trial kinematics across adjacent occlusion intervals and identify the kinematic features that carry this information. Results using Linear Mixed Effects Models revealed a significant effect of occlusion level (Supplementary Table 2, in Appendix B). As shown in Figure 12B, size information, as measured by the cross-validated performance of the encoding model, was present at 10% of movement duration, more than doubled at 20%, and then steadily increased reaching over 95% at 60% of movement duration (Figure 12B and Supplementary Table 4, in Appendix B). Figure 12C visualizes the contribution of individual kinematic features to size encoding as measured by the normalized magnitude of regression coefficients of the feature in the encoding model at each occlusion level. Consistent with (Ansuini et al., 2015), grip aperture (GA), the most informative variable, encoded size information starting from 10% of movement duration, with its contribution peaking at 20 and

30% of movement duration. In other variables, such as IZ, size encoding increased as time progressed. Finally, other variables such as WH encoded size more stably across time. Overall, the pattern of encoding showed a high stability from 40% of movement duration as quantified by the correlation of the encoding vectors at different occlusion levels (Figure 12D).

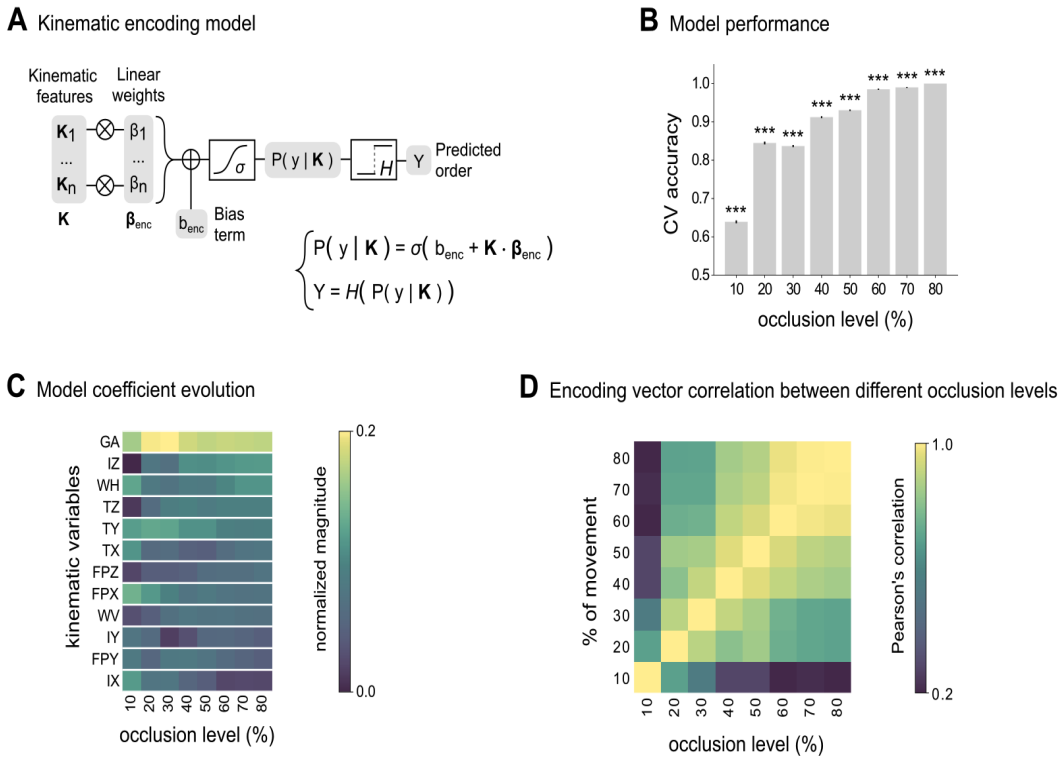


Figure 12. Encoding of size information from single-trial kinematics. (A) Block diagram and equation of the kinematic encoding model used to quantify size information at a given occlusion level. $\beta_{enc}$ is the model linear coefficient vector, $b_{enc}$ is the intercept coefficient, $\sigma$ is the sigmoid function, and $H$ is the Heaviside function. (B) Cross-validated (CV) performance of kinematic encoding models as a function of occlusion level. Bars represent mean ± SEM across stimuli. (C) Contribution of individual kinematic features to kinematic encoding of size information. Kinematic variables are ordered by decreasing coefficient magnitude in the encoding model fitted at the 80% occlusion level. (D) Pearson's correlation of coefficient distribution across kinematic variables between different occlusion levels.

Having quantified size information encoded across progressive occlusion periods, we next used a readout model (Figure 13A) to determine how observers in both groups read the encoded size information at the single-trial level. Model performance increased across progressive occlusion

times for both groups (Supplementary Table 2, in Appendix B). The model performed at chance only for observers with psychosis at 10% and 20% occlusion intervals (Figure 13B and Supplementary Table 4, in Appendix B). The tight correlation between predicted and observed individual accuracies indicates that the readout model accurately captured the dependence of observers' choice on single-trial kinematics at the single-observer level (Figure 13C). As shown in Figure 13C, although confidence ratings were not used for model fitting, the model also accurately predicted the confidence with which observers endorsed single-trial size choices. Collectively, these results indicate that our readout model was able to predict how well and how confidently individual observers predicted object size from single-trial kinematics.

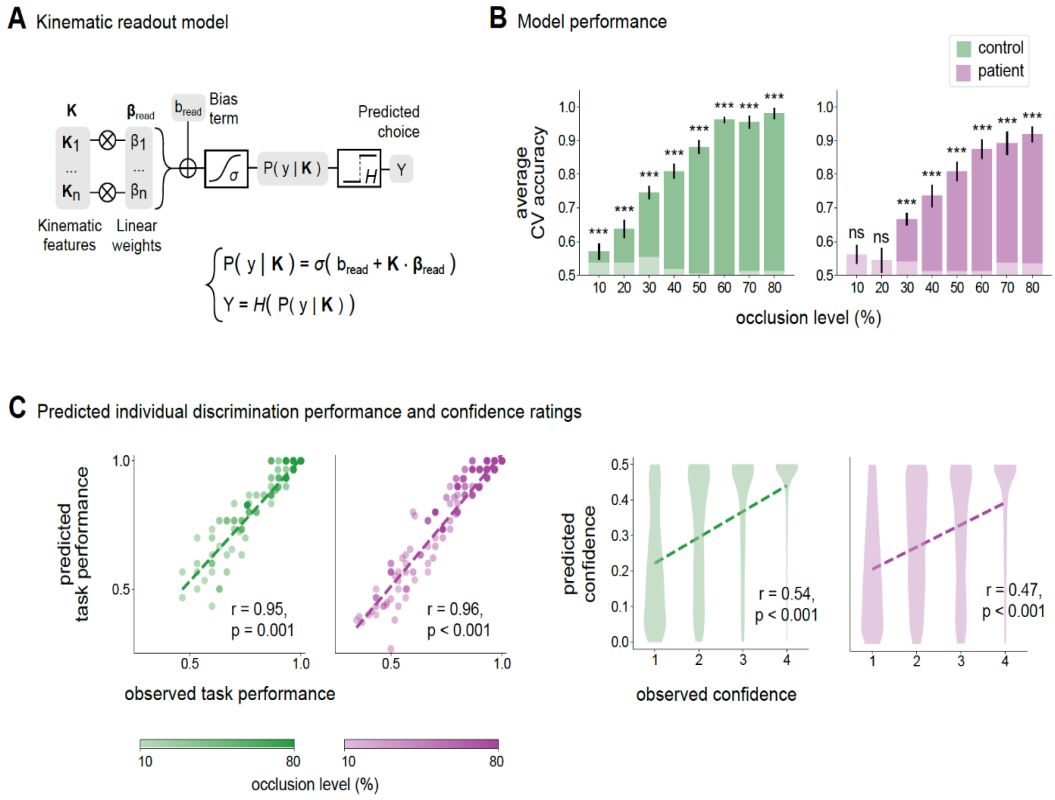


Figure 13. Readout of size information from single-trial kinematics. (A) Block diagram and equation of the kinematic readout model used to quantify the readout of size information from single-trial kinematics at a given occlusion level. $\beta_{read}$ is the model linear coefficient vector, $b_{read}$ is the intercept coefficient, $\sigma$ is the sigmoid function, and $H$ is the Heaviside function. (B) Cross-validated (CV) performance of kinematic readout models as a function of occlusion level for control observers and observers with psychosis. Bars represent mean ± SEM across participants. The light sub-bars represent chance-level performance, quantified as the mean of the null-hypothesis distribution of cross-validated model performance. (C) Left panels. Scatter plots of the relationship between the observed size discrimination performance and the performance predicted by the kinematic

readout model across individual participants in the control group and in the psychotic group. Darker shades correspond to later occlusion levels. Right panels. Violin plots of the within-group relationship between reported confidence ratings and model prediction confidence rating, computed as the deviation of the estimated probability of answering "small first" from chance. Fitted regression lines are displayed over the data. Pearson's correlation coefficients (r) and their significance values (p) are reported.

### 4.3.4 Readout profiles of individual observers

Readout model performance measures the relationship between trial-to-trial fluctuations in movement kinematics and observer's choice. For observers with psychosis, readout model performance was at chance at 10% and 20% occlusion intervals, reached significance at 30% and then progressed steadily up to 80%. This time course matches the integration periods identified in Figure 12A and suggest that observers with psychosis read little of the size information encoded in single-trial movement kinematics in the period up-to-20% of movement duration.

To determine which kinematic features observers read (and failed to read), we next computed the contribution (weight) of each feature to size readout as the normalized regression coefficient of the feature in the readout model. Figure 14 shows the alignment of readout weights (Figure 14B) relative to encoding weights (Figure 14A) in each observer group. The prevalence of positively aligned readout weights (denoted by blue bars in Figure 14B) indicates that observers in both groups mostly read out correctly the encoded information. What differed between groups was the time course of information readout. Observers in the control group correctly read size information specified in grip aperture, the most informative feature, as early as 10% and 20% of movement duration. As time progressed, readout weights were distributed across a wider set of features, reflecting the progressively more distributed encoding of size information across features. Observers with psychosis showed a qualitatively similar, but overall delayed and reduced readout pattern from 30% of movement duration. In the initial period, up to 20% of movement duration, they assigned little, if any, readout weight to grip aperture or any other feature.

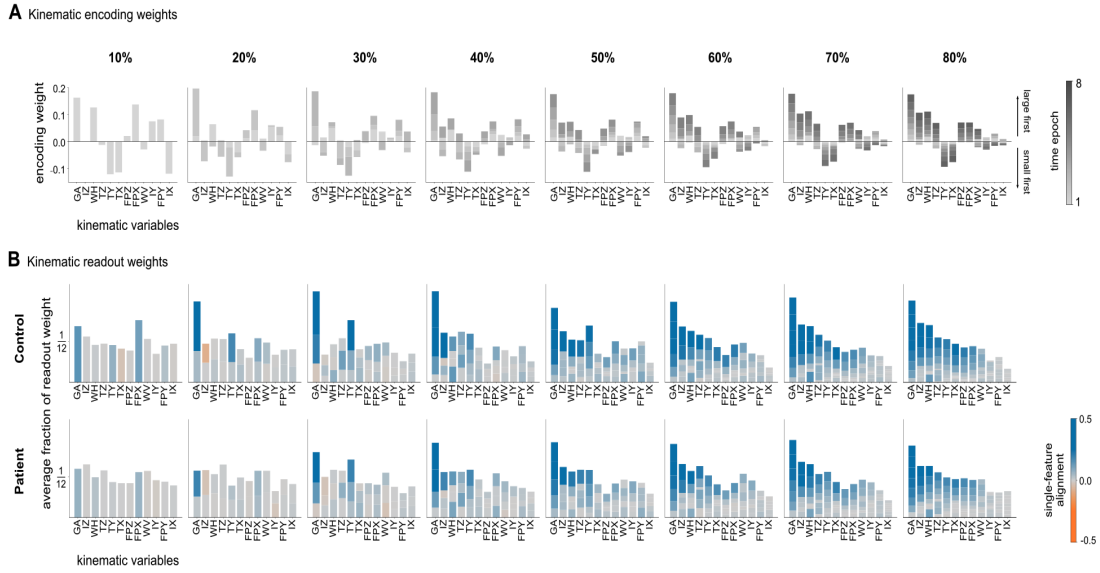


Figure 14. Relative distribution of kinematic readout weights relative to encoding weights. (A) Encoding model weights (coefficients) normalized by the total encoding weight at each occlusion level. Different shades of stacked bars indicate time epochs. Across occlusion levels, kinematic variables are ordered by the value of the encoding weight at the 80% occlusion level (in descending order). (B) Average fraction of readout weights across participants at each occlusion level in the control group and in the psychotic group. Different colors of stacked bars indicate single-feature alignment of readout weights relative to encoding weights. Stacking order reflects the order of time epochs (from bottom to top). The ordering of kinematic variables is the same as in panel A.

### 4.3.5 Relation to symptoms

To explore the relationship between prediction accuracy and psychotic symptoms, we correlated individual action prediction performance with BPRS, BNSS, PANSS, TMT(B-A), NES and SLOF (Supplementary Figure S8, in Appendix B). We found a significant negative correlation between BNSS and action prediction accuracy, indicating that patients with more severe negative symptoms were less able to predict others' actions. The only other significant correlation was between SLOF functioning in social relationships and prediction accuracy; patients with reduced functioning in relationships being less able to predict others' actions.

## 4.4 Discussion

Aberrant motor-sensory predictive functions have been linked to symptoms of psychosis, most prominently to decreased attenuation of self-generated sensations relative to externally generated sensations and misattribution of self-generated actions to external sources (Fletcher & Frith, 2008). Here, we provide direct evidence that prediction deficits generalize to other-generated actions. By combining a temporal occlusion paradigm with the kinematic coding framework, we were able to rigorously quantify the information encoded and readout across adjacent occlusion levels and demonstrate an overall reduced and discontinuous integration pattern associated with psychosis. As shown in Figure 11A, whilst the psychotic integration pattern was reduced but qualitatively similar to controls at occlusion periods later than 30% of movement duration, it exhibited a pronounced central plateau in the period up-to-20%.

Plateaus are rarely visible or reported in psychometric distributions, possibly due to the fact that temporal intervals are often too broadly spaced for plateaus to be visible (Tünnermann & Scharlau, 2018). Our approach enabled us to reveal a discontinuity in the psychotic integration pattern that would not have been visible with a smaller number of temporal intervals or when examining only late intervals.

Our single-trial analysis allowed us to further demonstrate that the initial plateau reflected a lack of sensitivity to variations encoding size information in single-trial kinematics. Size information is specified early in the movement, with some kinematic variables encoding size information as early as 10% of movement duration (80 ms). Our results show that control observers, but not psychotic observers, were able to read some of this information. Specifically, while control observers' choices revealed a dependency on single-trial movement kinematics as early as at 10% of movement duration, psychotic choices did not show a dependency on single-trial kinematics until 30% of movement.

Plateaus are often taken to indicate ranges of indecisions (Tünnermann & Scharlau, 2018). Based on this idea, one might expect that individuals with psychosis would be highly uncertain about the size of the object to be grasped during the initial phase of the task. Contrary to this prediction, our results that observers with psychosis were actually overconfident compared to

controls in the initial integration period (up to 20% of movement duration), but not at later intervals (30-80%).

Psychosis has been associated with "jumping to conclusions", operationalized as a tendency to make hasty decisions when probabilistic judgments based on the "draws to decision" task are required (Evans, 2015). In this task, the participant is presented with two containers (urns) that contain a large number of beads in different colors, with the proportions of the colors differing between the two urns. The participant is informed of these proportions, although the urns are hidden from view. The experimenter then presents a series of beads one at a time to the participant. After each draw, the participant can either make a guess as to which urn is being used or see another bead. Individuals with schizophrenia tend to make early decisions on this task, often making a decision after just one draw (Moritz & Woodward, 2005). It is tempting to link the overconfidence of observers with psychosis at earlier intervals to this bias. To test this hypothesis directly, future studies could use an adapted, temporal version of "draws to decision" procedure, in which, at each occlusion level, observers can either make a guess about the size of the object-to-be-grasped or see another interval. We would predict observers with psychosis to make decisions already at 10% and 20% of movement duration.

Interpersonal prediction is essential for successful social interaction and coordinated behavior. Without the ability to anticipate the action of others, we could never achieve the rapid coordination needed to pass a ball, lift a tray full of glasses together or walk in a crowded street (Sebanz & Knoblich, 2009). Our correlational analysis suggests the intriguing possibility of a connection between altered action prediction mechanisms and social dysfunction in psychosis. Specifically, it is possible that individuals with psychosis lose interest in social interactions because they have difficulties predicting the actions of others. To directly test this hypothesis, it will be important to examine whether difficulties in interpersonal prediction predict difficulties during on real-time reciprocal social interactions (Redcay & Schilbach, 2019).

## General Conclusions

In the present thesis, I describe two research projects in the field of human movement research: one is about motor learning in norm-typical subjects, and the other is about the ability to predict actions based on movement observations. First, we showed that individual baseline motor variability does not predict faster learning rates in motor adaptation tasks with multiple directions. This study contributes to research on the role of individual motor variability in motor learning. Further studies will be necessary to expand knowledge in this scientific area, as some aspects deserve more attention in the study of motor variability, such as muscle fatigue and limb inertia in reaching targets located in large workspaces.

Second, we provide direct evidence that prediction deficits exhibited by patients with psychotic disorders with respect to self-generated actions are also generalized to other-generated actions. Our results suggest that patients show impairment in predicting object size by observing others reach-to-grasp movements compared with healthy controls. Patients' accuracy was at chance level for the first two temporal occlusions, but they still show to be overconfident compared to control subjects. In addition, our analysis suggests a relationship between prediction accuracy and SLOF test score, which assesses performance in the social domain. Patients with impaired relationship skills are less able to predict the actions of others.
These results could be a starting point for further understanding of this deficit in patients with psychosis. Future research could take into account the possibility to explore other aspects of psychosis patients' behavior such as 'jumping to conclusions'. The tendency to make hasty decisions may in fact have influenced the poor performance of patients in the first time-occlusions. A readapted version of the two-alternative forced-choice task could be used to establish whether the overconfidence of observers with psychosis is linked to earlier intervals.

*Limitations*. Individual motor variability was quantified using the force profiles applied by the participants during the execution of the reaching movements. This was possible by using a robotic manipulandum on which a specific type of trials, called ‘error-clamp’ trials, were programmed and implemented. However, the use of a robotic manipulandum restricts the movements to only two dimensions, making the reaching movements less natural and requiring

a long familiarization with the robot, before the subject is asked to complete the task. Familiarization makes the experiment longer and more tiring, which may have affected the extension of motor variability and the performance of the motor task.

The second research project described in this dissertation aims to determine the ability of patients with psychosis to predict the size of a to-be-grasped object. Therefore, in addition to control subjects, patients with non-affective psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorder, and brief psychotic disorder) were recruited for the study. In order to make data acquisition possible, i.e., to allow patients to perform the behavioral task on the computer, we used a personal computer to move the experimental set-up according to the patients' needs. It was therefore not possible to keep the experimental setup fixed and the same for all, as is desirable in experimental studies. Some conditions, such as the distance to the monitor, were easier to control and maintain, while others were more complex, such as the lighting conditions of the room in which the task was completed, the sound insulation of the room, the height of the surface on which PC was placed.

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# Appendix A

# Supplementary Information for

"The role of Individual Motor Variability in Motor Learning"

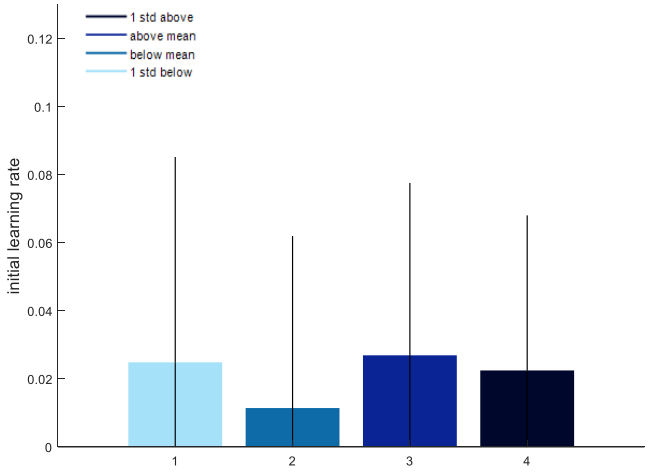



Figure S1. All participants were divided into 4 subgroups based on their individual baseline variability. The average task-relevant variability was 0.43±0.08 N. We have subjects (n = 6) with variability that was at least one standard deviation below average (average variability 0.31±0.02), subjects (n = 22) with variability that was below average (average variability 0.37±0.04), subjects (n = 19) with variability that was above average (average variability 0.51±0.07), and subjects (n = 7) with variability that was at least one standard deviation above average (average variability 0.58±0.05). All comparisons with initial learning computer over the first two error-clamp trials are reported here: - below average v. above average: $p = 0.33$, $t(39) = -0.97$; - one standard deviation below average v. one standard deviation above average: $p = 0.93$, $t(11) = 0.08$; - one standard deviation below average v. above average: $p = 0.93$, $t(23) = -0.08$; - below average v. one standard deviation above average: $p = 0.61$, $t(27) = -0.51$.

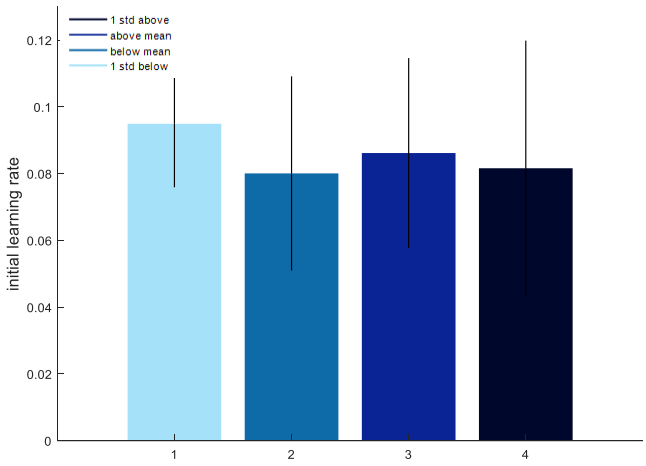
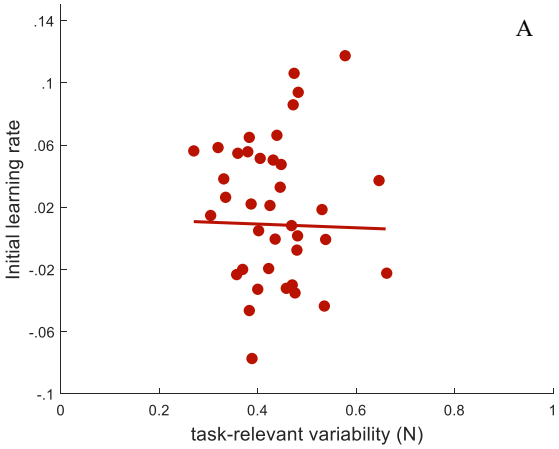
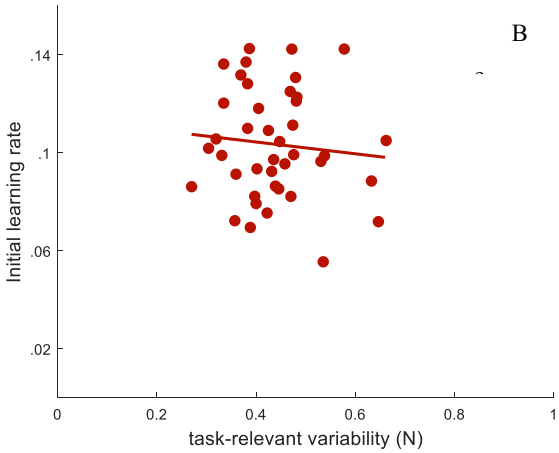



Figure S2. All comparisons of individual task-relevant variability with initial learning computer over the first eight error-clamp trials are reported here: - below average v. above average: $p = 0.50$, $t(39) = -0.67$; - one standard deviation below average v. one standard deviation above average: $p = 0.45$, $t(11) = 0.77$; - one standard deviation below average v. above average: $p = 0.48$, $t(23) = 0.70$; - below average v. one standard deviation above average: $p = 0.91$, $t(27) = -0.11$.




*Comparison of task-relevant variability with the initial learning over the first error-clamp trials across subjects.*




*Comparison of task-relevant variability with the initial learning over the first sixteen error-clamp trials across subjects.*

Figure S3. (A) We found no significant correlation between the individual baseline variability with the average learning rate over the first trial (r = -0.01, P = 0.90, t(39) = -0.11) and with (B) average learning rate over the first sixteen trials (r = -0.09, P = 0.54, t(39) = -0.60).

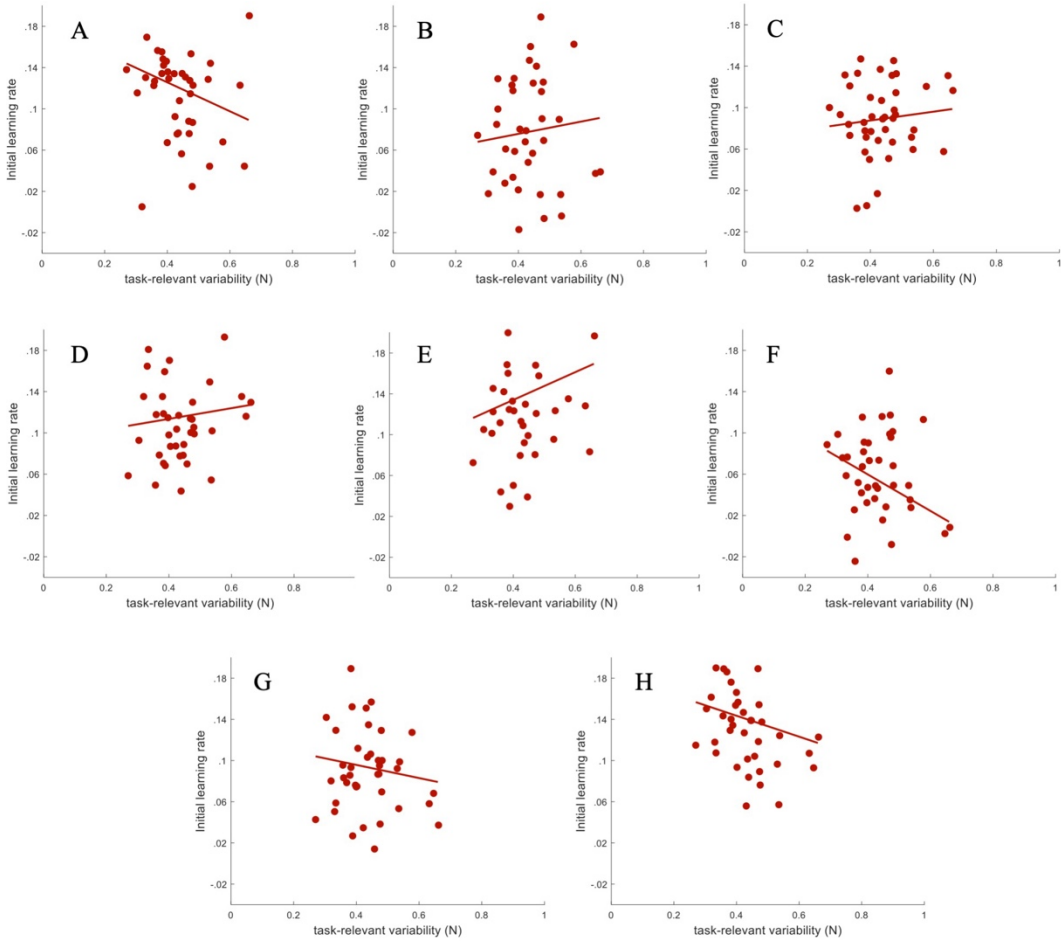



Figure S4. Comparisons of task-relevant with the initial learning rate over the two first error-clamp trials of each target, from target 0° to 315° (A-H). We see no significant correlations in any target position (from A to H: r = -0.22, P = 0.15, t(39) = -1.43; r = 0.08, P = 0.61, t(39) = 0.50; r = 0.10 P = 0.50, t(39) = 0.67; r = 0.10 P = 0.51, t(39) = 0.66; r = 0.18 P = 0.24, t(39) = 1.19; r = -0.29 P = 0.06, t(39) = -1.95; r = -0.12 P = 0.43, t(39) = -0.79; r = -0.19 P = 0.23, t(39) = -1.21).

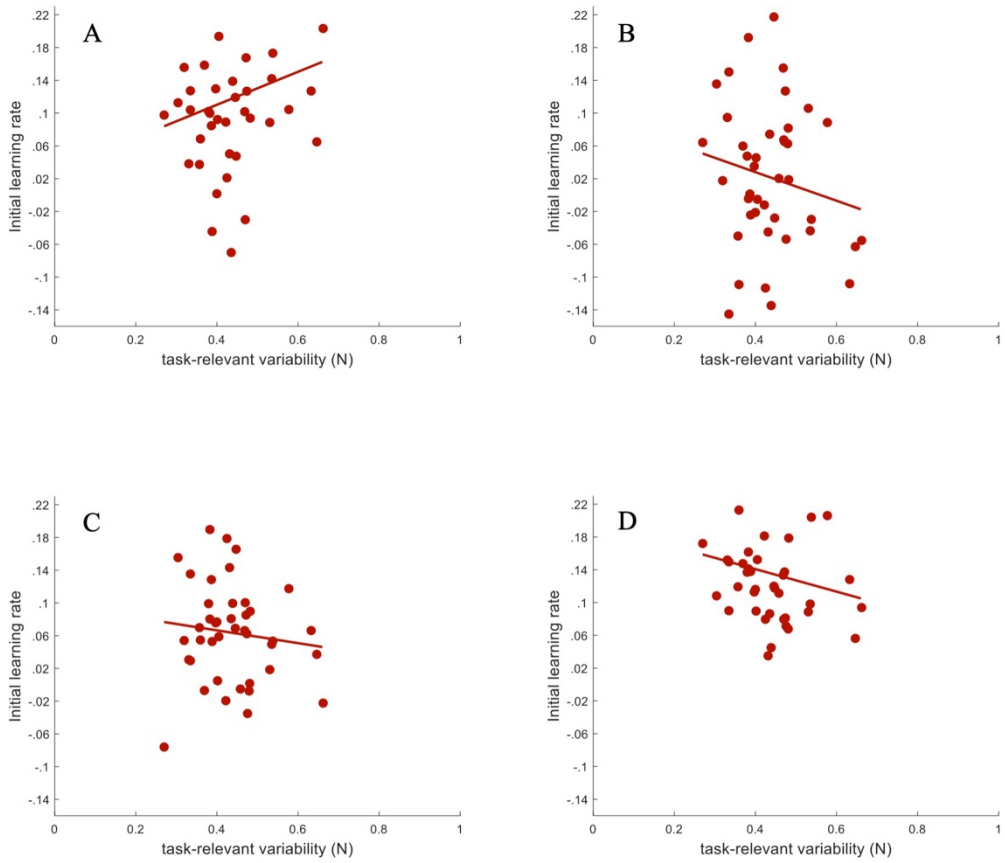



Figure S5. Comparisons of task-relevant with the initial learning rate over the two first error-clamp trials of each direction. We have four target directions: 0°-180°, 45°225°, 90°-270°, 135°-315° (A-D). We see no significant correlations in any target direction (from A to D: r = 0.18, P = 0.25, t(39) = 1.15; r = -0.17 P = 0.26, t(39) = -1.13; r = -0.11, P = 0.46, t(39) = -0.73; r = -0.17 P = 0.26, t(39) = -1.12).

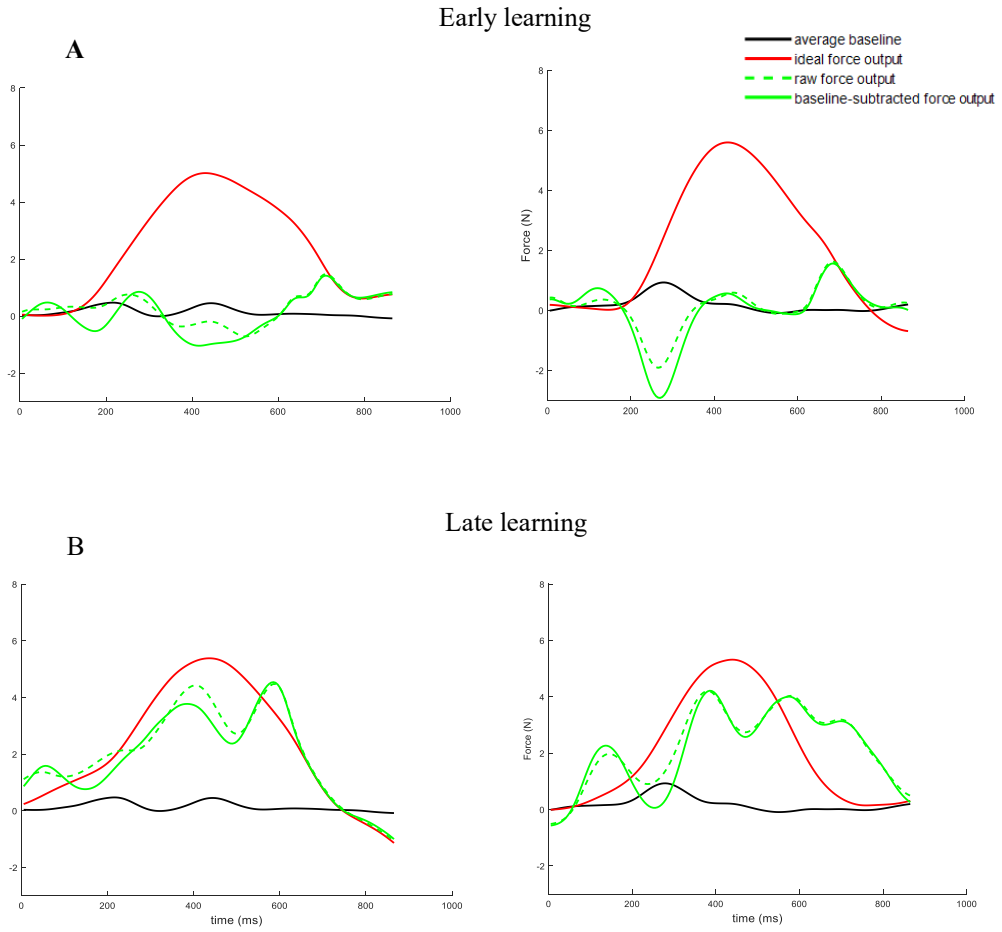



Figure S6. Panels A and B show two example subjects lateral forces during early (first two error-clamp trials) and late learning (last two error-clamp trials). The plots show mean force output each subject generated on baseline error-clamp trials (black line), the raw force trace measured on error-clamps during the learning session (dashed green line), the baseline-subtracted force output (solid green line), and the ideal force output subjects should have applied to perfectly counteract the velocity dependent force-field (red line). Comparing early learning with late learning, we can see that the motor output of both subjects at the end of the learning session was close to the ideal force output.

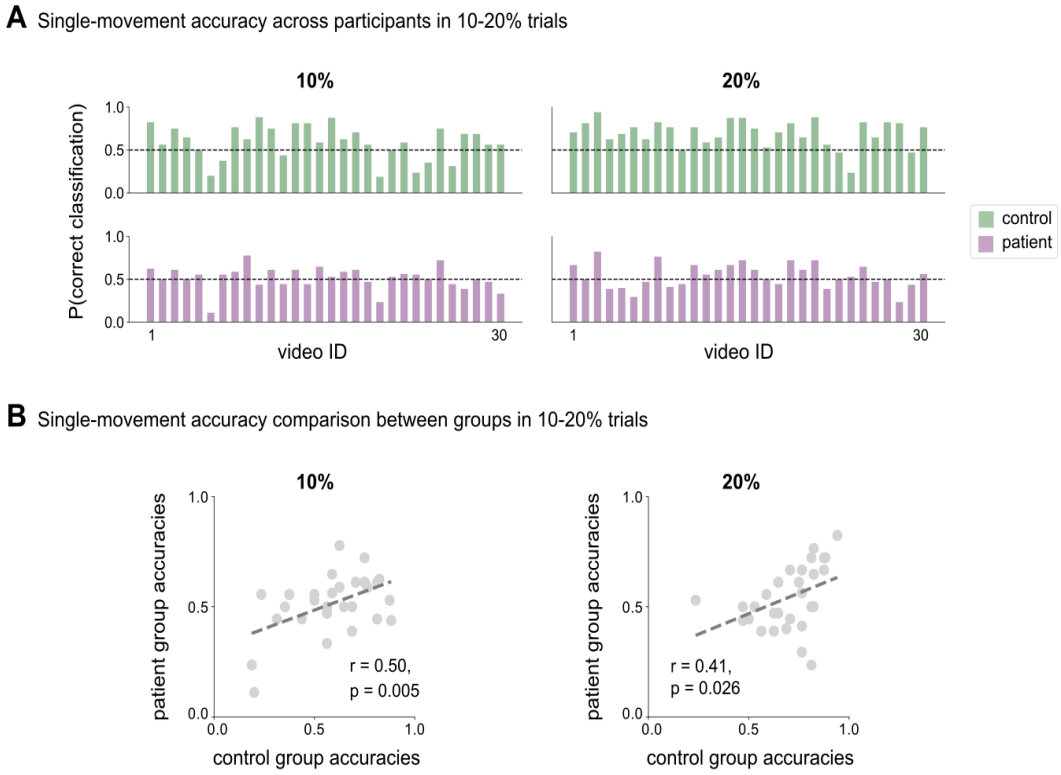
# Appendix B

# Supplementary Information for

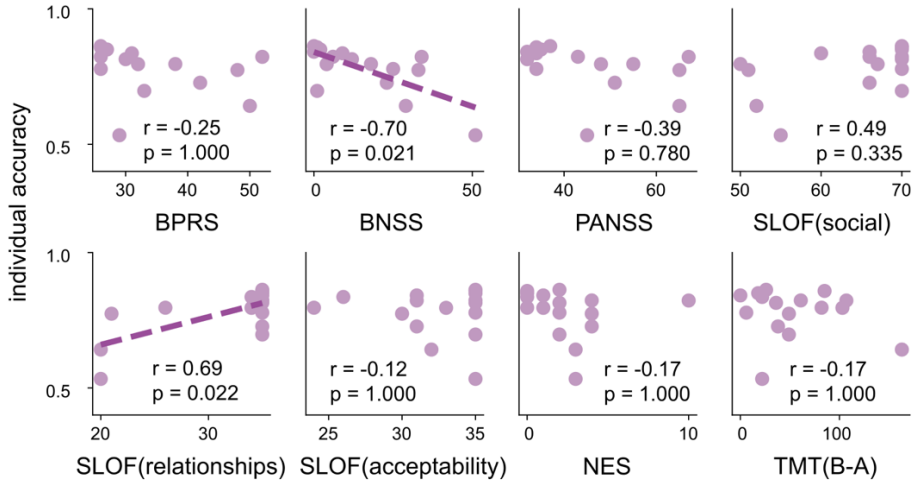
"Action Prediction in Psychosis"

**Supplementary Methods**

*Statistical analyses on encoding and readout model performance.* We used Linear Mixed Effects Models to quantify the effect of occlusion level and group on encoding and readout model performance, and to compare model performance against chance and between groups. We used the fraction of correct model predictions of each video across cross-validation repetitions as dependent variable. For encoding model performance, we considered occlusion level as fixed effect, and video ID (random intercept) as random effect. For readout model performance, we considered occlusion level, group and their interaction as fixed effects, and subject (random intercept, and random slope of occlusion level) and session block (random intercept) as random effects (Supplementary Tables 2 and 4). Although there was no overall response bias, the ratio between "small first" and "large first" responses varied across observers and occlusion levels – thus determining different chance-level null-hypothesis distributions of readout model performance. We estimated null-hypothesis distributions, separately for each participant and each occlusion level, by fitting the model on permuted data (see Methods). To make all single-trial readout model performance values comparable, we then z-scored all values for a given participant and occlusion level using the mean and standard deviation of the single-subject, single-occlusion null-hypothesis distribution.




Supplementary Figure S7. *Object size prediction accuracy at the single stimulus level.* (A) Bar graphs of single-stimulus prediction accuracy averaged across control observers and observers with psychosis, for 10% (left) and 20% (right) occlusion levels. (B) Scatter plot of the relationship between object size prediction accuracy in the patient group and in the control group at 10% and 20% occlusion levels. Data points represent single-stimulus object size prediction accuracy averaged across observers in each group. Fitted regression lines are displayed over the data. Pearson's correlation coefficients (r) and their significance values (p) are reported.




Supplementary Figure S8. *Relationship between neuropsychiatric scales and individual discrimination accuracy of participants with psychosis.* Scatter plots of BPRS, BNSS, PANSS, SLOF (social), SLOF (relationships), SLOF (acceptability), NES and TMT (B-A) against individual prediction accuracy of observers with psychosis. Pearson's correlation coefficients (r) and their Holm-Bonferroni corrected significance values (p) are reported. For significant linear trends, fitted regression lines are displayed over the data.

**Psychometric curve (probability of reporting small first)**

| Random effect structure selection (BIC) | | | | |
|---|---|---|---|---|
| Fixed effects: Observer Group * Occlusion Level | | | | |
| *Random effect structure* | *df* | *BIC* | *Deviance* | |
| **Subject (intercept and Occlusion Level slope), Block** | **8** | **5695** | **5623** | |
| Subject (intercept), Block | 6 | 5918 | 5864 | |
| Block | 5 | 5964 | 5920 | |
| Subject (intercept and Occlusion Level slope) | 7 | 5728 | 5666 | |
| Subject (intercept) | 5 | 5947 | 5903 | |
| null | 4 | 5992 | 5956 | |
| Fixed effect structure selection (LRT) | | | | |
| Random effects: Subject (intercept and Occlusion Level slope), Block | | | | |
| *Fixed effect tested* | *df* | *BIC* | *Deviance* | *p (LRT)* |
| **Observer Group : Occlusion Level** | **8-7** | **5695-5697** | **5623-5634** | **<0.001** |
| Observer Group | 8-7 | 5695-5686 | 5623-5624 | 0.393 |
| Piecewise-sigmoidal fit (BIC) | | | | |
| *Change points* | *df* | *BIC* | *Deviance* | |
| ± 10% | 13 | 5667 | 5551 | |
| **± 20%** | **13** | **5664** | **5548** | |
| ± 30% | 13 | 5680 | 5564 | |
| none | 7 | 5687 | 5624 | |
| Selected model | | | | |
| *Fixed effects* | Observer Group : Occlusion Level (piecewise-sigmoidal with change points at ±20%) | | | |
| *Random effects* | Subject (intercept and Occlusion Level slope); Block | | | |

**Confidence-accuracy calibration**

| Random effect structure selection (BIC) | | | | |
|---|---|---|---|---|
| Fixed effects: Observer Group * Integration period | | | | |
| *Random effect structure* | *df* | *BIC* | *Deviance* | |
| **Subject (intercept and Integration period slope), Block** | **9** | **23670** | **23590** | |
| Subject (intercept), Block | 7 | 24603 | 24540 | |
| Block | 6 | 26595 | 26541 | |
| Subject (intercept and Integration period slope) | 8 | 23696 | 23625 | |
| Subject (intercept) | 6 | 24619 | 24565 | |
| null | 5 | 26602 | 26557 | |
| Fixed effect structure selection (LRT). | | | | |
| Random effects: Subject (intercept and Occlusion Level slope), Block. | | | | |
| *Fixed effect tested* | *df* | *BIC* | *Deviance* | *p (LRT)* |
| **Observer Group : Integration period** | **9-8** | **23670-23718** | **23590-23647** | **<0.001** |
| Selected model | | | | |
| *Fixed effects* | Observer Group * Integration period | | | |
| *Random effects* | Subject (intercept and Integration period slope); Block | | | |

Supplementary Table 1. *Generalized Mixed Effects Model. Selection of random and fixed effects structure and piecewise-sigmoidal fit* (related to Figure 11). For the backward selection of the fixed structure effects, we conducted likelihood-ratio tests (LRTs) between models differing by one predictor only. We report the tested predictor and the difference in degrees of freedom, BIC and deviance determined by its removal. Tests on effects that are redundant in presence of significant interactions (LRT between equivalent models) are omitted. Retained models and effects are highlighted in bold. The notation A*B indicates both main effects A and B and their interaction (denoted as A:B).

**Encoding model performance**

| | | | | |
|---|---|---|---|---|
| Random effect structure selection (BIC) | | | | |
| Fixed effects: Occlusion Level | | | | |
| *Random effect structure* | | *df* | *BIC* | *Deviance* |
| Stimulus (video ID) | | 4 | -184.2 | -206.14 |
| **null** | | **3** | **-189.7** | **-206.14** |
| Fixed effect structure selection (LRT). | | | | |
| Random effects: none. | | | | |
| *Fixed effect tested* | | *df* | *BIC* | *Deviance* | *p (LRT)* |
| **Occlusion Level** | | **3-2** | **-** | **-** | **<0.001** |
| | | | **189.7+106.0** | **206.1+117.0** | |
| Selected model | | | | |
| *Fixed effects* | Occlusion Level | | | |
| *Random effects* | - | | | |

**Readout model performance**

| | | | | |
|---|---|---|---|---|
| Random effect structure selection (BIC) | | | | |
| Fixed effects: Observer Group * Occlusion Level | | | | |
| *Random effect structure* | | *df* | *BIC* | *Deviance* |
| Subject (intercept and Occlusion Level slope), Block | | 9 | 45791 | 45711 |
| **Subject (intercept), Block** | | **7** | **45790** | **45728** |
| Block | | 6 | 45890 | 45836 |
| Subject (intercept and Occlusion Level slope) | | 8 | 45795 | 45724 |
| Subject (intercept) | | 6 | 45797 | 45743 |
| null | | 5 | 45887 | 45843 |
| Fixed effect structure selection (LRT) | | | | |
| Random effects: Subject (intercept), Block | | | | |
| *Fixed effect tested* | | *df* | *BIC* | *Deviance* | *p (LRT)* |
| Observer Group : Occlusion Level | | 7-6 | 45790-45778 | 45728-45724 | 0.837 |
| **Observer Group** | | **6-5** | **45778-45775** | **45724-46465** | **0.013** |
| **Occlusion Level** | | **6-5** | **45778-46510** | **45724-46465** | **<0.001** |
| Piecewise-linear fit (BIC) | | | | |
| *Change point* | | *df* | *BIC* | *Deviance* |
| 10% | | 7 | 45785 | 45723 |
| **20%** | | **7** | **45758** | **45695** |
| 30% | | 7 | 45783 | 45721 |
| none | | 6 | 45778 | 45724 |
| Selected model | | | | |
| *Fixed effects* | Observer Group; Occlusion Level (piecewise-linear with change point at 20%) | | | |
| *Random effects* | Subject (intercept and Occlusion Level slope); Block | | | |

Supplementary Table 2. *Linear Mixed Effects Model selection. Selection of random and fixed effects structure and piecewise-linear fit* (related to Figures 12B and 13B). For the backward selection of the fixed structure effects, we conducted likelihood-ratio tests (LRTs) between models differing by one predictor only. We report the tested predictor and the difference in degrees of freedom, BIC and deviance determined by its removal. Tests on effects that are redundant in presence of significant interactions (LRT between equivalent models) are omitted. Retained models and effects are highlighted in bold. The notation A*B indicates both main effects A and B and their interaction (denoted as A:B).

**Object size prediction accuracy**

| | Comparisons against chance (0.5) | | | | | | | | Comparisons between groups | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | Patient | | | | Control - Patient | | | |
| *Occlusion Level* | *Estimate* | *SE* | *z* | *p* | *Estimate* | *SE* | *z* | *p* | *Difference* | *SE* | *z* | *p* |
| -80% | **0.007** | **0.003** | **-160.8** | **<0.001** | **0.035** | **0.013** | **-34.54** | **<0.001** | 0.028 | 0.013 | 2.141 | 0.059 |
| -70% | **0.013** | **0.005** | **-97.89** | **<0.001** | **0.054** | **0.017** | **-25.64** | **<0.001** | 0.040 | 0.017 | 2.331 | 0.059 |
| -60% | **0.025** | **0.008** | **-60.50** | **<0.001** | **0.080** | **0.022** | **-19.21** | **<0.001** | **0.056** | **0.022** | **2.523** | **0.049** |
| -50% | **0.046** | **0.012** | **-37.85** | **<0.001** | **0.119** | **0.026** | **-14.39** | **<0.001** | **0.073** | **0.027** | **2.699** | **0.042** |
| -40% | **0.083** | **0.018** | **-23.65** | **<0.001** | **0.172** | **0.031** | **-10.54** | **<0.001** | **0.089** | **0.031** | **2.836** | **0.034** |
| -30% | **0.147** | **0.025** | **-14.15** | **<0.001** | **0.243** | **0.036** | **-7.169** | **<0.001** | **0.095** | **0.033** | **2.923** | **0.031** |
| -20% | **0.268** | **0.034** | **-6.873** | **<0.001** | 0.422 | 0.041 | -1.901 | 0.229 | **0.154** | **0.037** | **4.169** | **<0.001** |
| -10% | **0.366** | **0.031** | **-4.336** | **<0.001** | 0.449 | 0.033 | -1.565 | 0.351 | **0.083** | **0.020** | **4.177** | **<0.001** |
| 10% | **0.589** | **0.030** | **2.950** | **0.003** | 0.504 | 0.031 | 0.125 | 0.901 | **-0.085** | **0.020** | **-4.188** | **<0.001** |
| 20% | **0.693** | **0.034** | **5.721** | **<0.001** | 0.531 | 0.039 | 0.805 | 0.841 | **-0.162** | **0.038** | **-4.215** | **<0.001** |
| 30% | **0.835** | **0.026** | **13.07** | **<0.001** | **0.716** | **0.037** | **5.780** | **<0.001** | **-0.120** | **0.035** | **-3.462** | **0.006** |
| 40% | **0.921** | **0.015** | **27.28** | **<0.001** | **0.822** | **0.029** | **11.05** | **<0.001** | **-0.100** | **0.030** | **-3.331** | **0.010** |
| 50% | **0.964** | **0.009** | **52.44** | **<0.001** | **0.894** | **0.022** | **18.02** | **<0.001** | **-0.070** | **0.023** | **-3.124** | **0.018** |
| 60% | **0.984** | **0.015** | **100.0** | **<0.001** | **0.939** | **0.016** | **28.04** | **<0.001** | **-0.045** | **0.016** | **-2.858** | **0.034** |
| 70% | **0.993** | **0.003** | **193.6** | **<0.001** | **0.966** | **0.011** | **43.53** | **<0.001** | **-0.027** | **0.011** | **-2.579** | **0.049** |
| 80% | **997** | **0.001** | **382.0** | **<0.001** | **0.981** | **0.007** | **68.32** | **<0.001** | -0.016 | 0.007 | -2.318 | 0.059 |

**Piecewise regression slopes of the psychometric curves**

| | Comparisons against 0 | | | | | | | | Comparisons between groups | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | Patient | | | | Control - Patient | | | |
| *Integration period* | *Slope* | *SE* | *z* | *p* | *Slope* | *SE* | *z* | *p* | *Slope difference* | *SE* | *z* | *p* |
| < - 20% | **5.112** | **0.526** | **9.716** | **<0.001** | **3.462** | **0.469** | **7.387** | **<0.001** | **-1.65** | **0.540** | **-3.054** | **0.002** |
| [-20%, 20%] | **3.642** | **0.479** | **7.598** | **<0.001** | 0.883 | 0.463 | 1.905 | 0.057 | **-2.76** | **0.661** | **-4.171** | **<0.001** |
| > 20% | **6.702** | **0.576** | **11.634** | **<0.001** | **4.834** | **0.508** | **9.513** | **<0.001** | **-1.87** | **0.518** | **-3.604** | **<0.001** |

**Confidence-accuracy calibration**

| | Comparisons between groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 10-20% integration period | | | | 30-80% integration period | | | |
| | *Estimate* | *SE* | *z* | *p* | *Estimate* | *SE* | *z* | *p* |
| Control - Patient | **-0.592** | **0.297** | **-1.991** | **0.047** | 0.073 | 0.281 | 0.261 | 0.794 |

Supplementary Table 3. *Coefficient analysis for the retained Generalized Mixed Effects for object size prediction accuracy, piecewise regression slopes of the psychometric curves and confidence-accuracy calibration* (related to Figure

11). For all comparisons, we report the model estimate and standard error (SE) of the tested quantity, the *z*-value and the two-sided *p*-value computed from the z-test. All *p*-values are Holm-Bonferroni corrected for the number of comparisons listed for each entry. Significant comparisons are highlighted in bold.

**Encoding model performance**

| Comparisons against chance (0.5) | | | | |
|---|---|---|---|---|
| *Occlusion Level* | *Estimate* | *SE* | *t* | *p* |
| 10% | **0.733** | **0.019** | **12.489** | **<0.001** |
| 20% | **0.779** | **0.015** | **18.458** | **<0.001** |
| 30% | **0.825** | **0.012** | **26.636** | **<0.001** |
| 40% | **0.871** | **0.010** | **35.517** | **<0.001** |
| 50% | **0.917** | **0.010** | **39.930** | **<0.001** |
| 60% | **0.963** | **0.012** | **37.973** | **<0.001** |
| 70% | **1.009** | **0.015** | **33.718** | **<0.001** |
| 80% | **1.056** | **0.019** | **29.807** | **<0.001** |

**Readout model performance (*z*-scored by permutation distribution)**

| Comparisons against 0 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Occlusion Level* | Control group | | | | Patient group | | | |
| | *Estimate* | *SE* | *z* | *p* | *Estimate* | *SE* | *z* | *p* |
| 10% | **0.884** | **0.246** | **3.594** | **<0.001** | 0.150 | 0.246 | 0.610 | 0.271 |
| 20% | **0.867** | **0.268** | **3.238** | **<0.001** | 0.133 | 0.268 | 0.496 | 0.310 |
| 30% | **2.609** | **0.244** | **10.68** | **<0.001** | **1.875** | **0.244** | **7.675** | **<0.001** |
| 40% | **3.178** | **0.236** | **13.46** | **<0.001** | **2.444** | **0.236** | **10.35** | **<0.001** |
| 50% | **3.749** | **0.232** | **16.14** | **<0.001** | **3.013** | **0.232** | **12.98** | **<0.001** |
| 60% | **4.316** | **0.233** | **18.53** | **<0.001** | **3.582** | **0.233** | **15.37** | **<0.001** |
| 70% | **4.885** | **0.238** | **20.50** | **<0.001** | **4.151** | **0.238** | **17.41** | **<0.001** |
| 80% | **5.454** | **0.248** | **22.00** | **<0.001** | **4.720** | **0.248** | **19.03** | **<0.001** |

Supplementary Table 4. *Coefficient analysis for the retained Linear Mixed Effects Models for encoding and readout model performance* (related to Figures 12B and 13B). For all comparisons, we report the model estimate and standard error (SE) of the tested quantity, the *t*-value or *z*-value and the two-sided *p*-value computed from the corresponding test. All *p*-values are Holm-Bonferroni corrected for the number of comparisons listed for each entry. Significant comparisons are highlighted in bold.