TOWARDS NOVEL, OBJECTIVE, BEHAVIORAL ANALYSES IN THE BASIC SCIENCES & CLINICAL RESEARCH

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Movement variability is inherently present in natural behaviors. In recent years, this source of information has been of great interest to motor control physiologists as it constitutes a physical, quantifiable form of sensory feedback to aid in the planning and execution of complex actions. In marked contrast, the psychological and psychiatric arenas mainly rely on verbal descriptions and interpretations of behavior through observation. Whether in the laboratory setting conducting basic science research, or in the clinic diagnosing and evaluating patients, behavior has not been physically quantified using proper statistical methods. Consequently, a large gap exists between the body’s manifestations of mental states (whether normative or pathological) and their descriptions (through observational inventories). This disconnect is partly responsible for a disembodied approach in the psychological and neural sciences, whereby contributions of the peripheral nervous system to central control, executive functions, and decision making processes are poorly understood.
Furthermore, the present gap between mind and body interactions severely impedes progress in translating basic scientific outcomes into clinical applications. How can we transition from a psychological theorizing approach to better understand complex behaviors in a more objective manner?

This dissertation introduces a novel, objective, statistical framework and motor control paradigm that characterizes the stochastic signatures of movement variability present in the continuous stream of natural behaviors. We characterize a new class of movements that occurs largely beneath conscious awareness but are interminably present in all complex behaviors. The moment-by-moment assessment of the continuous flow of sensory-motor fluctuations is possible for goal-directed segments of complex actions, (which researchers have focused on for decades), and this newly introduced class of supplementary, goal-less movements. To illustrate these points, we present the application of our statistical framework to perceptual tasks involving visual illusions, as well as to the automatic detection of sensory-motor disruptions in individuals with schizophrenia. Lastly, we discuss the potential impact our discoveries have on translating basic science research into practical, societal applications. We conclude that analyses of motor output variability can transform the way in which we currently conduct research, determine clinical diagnoses, and administer therapeutic interventions in the social, health, and neural sciences.
Dedication

This dissertation is dedicated to Kenneth Tarlowe, my loving fiancé and best friend. You are my rock, always believing in me and encouraging me to be my very best.

No one has seen me through this journey as intimately as you have, and I thank you for taking on the challenge of being there every step of the way. I am truly grateful for all the love you surround me with, and for the strength you bestow unto me when I am weak. I cannot express how happy I am to begin the next chapter of our lives, as this chapter now comes to a close. Thank you for simply being you. I look forward to our future together and to the day that you can finally call me “Dr. Tarlowe.”
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Chapter 1 Introduction

The movements of the body are as complex as the human… [They] are too fast and fleeting to be caught by the ordinary eye. One should manage, precisely and finely, to record their complex patterns.

- Nikolai Bernstein, Neurophysiologist (1948)

1.1 There’s More than Meets the Eye: Motor Variability in Natural Behaviors

Our bodies are in constant motion. Whether motor acts are under voluntary control, or occur largely under conscious awareness, movement variability is inherently present within natural behaviors (Torres, 2011; Uno, Kawato, & Suzuki, 1989). The naked eye is incapable of detecting every degree of these motions, as the human brain must select, prioritize, and integrate a vast amount of information from multiple sensory modalities to interact and rapidly adapt to our environments (Mesulam, 1998). We as observers simply cannot analyze the continuous flow of movement in detail, as we are only able to subjectively detect unambiguous features of our motor actions. Although many researchers in the psychological sciences may lay claim to objectivity in their studies, they still must decide on what they believe to be relevant features of human behavior. This adds a layer of subjective bias to results, possibly obscuring significant contributions of the sensory-motor system that inform us of the very behaviors under study and are physically quantifiable (Torres, Brincker, et al., 2013).
1.2 Current Approaches in the Psychological Sciences

To expand on this notion, we discuss the current scope of research methods in the psychological sciences. To characterize complex human behaviors, researchers tend to rely upon observational records, verbal reports, eye movements data, kinematics data, and brain imaging techniques (Dima, Frangou, Burge, Braeutigam, & James, 2012; Dima et al., 2009; Matthews, Hill, & Palmisano, 2011; Schenk, 2012; Thaler & Goodale, 2011; Wagner, Ehrenstein, & Paphathomas, 2009). Note that we do not discredit the value of observational data in providing descriptive accounts. Instead we raise the issue of solely relying on these interpretations when objective metrics are available to supplement these findings. A large gap exists in our understanding of the body’s manifestations of mental states by relying on subjective observational inventories. This disconnect has been partly responsible for a disembodied approach to the study of brain-body interactions, whereby the contribution of the peripheral nervous system to central control, executive functions, and decision-making processes is poorly understood.

In addition, the issue with methods that attempt to measure behavior computationally lies in the way in which epochs are deconstructed for analysis. For example, when scrutinizing kinematics data, motor control researchers tend to select for unambiguously visible features, focusing on deliberate, goal-directed movements. By only scrutinizing the goal-directed action, studies leave out key information about the continuous behavioral stream that falls largely below our conscious awareness. Aspects of motor behavior generated during these assessments are therefore left largely
underexplored, even though goal-directed and goal-less motions contribute to our kinesthetic percept. Goal-less supplementary motions, as it turns out, define a new statistical class of movements that are just as important as goal-directed actions to complex behaviors.

### 1.3 A Newly Defined Statistical Class of Movement: Supplementary Motor Actions

Motor control researchers highlight the importance of studying micro-movement variability as a physical, quantifiable form of sensory feedback that is imperative to the planning and execution of complex actions (Andersen & Buneo, 2003; Bernstein, 1967; Shadmehr & Wise, 2005; Terzuolo et al., 1982; Torres, Cole, & Poizner, 2014). Movement can be defined over a continuum, spanning the range from deliberate, goal-directed movements, to the involuntary functions that occur largely under our conscious awareness (Fig. 1.1a). Here we focus on the delicate balance between goal-directed actions and supplementary movements that help us transition between each goal to understand how the hierarchical regulation of these movement classes gives us the ability to interact with dynamic environments with fluidity and ease. Inspired by the works of neurophysiologist Nikolai Bernstein, we set out to investigate the stochastic signatures of motor variability by addressing the full visuomotor action loop that constitutes natural behavior (Bernstein, 1967). Movements, both goal-directed and goal-less, constitute a form of active sensing (re-afferent kinesthetic sensory input) (Von Holst, 1954; Von Holst & Mittelstaedt, 1950). This form of feedback, caused by our own peripheral movements, internally informs central motor control systems of the brain about important
on-line spatio-temporal aspects of human behavior as it unfolds, enabling the anticipation of sensory consequences of impending actions (Fig 1.1b).

Fig. 1.1: The Continuum of Movement and Sensory-Motor Processing. Movement can be defined over a continuum (Fig. 1.1a), spanning conscious, voluntary actions, to involuntary functions of the autonomic nervous system. Each level of functionality contributes to the shaping of complex human behaviors, yet most research focuses solely on the deliberate component of this spectrum without attending to the balance of these modes. Fig. 1.1b illustrates the flow of afferent and efferent signals to and from the central nervous system and the periphery. Movement variability can be thought of as a form of kinesthetic re-afference that can inform us of the balance between movement classes, serving as a physical, quantifiable measure of sensory-motor control.
However, as we previously mentioned, researchers investigating motor control systems primarily concentrate their work on goal-directed movements, despite the fact that a large number of actions that constitute our natural behaviors are executed without a clearly defined goal (Torres, 2011). Less is known about the spontaneous fluctuations present in supplementary movements, even though both movement classes contribute to our kinesthetic awareness. Our kinesthetic awareness is an integral component of the different stages of motor planning, enabling us to optimize our movement trajectories as they unfold (Archambault, Ferrari-Toniolo, & Battaglia-Mayer, 2011; Kalaska, Cohen, Prud'homme, & Hyde, 1990; Wurm & Lingnau, 2015). Recent works in the clinical and sports domains highlight the significance of studying the balance between goal-directed, intentional actions, and spontaneous, supplementary motions, once thought to be motor noise, for predictive and anticipatory control (Torres, 2011, 2012, 2013b; Torres, Brincker, et al., 2013; Torres et al., 2014; Torres, Heilman, & Poizner, 2011). The statistical characterization of movement, both goal-directed and supplementary, can therefore provide reliable, objective measures to investigate controversial issues in the psychological sciences and possibly reevaluate them under a unifying statistical platform.

1.4 Motor Disturbances in Clinical Diagnoses and Treatments for Neurological Disorders and Mental Illnesses

In addition to addressing issues in the psychological sciences, we translate our statistical framework and characterization of the continuous flow of movement in natural behaviors to the clinical domain. A number of neurological disorders and mental illnesses experience perceptual abnormalities, yet the underlying mechanisms that give rise to
these disturbances is less understood (Butler, Silverstein, & Dakin, 2008; Dakin & Frith, 2005; Diederich, Fenelon, Stebbins, & Goetz, 2009; Keane, Silverstein, Wang, & Papathomas, 2013; Silverstein & Keane, 2011a; Uhlhaas & Singer, 2006). Because several neurological disorders often report motor impairments in addition to cognitive issues (Liberg et al., 2013; Montero-Odasso & Hachinski, 2014; Reuter, Jager, Bottlender, & Kathmann, 2007), it is critical to objectively characterize the motor component of this dichotomy.

1.5 Organization of the Dissertation

This dissertation introduces a novel, objective, statistical framework and a new motor control paradigm that characterizes the stochastic signatures of the micro-movement variability present in the continuous stream of natural behaviors. In Chapter 2, we present the application of this new statistical platform and experimental paradigm to clarify longstanding issues in perception-action modeling. Specifically, we investigate the role of perceptual inputs in shaping sensory-motor processes using a physical 3D depth inversion illusion that causes signals from the ventral and dorsal visual cortical streams to compete. In Chapter 3, we further extrapolate our findings of Chapter 2 to explore the influence of speed instructions on perception-action processes.

To demonstrate the utility of our statistical framework in the clinical domain, we apply our methodology to the automatic detection of sensory-motor disruptions in individuals with schizophrenia that exhibit executive dysfunction. Since little is known about sensory-motor integration and kinesthetic re-afferent sensing in schizophrenia, we
aim to gain a better understanding of these mechanisms through the application of this research. Lastly, we discuss the potential impact our discoveries have on translating basic science research into practical, clinical applications. We present strong arguments on why objective analyses of micro-movement variability can transform research practices in the basic sciences and clinical setting.
Chapter 2 Quantifying the Influence of Perceptual Inputs on Sensory-Motor Behavior

2.1 Motivation

It is unknown if perceptual inputs may leak into active sensations from self-generated movements in such a way that they enable us to blindly separate different types of percepts. Here we aim to detect separable perceptual leaks into the moment-by-moment speed output variability generated by hand reach-to-grasp movements. More precisely, this work re-examines the interplay between visual perception and action processes through a new statistical lens. We aim at clarifying the arguments of two camps that disagree on whether illusory percepts, mainly processed in the ventral visual stream, influence our motor action that obtains most of its input from the dorsal visual stream, or whether the ventral and dorsal visual cortical streams are impenetrable to each other (Franz, Gegenfurtner, Bulthoff, & Fahle, 2000b; Gegenfurtner, Henriques, & Krauzlis, 2011; Hartung, Schrater, Bulthoff, Kersten, & Franz, 2005b; Kroliczak, Heard, Goodale, & Gregory, 2006; Schenk, 2012; Westwood & Goodale, 2011).


Neuropsychological and electrophysiological studies provide evidence for anatomical and functional divisions in ventral and dorsal stream processing for sensory modalities such as vision, audition, and touch (Mishkin & Ungerleider, 1982; Sedda & Scarpina, 2012; Tapia & Breitmeyer, 2011). However, the notion that the human brain processes, for instance, visual information into distinct, dissociated pathways for perception and action is widely debated (Schenk, 2012; Whitwell, Milner, & Goodale,
This chapter investigates this controversy by clarifying the role of perceptual inputs on sensory-motor processing.

Two major anatomical projections arise from the primary visual cortex to form the “vision-for-perception” ventral pathway, extending to the inferotemporal area, and the “vision-for-action” dorsal pathway, to the posterior parietal lobe (Goodale & Milner, 1992; Schneider, 1969; Ungerleider & Mishkin, 1982). The ventral visual stream is implicated in utilizing “top-down” visual information for perceptual processes, such as object recognition and identification, whereas the dorsal stream is thought to exclusively process “bottom-up” signals, such as motion parallax and binocular disparity, for action guidance and spatial awareness (Fig. 2.1). “Top-down” refers to the influence of high-level mental processes that contribute to the control of executive functions such as attention, working memory, familiarity, and expectation (Gilbert & Li, 2013). In contrast, bottom-up signals are thought to be stimulus-driven, relying primarily on sensory feed-forward information to carry out tasks (McMains & Kastner, 2011).
Fig. 2.1: Illustration of Brain Regions associated with Visuomotor Planning. Top-down processes and bottom-up signals modulate the planning and execution of our motor actions, but the relationship between these mechanisms remains unclear. Our aim is to investigate these mechanisms by quantifying sensory-motor behavior by analyzing micro-movement variability inherent in our actions. Figure adapted from Scott (2004).

The famous case study of Patient DF, evaluated by Goodale and Milner in 1992, provided strong evidence and support for the “two-visual systems” (TVS) hypothesis, which claims that ventral and dorsal visual pathways are separable for perception and action, respectively (Goodale & Milner, 1992). This theory suggests that motor planning is impervious to top-down ventral stream processes such as prior knowledge and
familiarity, implicating an exclusive reliance on dorsal stream visual information for motor control. DF, who suffered from visual form agnosia caused by carbon monoxide poisoning that resulted in bilateral ventral occipital lesions, retained accurate grasping ability towards objects that she had difficulty recognizing, supporting the premise of the TVS hypothesis (Goodale & Milner, 1992; James, Culham, Humphrey, Milner, & Goodale, 2003). Conversely, others have argued that DF’s ability to grasp objects accurately was not a result of a functional dissociation between two visual pathways, but instead an outcome of the use of haptic feedback to compensate for visual impairments caused by damage to the visual ventral stream (Hesse, Ball, & Schenk, 2012; Schenk, 2012; Schenk & McIntosh, 2010). Extensive testing of DF has only resulted in conflicting evidence, thereby calling for the need for advanced metrics to re-evaluate the TVS hypothesis.

Moreover, because of case studies similar to DF, it was assumed that the functional segregation of top-down and bottom-up signals also existed in healthy, non-pathological individuals. However, whether or not these findings provide evidence for an absolute division of labor between vision-for-perception and vision-for-action processes in neurotypical populations has been hotly debated over the past twenty years (Binkofski & Buxbaum, 2013; Gegenfurtner et al., 2011; Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006; Whitwell et al., 2014).
2.1.2 Segregation of Perception and Action Processes by Way of Visual Illusions

Visual illusions have served as the primary vehicle to test these hypotheses since they provide a way to investigate how skewed perceptual judgments of the environment affect our motor actions. The Ebbinghaus/Titchener Illusion, for example, is one such illusion that uses a disk target surrounded by smaller disks that appears to be larger than another disk of the same size surrounded by larger circles; this is due to a size-contrast effect (Aglioti, DeSouza, & Goodale, 1995). When participants reach to grasp the disk target, if sensory-motor processes are impenetrable to illusory percepts, then the grip aperture of the hand grabbing at the disk target would be unaffected by the visual illusion, causing the participant to act on the true geometry of the disk target rather than rely on incorrect perceptual size estimates. Aglioti et al. in fact report this behavior, reasoning that separate visual processes govern skilled actions and conscious perception.

Conversely, other groups have contested these results, finding no dissociation between visual perception and action processes when controlling the matching of perceptual and grasping tasks, proposing that there is an integration of visual stream information rather than concluding that visuomotor behavior is subject to a functional separation (Franz, Gegenfurtner, Bulthoff, & Fahle, 2000a). Despite several follow-up studies conducted to validate or refute the TVS hypothesis using the Ebbinghaus Illusion, there are competing pieces of evidence to support both sides of the argument (Gilster, Kuhtz-Buschbeck, Wiesner, & Ferstl, 2006).
2.1.3 Depth Inversion Illusions

To further explore the role of perceptual inputs on the sensory-motor system, 3D depth inversion illusions (DII) have also been utilized. DIIs produce illusory motion and perceived depth reversal of scenes in which physically concave angles are perceived as convex and vice versa (Papathomas, 2007). The Hollow Face Illusion is an example of a DII that generates the perception of a normal, convex face although the stimulus is physically concave, implicating the role of top-down influences such as prior knowledge and convexity bias to elicit the illusory percept (Hill & Johnston, 2007; Keane et al., 2013; Papathomas & Bono, 2004). Despite efforts to characterize reaching behavior towards targets on the Hollow Face Illusion, evidence still remains equivocal: studies report an effect of the illusory percept on goal-directed motor outputs (Hartung et al., 2005b) while others do not (Kroliczak, Heard, et al., 2006). These studies rely on comparing perceptual depth estimates to endpoint distance calculations of the hand relative to targets located on the Hollow Face Illusion. Conflicting results on actions performed on this type of stimuli may be a result of the variations in methods used by researchers. In addition, supplemental actions that provide significant contributions to the completion of the visuomotor action loop have not been taken into account in these analyses.

In this chapter, we present analytics that quantify both goal-directed and supplemental motor actions to provide an objective framework to study natural human behaviors under illusory and veridical visual percepts using a robust physical DII that produces nearly 90 degrees (maximal) difference in the surface orientation of the target.
between two competing percepts. The paradigm implemented in this study utilizes a class of DIIs commonly referred to as reverse-perspectives or reverspectives (Papathomas, 2007; Wade & Hughes, 1999). Linear perspective cues that are painted on piecewise 3D planar surfaces produce competition between the physical geometry of the stimulus and the actual painted scene. Data-driven sensory signals, such as binocular disparity and motion parallax, favor the veridical percept of the physical geometry, whereas experience-based familiarity with perspective favors the depth-inversion percept. The advantage of the reverspective is that it allows for the placement of a target on a stimulus surface whose perceived spatial orientation under the illusion differs by nearly 90 degrees from its physical orientation.

This maximal difference greatly facilitates testing whether or not movement kinematics is influenced by the illusion. If different motor strategies are employed under illusory and veridical percepts when grabbing towards a target on a reverspective stimulus, then it can be easily tracked by quantifying sensory-motor changes. The curvature of the hand’s approach towards the target, for example, is a measure that has been overlooked in past research (Hartung et al., 2005b; Kroliczak, Heard, et al., 2006). By analyzing the entire unfolding movement from initiation of the goal-directed movement to the spontaneous, automatic retraction of the hand back to its resting state, we may in fact bypass any shortcomings found in past methods that test for perceptual influence on motor outputs. We therefore emphasize the importance of studying automatic motions to fully capture both modes of sensory-motor behavior in our paradigm. We also investigate (in the natural speed variability patterns of the unfolding
hand motions) how the illusory percept “leaks” into this implicit automatic motor processing. By using this unique analysis, the metrics employed in this dissertation afford us the opportunity to advance our understanding of visuomotor action and perception loops to clarify the existing issues at hand.

2.1.4 Hypothesis

If top-down visual processes do not impact the movement trajectory, then it is hypothesized that reaches made under the illusory percept would exhibit the same characteristics as reaches made under the veridical percept on the reverspective stimulus. In other words, reaches performed under the illusory and veridical percepts would be similar in nature, because motor trajectory paths would act on the true geometry of the stimulus. However, if perceptual inputs do in fact affect sensory-motor behavior, then we predict that movement trajectories will exhibit different signatures of micro-movement variability. The following section will describe our methodology.

2.2 Methods

2.2.1 Participants

Participants were screened for visual acuity using a logarithmic visual acuity chart, for stereopsis using a Random-Dot Stereo Test, and for eye dominance. Written informed consent of the Rutgers University Institutional Review Board approved protocol in compliance with the Declaration of Helsinki was obtained before beginning experimental sessions. Compensation was provided for partaking in each experimental
session. We recruited healthy right-handed participants with normal or corrected-to-normal visual acuity.

Exclusion criteria for participants are as follows: (1) if participants experienced difficulty in perceiving the illusion and the blurring lens used to reduce stereopsis caused discomfort or dizziness; (2) if participants caused extraneous motion artifact by frequently moving during the recording period and the execution of the task (e.g. shaking of the leg, tapping of the fingers on the table, etc.); (3) if participants had existing drug and/or alcohol dependencies as it is known that binocular depth inversion is impaired in these populations (Leweke, Schneider, Thies, Munte, & Emrich, 1999; Schneider, Leweke, Sternemann, Weber, & Emrich, 1996). In addition, we rejected from further analysis partial data that were obtained if there was malfunctioning of the motion-capture system due to sensitivity to electromagnetic fields, causing significant losses in data. We discuss the exclusion of experimental trials in further detail in Section 2.2.3. Out of 24 subjects tested, a total of 16 participants were included in the present study, 8 males (ages 21-35) and 8 females (ages 19-33). All subjects were right handed. We selected a sample size of N = 16 since comparable studies used a similar number of subjects (Hartung, Schrater, Bulthoff, Kersten, & Franz, 2005a; Kroliczak, Heard, et al., 2006; Prime & Marotta, 2013; Wagner et al., 2009). Furthermore, we used kinematic parameters such as the angular velocity, with high frequency of peaks. This ensured that across trials each participant had at least 100 measurements (peaks) for each condition. We can then estimate with high confidence the statistical parameters that empirically characterized the
probability distribution family most likely associated with the random process underlying each condition.

### 2.2.2 Motion Capture System

We used 15 electromagnetic sensors at a sampling frequency of 240 Hz (Polhemus, Liberty, Colchester, VT) and motion-tracking software (The Motion Monitor, Innovative Sports Training, Inc., Chicago, IL) for continuous motion capture. Sensors 1-12 were placed on the following body segments using sports bands designed to optimize unrestricted movement of the body: center of the forehead, the trunk at thoracic vertebrate T12, right and left scapula, left upper arm, left forearm, left wrist, right upper arm, right forearm, right wrist, right hand index finger, and right hand thumb (Fig. 2.2a). An additional sensor was used to digitize the body to construct a biomechanical model using the Motion Monitor software. The remaining two sensors were placed on the backside of each stimulus directly behind each target’s location to attain an accurate position of each target in 3D space relative to the participant during the training and experimental blocks. We recorded the full motor response of each participant in real-time both in the forward motion (from initiation of hand movement up to their furthest reach), and in the non-instructed, automatic retraction of the arm back to resting position.
Fig. 2.2: Sensor Assignments and Separation of Movement Classes.  
Fig. 2.2a depicts the location of each sensor on the participant. XYZ coordinates [0,0,0] indicate the starting position of the hand on the switchbox. Moving in the positive Y direction indicates the forward motion towards the target, whereas the x- and z-axes are for the horizontal and vertical dimensions, respectively. Fig. 2.2b show a sample hand trajectory for a participant in the forward (cyan) goal-directed reach and the uninstructed retraction back to rest (magenta). For illustration purposes, the arrows indicate a down-sampled set of velocity vectors throughout the trajectory profile (the sampling resolution of 240Hz gives a very large number of such vectors, all of which we use in the analyses). The initial target location is shown in red to demonstrate where participants were reaching. The movement trajectory is split into two components by finding the point at which the linear hand speed nears instantaneous zero velocity (Fig. 2.2c). The magnitude of each sampled velocity vector from the motion trajectory is obtained using the Euclidean norm. This yields a speed profile over the motion time in Fig. 2.2c. Underlying the linear displacements is the peak angular velocity registered for each joint and for each movement class. A subset of angular velocity measurements is shown in Fig. 2.2d corresponding to the linear speed in Fig. 2.2c. The peak angular velocities are given by the black points along the angular velocity traces. The peak angular velocity is normalized by dividing the value by the sum of the peak angular velocity and the average angular velocity between two minima (the maximum is between two points where the joints are at near zero rotation value).
2.2.3 Stimulus Apparatus and Experimental Procedure

In order to present physical stimuli to the participant, a moveable platform on a sliding track was constructed on a table at an appropriate height that allowed for the stimulus to be presented at eye-level when the participant was seated in front of the table. A spring mechanism was used to control the retraction of the stimulus platform. A set of lamps placed behind the participant’s chair illuminated the stimulus platform evenly since uneven lighting may cast shadows that interfere with perceptual judgments. A switch box was added to the edge of the table closest to the where the participant was seated. Participants placed their right hand on the switch box at the beginning of each trial and activated the switch as soon as they lifted their hand to execute the reach movement (Fig. 2.3b, e).

The switch box, lights, and spring mechanism for the stimulus platform were connected to a microcontroller (Arduino, Smart Projects, Italy) that executed the simultaneous activation of the retraction of the stimulus platform via the spring mechanism and the turning off of lights once the switch box is triggered. The stimulus must retract and the lights must turn off after the initiation of the reach movement in each trial to prevent any online visual corrections and haptic feedback from occurring. The switch box mechanism was used so that retraction of the stimulus and the onset of darkness were implemented only after the movement had been initiated to produce an immediate reach task. This is a critical detail to emphasize as researchers argue that delays in movement onset after removal of visual and haptic cues are memory-guided, relying on ventral stream contributions, whereas real-time motor planning only occurs
when vision information is present at the time of movement onset (Prime & Marotta, 2013; Westwood & Goodale, 2003). By employing an immediate reach task, our methods should then clarify how top-down signals affect motor strategies upon approach of the target on the DII stimulus.

Fig. 2.3: The Reverspective Depth Inversion Illusion (DII) and the Proper-Perspective Stimulus.

Fig. 2.3a and 2.3d depict the physical reverspective stimulus and the proper-perspective stimulus, respectively, with their target locations. Fig. 2.3b and 2.3e demonstrate how a participant reaches forward towards the stimulus (in green and red, respectively) and how a participant retracts after completion of the goal-directed task. The distance between the moveable platform upon which stimuli are placed and the edge of the table where the switch box is located is 40 cm. Once
subjects initiate movement by lifting their hands off the switchbox, the platform retracts to a distance of 71 cm from the switchbox. Fig. 2.3c illustrates the physical geometry of the reverspective stimulus from a top view (solid lines) with respect to the target (red disk). The solid lines also represent the veridical percept for the reverspective stimulus. The dotted lines in Fig. 2.3c indicate its illusory percept. Fig. 2.3f illustrates the veridical percept and physical geometry of the proper-perspective stimulus. Note that the reverspective illusory percept in Fig. 2.3c matches the veridical percept of the proper-perspective stimulus in Fig. 2.3f.

A set of training stimuli was utilized to familiarize participants with the paradigm prior to exposure to the test stimuli (Fig. 2.4) (Nguyen, Papathomas, Ravaliya, & Torres, 2014). This step also allowed us to gather baseline data to better understand the motor performance of the subjects. Training stimuli consisted of two painted rectangular panels representing the isolated right surface wall of the middle building embedded in the reverspective stimulus and the proper-perspective stimulus. Each rectangular panel assumed the same spatial orientations as that of the right-hand side wall of the middle building found in the 3D scene for both the proper- and the reverse- perspective stimuli (Fig. 2.3). Participants were able to recover the true physical slant of the training stimuli at all times. Elliptical red planar disk targets were positioned on the training stimuli to match the location of the red planar disk targets on the experimental stimuli.
To determine whether or not top-down visual processes affect sensory-motor control, two 3D stimuli, a proper-perspective and a reverse-perspective (the DII), were used to elicit three distinct experimental conditions (Fig. 2.3). For the proper-perspective (Fig. 2.3d-f), the perspective-painted cues were congruent with the bottom-up signals of binocular disparity and motion parallax elicited by the physical geometry of the stimulus. This congruency produces a stable concave percept of two concave truncated pyramids with two streets that recede away from the viewer: the right wall of the central building slants with its right vertical edge further away than the central vertical edge. For the
reverspective (Fig. 2.3a-c), the painted cues compete with bottom-up signals that are elicited by the physical stimulus, thus creating a bistable stimulus that produces two main percepts: (a) a veridical depth configuration of two convex truncated pyramids that protrude toward the viewer, in which the right wall of the central building slants with its right vertical edge closer to the viewer than the central vertical edge (indicated by solid lines in Fig. 2.3c), and (b) an illusory inverted-depth configuration (indicated by dotted lines in Fig. 2.3c) of two concave truncated pyramids with two streets that recede away from the viewer, similar to the percept elicited by the proper perspective.

As a result of the illusory percept, the perceived 3D orientation of surfaces is affected drastically. Specifically, the right wall of the central building is misperceived as slanted with its right vertical edge further away than the central vertical edge. Notice that the perceived spatial orientation of this wall is almost orthogonal to its physical orientation. The illusory depth inversion causes convexities and concavities to be perceived as concavities and convexities, respectively.

Elliptical red planar disk targets were placed on the proper- and reverse-perspective stimuli as shown in Fig. 2.3. The perceived location and spatial orientation of the target on the proper perspective remains stable since the perceived depth configuration is static. In contrast, the perceived location and spatial orientation of the target in the reverspective depends on whether viewers do not obtain the DII (in which case its orientation will be veridical), or do obtain the illusion (in which case the perceived orientation will be nearly orthogonal to the true physical orientation).
All stimuli were placed out of view from the participant before starting the experiment. All lights were turned off except for the lamps used to illuminate the stimulus platform. Any computer screens that were in use to run the experiment were dimmed so that their lights did not interfere with the even lighting projected onto the apparatus. Before beginning any trials, each participant was informed of the experimental procedure. The experimenter demonstrated how to grab at where he or she last remembered seeing the target by approaching it perpendicular to the surface it was perceived on. The participants were told to grab towards the location at which they last visualized the target.

Three practice trials were first executed to allow the participant to become comfortable with the setup. Stimuli were not added to the platform at this time - only a black board with a center pole protrusion - used to later attach training stimuli - was visible. Participants reached towards the center pole and brought their hands back to rest upon completing the reach at their own pace. Note that no instructions were given on how to retract the hand; this component was unprompted and occurred automatically, largely below the subject’s awareness.

After the practice trials, training trials were implemented on the training stimuli (Fig. 2.4). The participant was instructed to close his/her eyes after each trial for the remainder of the experiment. The order of training stimulus presentation was randomized by the MATLAB program. Training stimuli help demonstrate the curvature of the reach,
and provide data on this reach curvature, when asked to grab at targets on physical surfaces representative of the targets used in the experimental stimuli (see Nguyen et al., 2014 for more details). There were four trials per stimulus, for a total of eight training trials.

Once training was completed, experimental trials were administered. Three stimulus conditions were used for the experimental trials: (1) reverspective under illusory percept (abbreviated “illusory”), (2) reverspective under veridical percept (“veridical”), and (3) proper-perspective (“proper”). Recall that stimulus conditions 1 (illusory) and 2 (veridical) utilize the same physical reverspective stimulus.

The reverspective stimulus was presented first to determine if participants could stabilize the illusory percept of the middle building “popping out” towards them. If participants had trouble stabilizing the illusory percept, a de-focusing lens on the non-dominant eye was used to weaken stereopsis in order to preserve the illusory percept while maintaining reaching distance to the target. This method was employed to preserve binocular viewing conditions in previous work (Kroliczak, Westwood, & Goodale, 2006). If participants required the de-focusing lens, they were instructed to put them on before each illusory trial. There were a total of eight participants who required the de-focusing lens. After the first illusory trial, the order of presentation of each stimulus was randomized. To ensure the presence of a stable percept for each trial, the experimenter, depending on the stimulus condition, gave the following instructions:
**Illusory and Proper:** “View the middle building as popping out towards you.”

**Veridical:** “View the middle building as caving in away from you.”

Once the participant confirmed a stable percept, they were instructed to grab at the target. Twelve trials for each condition were performed for a total of 36 experimental trials.

In order to address whether or not reaches performed on the reverse perspective stimulus under the illusory percept were similar to reaches made under the veridical percept on the same stimulus, entire trajectory paths starting from the initiation of movement to the return to resting position were analyzed in 3D space. We analyzed both the forward goal-directed reaches and the (uninstructed) supplementary, transitional movements to retract to a resting position. Each trial’s trajectory was decomposed into two movement classes (forward, goal-directed reach and retracting, supplementary motions) by detecting the point at which the velocity of the movement, after its initiation, nears instantaneous zero velocity (Fig. 2.2b,c). Trials were excluded from analyses if data capture did not record the entire motor loop due to equipment malfunctioning. We included subjects in our dataset only if they met the criteria mentioned in Section 2.2.1 and on the condition of having at least 11 out of 12 trials per condition recorded without any partial data loss. Although each participant completed 12 trials per condition, after inspection of the data, we omitted one trial per condition due to partial data losses related to possible equipment malfunctioning. We therefore analyzed 11 trials per condition for each subject. For participants that performed 12 trials per condition without any data collection errors, 11 out of 12 trials were randomly selected for analysis. It is important to
reiterate that our analyses rely on kinematic parameters that contain a high frequency of data points of interest. For instance, when analyzing the distribution of peak angular velocities, we are able to obtain at least 100 sample data points (peaks) within each stimulus condition. This ensured that across trials, each subject had at least 100 measurements (peaks) for each condition.

2.2.4 Raw Kinematics

Hand path trajectories were position-normalized for each participant. For each condition, all points in each trajectory family were translated to center the mean starting position at the origin. This was performed in order to account for variations in hand placement on the switch box that occurred across participants. For each condition, trajectory paths were then resampled to 100 points in order to calculate the Wilk’s lambda test statistic of the geometric curve.

The Wilk’s lambda test is a multivariate generalization of the univariate F-distribution, which allows for the reduction of the likelihood test statistic $\Lambda$ to a scalar value by way of determinants (Rencher & Christensen, 2012). Since each three-dimensional vector was analyzed along the hand trajectory, the Wilk’s lambda test statistic helps deduce whether or not a pairwise difference of mean vectors is significant.

The Wilk’s lambda statistic uses the likelihood ratio test $\Lambda = \frac{\det(E)}{\det(E+H)}$ in which the ‘within’ sum of squares and products are matrix $E$, and the ‘total’ sum of squares and products is matrix $(E + H)$. The matrix $E = \sum_{ij} y_{ij}y_{ij}^t - \sum_{i}^{k} \frac{1}{n} y_{i}y_{i}^t$, where $y_{ij}$ is a sample
point and \( y_i = \sum^n_i y_{ij} \) is the total sum of the \( ith \) sample. The matrix \( H = \sum^k_i \frac{1}{n} y_i y_i^T - \frac{1}{kn} y_y^T \), in which \( y_\cdot = \sum^k_i \sum^n_j y_{ij} \) is the overall total. When \( \Lambda \leq \Lambda_\alpha, p, vH, vE \), the null hypothesis is rejected. In \( \Lambda_\alpha, p, vE, vH \), \( \alpha \) is the level of confidence, \( p \) is the number of variables or dimensions, \( vH = k - 1 \) and \( vE = k(n - 1) \) are the degrees of freedom for hypothesis and error respectively, where \( k \) is the number of conditions and \( n \) is the number of trials.

For our experimental design, the confidence interval \( \alpha = 0.05, p = 3 \) for three dimensions, \( vH = (3 - 1) = 2 \) since the number of samples is \( k = 3 \) for three conditions, and \( vE = 2(11 \times 16 - 1) = 350 \) since 11 trials per condition were analyzed for each of the 16 participants (\( n = 11 \times 16 = 176 \)). The values of \( \Lambda_\alpha, p, vH, vE \) used to determine statistical significance are \( \Lambda_{lower} = \Lambda_\alpha = 0.05, p = 3, vE = 320, vH = 2 = 0.961 \) and \( \Lambda_{upper} = \Lambda_\alpha = 0.05, p = 3, vE = 440, vH = 2 = 0.972 \), as taken from Rencher & Christensen. These values define the range in which \( \Lambda_{lower} : \Lambda_{upper} \) lies. Therefore, values of \( \Lambda > [\Lambda_{lower} : \Lambda_{upper}] \) cannot reject the null hypothesis.

### 2.2.5 Changes in Hand Orientation Toward the Target

To quantify differences in hand orientation towards the target, positional information from sensors located on the thumb, index finger, and wrist of the right hand at the end of the forward goal-directed reach was analyzed. Since perceived veridical and illusory surface orientations on the reverspective stimulus differ by nearly 90 degrees, the angle at which the hand approached the target may show an effect if the illusory percept impacted the immediate reach.
Fig. 2.5: Hand Orientation Towards Target.
Fig. 2.5a demonstrates how a participant reaches towards the target on the reverspective stimulus. Fig. 2.5b illustrates how hand-approach unit vectors are calculated using sensors located on the thumb, index finger, and wrist (black). The midpoint between the thumb and index finger is used to define the vector of approach with respect to the wrist sensor position. Fig. 2.5c shows the unit vector normal to the target location on the reverspective stimulus (solid lines) and the proper-perspective stimulus (dotted lines).

For each trial, normalized approach unit vectors were derived by calculating the midpoint between the thumb and index finger in relation to the wrist position for each trial (Fig. 2.5a,b). We defined all possible angle configurations when comparing approach unit vectors in each condition for every participant by taking the dot product for each unit approach vectors group. The dot product is given by $A \cdot B = \| A \| \| B \| \cos \theta$, in which $\| A \|$ and $\| B \|$ represent the magnitudes of approach unit vectors, and $\theta$ represents the angle between $A$ and $B$. Denoting $I$ for illusory, $P$ for proper and $V$ for veridical, for each participant, $[f_{1,...,11}] \cdot [\vec{p}_{1,...,11}]$, $[f_{1,...,11}] \cdot [\vec{v}_{1,...,11}]$, and $[\vec{v}_{1,...,11}] \cdot [\vec{p}_{1,...,11}]$ is calculated, resulting in 121 angle values per comparison per subject. Since the frequency histograms of these motion parameters are non-symmetric, the non-parametric ANOVA, the Kruskal-Wallis Test, is utilized to determine whether or not each angle comparison group ($\angle$ Illusory vs. Proper, $\angle$ Illusory vs. Veridical, and $\angle$ Veridical vs. Proper) is statistically different from one another (Ross, 2014). The Kruskal-Wallis Test
determines if the mean ranks from each condition are similar. The null hypothesis of the Kruskal-Wallis Test indicates that each condition comes from the same distribution.

In addition to finding all possible angle configurations between each approach unit vector, the mean approach unit vector for each condition was found to compute the angles formed with the unit vector normal to each stimulus’ target location (Fig. 2.5c). Each possible angle is calculated using the dot product, as previously discussed, to obtain 

\[ \mathbf{I}_{1,\ldots,11} \cdot [\widehat{T}_{R1,\ldots,11}], \quad [\widehat{V}_{1,\ldots,11}] \cdot [\widehat{T}_{R1,\ldots,11}], \quad \text{and} \quad [\widehat{P}_{1,\ldots,11}] \cdot [\widehat{T}_{P1,\ldots,11}], \]

in which \( \widehat{T}_R \) and \( \widehat{T}_P \) represent the target surface unit vector normal to the reverespective stimulus and the proper-perspective stimulus, respectively. To further elucidate the relationship between hand orientations and target locations on each stimulus, hand approach unit vectors for each condition were also compared to the target surface normal of the proper-perspective for the illusory and veridical mean approach unit vectors (\( [\widehat{I}_{1,\ldots,11}] \cdot [\widehat{T}_{P1,\ldots,11}], [\widehat{V}_{1,\ldots,11}] \cdot [\widehat{T}_{P1,\ldots,11}] \)), and the reverespective for the proper mean approach unit vector (\( [\widehat{P}_{1,\ldots,11}] \cdot [\widehat{T}_{R1,\ldots,11}] \)). This allows us to determine whether or not there are similarities in hand approach under the illusory, veridical, and proper conditions.

2.2.6 Speed Profiles

To investigate whether or not changes in speed profiles occur for the task required in each condition, motor output variability from the trial-by-trial angular velocities in each trajectory family were analyzed. Peak angular velocities were normalized. Dividing the peak velocity between two minima by the sum of the peak velocity and the average
velocity between the two minima attains the normalization. This normalization minimizes possible allometric effects from different limb sizes across subjects (Lleonart, Salat, & Torres, 2000).

The normalized angular velocities are grouped by condition for the forward goal-directed reach and retractive movement across subjects (Fig. 2.2d). Distributional analyses were performed to estimate the parameters of the continuous Gamma family of probability distributions (Fig. 2.6). The Gamma distribution family has been previously used to parameterize the variability inherently present in natural human motions, ranging from normal (Torres, 2011, 2013b) to pathological (Torres, 2012; Torres, Brincker, et al., 2013; Torres et al., 2014).

The Gamma probability distribution function is given by: \( y = f(x|a, b) = \frac{1}{b^a \Gamma(a)} x^{a-1} e^{-x/b} \), in which \( a \) is the shape parameter, \( b \) is the scale parameter, and \( \Gamma \) is the Gamma function (Ross, 2014). The shape and scale parameters allow us to capture participant-dependent variations in velocity-dependent variability. These stochastic signatures range from Gaussian-like symmetric distributions of average speed patterns found in typical adult systems, to exponential distributions found in compromised systems concerning pathologies such as autism and Parkinson’s disease (Torres, Brincker, et al., 2013; Torres et al., 2014; Yanovich, Isenhower, Sage, & Torres, 2013), where power-law distributions of velocity-dependent indexes have been found across the human life span.
Within the typical ranges of the human population, our Gamma distribution analysis should therefore characterize potential differences between the types of movements generated by each stimulus. If the reverspective illusory condition instigated a trajectory speed profile similar to that of the proper-perspective condition, then their Gamma distributions are hypothesized to be similar. In contrast, if it is similar to the reverspective veridical condition, then both of these reverspective conditions should reveal similar Gamma distributions for normalized peak velocity values.

The empirical estimation of the appropriate family of probability distributions to characterize sensory-motor control stands in contrast to traditional approaches. The latter simply assumes the theoretical Gaussian distribution and take the mean and variance of kinematic parameters linked to the motion trajectories across a number of trials. The probability distributions empirically derived from unconstrained movements in three dimensions are in fact skewed, governed by power laws and inclusive of multiplicative random processes (Torres, 2011, 2013b).
Fig. 2.6: Empirical Estimation of Normalized Peak Angular Velocities.

The underlying probability distribution for the normalized peak angular velocity profiles (Fig. 2.6a, Fig. 2.6b) are empirically estimated using the continuous Gamma family of probability distributions (red curve) for each movement class. Fig. 2.6c shows the Gamma parameter plane with the estimated shape ($a$) and scale ($b$) parameters using maximum likelihood estimation. The 95% confidence intervals are also plotted for the given example. Points on this map provide a characterization of how external perceptual stimuli affect the fluctuations of the speed of trajectories in each condition, thus making it variable from trial to trial. Note the differences in the shape and scale parameters of the forward reach (cyan) and uninstructed retraction (magenta) in Fig. 2.6c. Fig. 2.6d plots the estimated means ($\mu_W$) and variances ($\sigma^2_W$) for the given trajectories using the empirically estimated shape ($a$) and scale ($b$) parameters. This plot provides an additional metric to characterize the influence of perceptual changes on sensory-motor control.
**Fig. 2.6c** shows an example of how these parameters can be mapped on the Gamma parameter plane spanned by the values of the shape (x-axis) and scale (y-axis). Each subject has a characteristic signature of micro-movement variability that is impacted by the movement type and context. Additionally, the mean ($\mu_w$) and variance ($\sigma_w^2$) of the Gamma family of distributions are calculated using the empirically estimated shape ($a$) and scale ($b$) parameters to analyze the dispersion of each Gamma distribution (**Fig. 2.6d**). To analyze the dispersion of each Gamma distribution, the noise-to-signal ratio, the Fano Factor was calculated for each condition (Fano, 1947). The Fano Factor is defined as $F = \frac{\sigma_w^2}{\mu_w}$, where $\sigma_w^2 = a \cdot b^2$ is the variance and $\mu_w = a \cdot b$ is the expected value operator, or the mean, during the time window $w$. The Fano Factor provides a noise-to-signal ratio measure that serves as an index for each condition. Recent work has shown how these parameters change as sensory-motor behavior adapts to external stimuli, highlighting the importance of the variability-dependent analyses of motor control experimental data (Torres, Brincker, et al., 2013; Torres et al., 2014).

**2.3 Results**

**2.3.1 Differences in the Unfolding of Movement: Hand Path Trajectory Analyses**

Mean trajectories are plotted in white with confidence intervals (colored tubes) for each point in the trajectory for veridical (green), illusory (blue), and proper (red) conditions for the intentional goal-directed, forward movement (**Fig. 2.7a**) and the uninstructed, automatic retraction (**Fig. 2.7b**). Note that each colored tube is representative of the collection of hand trajectories performed on each stimulus like the sample trajectory found in **Fig. 2.7b**. Since the unfolding of movement is critical in
determining differences in approach, Wilk’s lambda values are plotted based on the percentage of hand path trajectory completed (e.g. 25%, 50%, 75%, and 100%) (Fig. 2.8). Averaging these values over the entire path does not accurately represent the kinematics of the entire hand trajectory action loop, as shown by the curvature of each movement (Fig. 2.7).

Hand path trajectory analysis using the Wilk’s Lambda Test reveals a statistically significant difference between veridical and illusory conditions in the forward, goal-directed movement, as $\Lambda \leq [\Lambda_{\text{lower}}:\Lambda_{\text{upper}}]$ throughout the entire path’s forward progression (Fig. 2.8a). Recall that $\Lambda_{\text{lower}} = \Lambda$ $\times$ $p=0.05,p=vE=320,pH=2 = 0.961$ and $\Lambda_{\text{upper}} = \Lambda$ $\times$ $p=0.05,p=vE=440,pH=2 = 0.972$, as taken from Rencher & Christensen. This behavior is also preserved in the non-instructed retraction (Fig. 2.8d). As expected, the comparison between the veridical and proper conditions differs significantly in both the forward and retractory movements (Fig. 2.8b,e). The Illusory and proper conditions do not differ significantly in either movement class, as $\Lambda > [\Lambda_{\text{lower}}:\Lambda_{\text{upper}}]$ for all lambda values based on the percentage of path complete in both the forward and retraction cases (Fig. 2.8c, f).
Fig. 2.7: Curvature of Hand Path Trajectories.

Fig. 2.7a depicts the hand path trajectory for the forward goal-directed movement, whereas Fig. 2.7b shows results for the uninstructed retraction of the hand back to rest. Hand path trajectory confidence intervals under the veridical percept are illustrated in green, under the illusory percept in blue, and under the proper percept in red. The mean of each trajectory family is designated in white. A red sphere in Fig. 2.7a denotes the location of the target on the stimulus. The y-axis denotes the direction of movement towards the target and back to rest. Note the curvature of reach under the veridical percept (green) is markedly different from those performed under the illusory percept (blue), although both conditions share the same physical stimulus. The illusory percept hand path trajectory follows a similar path found in the proper condition (red). See Fig. 2.8 for the statistical analysis of the hand path trajectories.
Fig. 2.8: Wilk’s Lambda Test Statistic.

Fig. 2.8a-c and Fig. 2.8d-f show pairwise comparisons of each condition’s hand path trajectory using calculated Wilk’s Lambda Values. Red lines found within each boxplot indicate the median Lambda value. The horizontal edges of each blue boxplot represent the 25th and 75th percentiles. Thick black dotted lines on each end of the boxplot indicate values that are not considered outliers, and red plus signs indicate any outlier values, such as in Fig. 2.8a-b. Since the unfolding of movement is critical in determining how a participant performs each trial, the Lambda Values are calculated based on percentage of path completed (e.g. 25%, 50%, 75%, and 100%). The Wilk’s Lambda Test Statistic is given by

\[ \Lambda_{\text{lower}} = \Lambda \ast \alpha = 0.05, \text{p} = 3, \nu E = 320, \nu H = 2 = 0.961 \text{ and} \]
\[ \Lambda_{\text{upper}} = \Lambda \ast \alpha = 0.05, \text{p} = 3, \nu E = 440, \nu H = 2 = 0.972, \text{ given by the dotted lines and gray area.} \]

If \( \Lambda \leq [\Lambda_{\text{lower}}, \Lambda_{\text{upper}}] \) (below the dotted lines and gray area), the trajectory families are statistically different. Fig. 2.8a and Fig. 2.8d show that veridical and illusory hand path trajectories are statistically different from one another in both the goal-directed movement (Fig. 2.8a) and uninstructed retraction (Fig. 2.8d). The same behavior is observed in the comparison of the veridical vs. proper forward hand path trajectories (Fig. 2.8b), as well as in the retraction (Fig. 2.8e). Fig. 2.8c and Fig. 2.8f show that Lambda values in the forward reach and uninstructed retraction, respectively, are statistically similar for the comparison of illusory and proper hand path trajectories.
2.3.2 Hand Orientations Under Different Perceptual States

When examining the orientation of the hand as it approaches the target in each condition, hand-approach unit vectors in the veridical cases differ from those in the illusory and proper cases as shown by comparing the angles formed between each hand approach unit vector (Table 2.1), and the angles formed between each hand approach unit vector and the unit vector normal to the target’s surface location (Table 2.2). Illusory and proper conditions produce similar hand postures when orienting towards the perceived target on the reverspective stimulus and the physical target for proper-perspective stimulus. The Kruskal-Wallis Test reveals a significant difference between angles formed by the illusory and proper hand approach unit vectors (∠ Illusory & Proper) vs. the angle formed between veridical and proper hand approach unit vectors (∠ Veridical & Proper) (Table 2.1). Note that illusory and veridical hand approaches are conducted on the same physical reverspective stimulus. No significant group differences were found for all other angle group comparisons (Table 2.1).
Table 2.1: Kruskal-Wallis Test for Angles between Unit Approach Vectors. Table 2.1 compares the angles formed (∠) by hand unit approach vectors in each condition using the Kruskal-Wallis Test. The Kruskal-Wallis Test is a non-parametric method (similar to an ANOVA) that uses ranks to determine whether or not samples come from the same distribution. When comparing ∠ Illusory & Proper vs. ∠ Veridical & Proper angle values, p = 9.5608e-10 ± 6.8917e-14. Values of p < 0.05 indicate significantly different groups. ∠ Illusory & Veridical vs. ∠ Veridical & Proper comparisons and ∠ Illusory & Proper vs. ∠ Illusory & Veridical comparisons do not reject the null hypothesis. This implicates that ∠ Illusory & Veridical vs. ∠ Veridical & Proper and ∠ Illusory & Proper vs. ∠ Illusory & Veridical are similar and belong to the same distribution.

<table>
<thead>
<tr>
<th>Angle Group Comparison</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>∠ Illusory &amp; Proper a vs. ∠ Veridical &amp; Proper b</td>
<td>9.5608e-10 ± 6.8917e-14*</td>
</tr>
<tr>
<td>∠ Illusory &amp; Veridical c vs. ∠ Veridical &amp; Proper</td>
<td>0.3288 ± 0.3607</td>
</tr>
<tr>
<td>∠ Illusory &amp; Proper vs. ∠ Illusory &amp; Veridical</td>
<td>0.0495 ± 0.1981</td>
</tr>
</tbody>
</table>

a ∠ Illusory & Proper = [I_{1m}11] · [P_{1m}11], Illusory Unit Vectors · Proper Unit Vectors

b ∠ Veridical & Proper = [V_{1m}11] · [P_{1m}11], Veridical Unit Vectors · Proper Unit Vectors

c ∠ Illusory & Veridical = [I_{1m}11] · [V_{1m}11], Illusory Unit Vectors · Veridical Unit Vectors

*Designates p < 0.05, indicating significant difference between groups

Next, we evaluated the angle formed between the mean unit approach vector and the unit vector normal to the target surface location in each condition (Fig. 2.5). Recall that the reverspective stimulus generates nearly 90-degree maximal differences between illusory and veridical perceptual states. The mean illusory hand approach unit vector and the actual unit vector normal to the target’s location produce an angle close to 90 degrees (84.008º ± 13.829), whereas the mean veridical hand approach unit vector and the target surface normal produce an angle close to 45 degrees (46.076º ± 16.101) (Table 2.2). Although one would assume that the angle between the veridical hand approach unit vector and the target surface normal would be close to zero, the physical geometry of the reverspective stimulus induces obstacle-avoidance behavior, hindering the orientation of the right hand to act on the target normal to its location due to constraints on the arm’s
degrees of freedom. Proper hand approach unit vectors in relation to the proper-perspective target’s surface normal produce an angle of $17.772^\circ \pm 8.362$. When the illusory hand approach unit vector is compared to the proper-perspective target’s surface normal, (which is representative of the illusory target surface normal if subjects act on the illusory geometry of reverspective stimulus), the mean angle is calculated as $18.377^\circ \pm 9.286$. This result suggests that hand orientation towards the illusory target on the reverspective stimulus mimics hand orientations performed on the proper-perspective stimulus, indicating a strong influence of the Illusory percept on the motor trajectory.
Table 2.2: Angle between Mean Hand Approach Unit Vectors and Target Surface Normals.
The angles formed between the mean hand approach unit vector and the target surface normals on each stimulus are given in Table 2.2. The angle between the mean illusory hand approach unit vector and the actual unit vector normal to the target’s location is nearly 90 degrees (84.008° ± 13.829), whereas the mean veridical hand approach unit vector and the target surface normal produce an angle close to 45 degrees (46.076° ± 16.101). Recall that the reverspective stimulus generates nearly 90-degree maximal differences between illusory and veridical perceptual states. When comparing the illusory hand approach unit vector to the proper-perspective target’s surface normal, (which is representative of the illusory target surface normal if subjects act on the illusory geometry of reverspective stimulus), the mean angle is calculated as 18.377º ± 9.286. This may indicate that the hand orients towards the illusory target on the reverspective stimulus as it would do so on the proper-perspective stimulus, signifying a strong influence of the illusory percept on the motor action.

<table>
<thead>
<tr>
<th>Target Surface Normal Unit Vector Location</th>
<th>Mean Hand Approach Unit Vector</th>
<th>Mean Angle ± S.D. (degrees) Between Unit Vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverspective Stimulus</td>
<td>Veridical</td>
<td>46.076 ± 16.101</td>
</tr>
<tr>
<td></td>
<td>Illusory</td>
<td>84.008 ± 13.829</td>
</tr>
<tr>
<td></td>
<td>Proper</td>
<td>86.314 ± 12.760</td>
</tr>
<tr>
<td>Proper-Perspective Stimulus</td>
<td>Veridical</td>
<td>49.443 ± 17.016</td>
</tr>
<tr>
<td></td>
<td>Illusory</td>
<td>18.377 ± 9.286</td>
</tr>
<tr>
<td></td>
<td>Proper</td>
<td>17.772 ± 8.3623</td>
</tr>
</tbody>
</table>

2.3.3 Normalized Peak Angular Velocity Distributions

Inspection of the underlying probability distribution of the normalized peak angular velocities for both the forward reach (Fig. 2.9a) and uninstructed retraction (Fig. 2.9b) reveals similarities between illusory and proper conditions. The shape and scale parameters of the gamma probability distribution exposes differences in the patterns of motor variability, illustrating a close clustering of the proper and illusory normalized
peak angular velocity distributions in the upper left-hand corner, as opposed to the shape and scale parameters of the veridical distribution (Fig. 2.9c).

We also uncovered a power law that governs the Gamma parameters of our model of motor-sensing behavior under perceptual state changes (inset in Fig. 2.9c). The power law is given by $f(x) = \alpha * x^\beta$, with coefficients given with 95% confidence intervals: $\alpha = 0.6387 \, [0.4475, 0.83]$ for the intercept and $\beta = -0.9923 \, [-1.068, -0.9164]$ for the slope. The goodness of fit for our model results in an $R^2$ value of 0.9983, with the Sum of Squares due to Error (SSE) at a value of $1.205 \times 10^{-7}$, and the Root Mean Square Error (RMSE) at 0.0001736. As we see in the inset of Fig. 2.9c, when we take the log of the Gamma parameters, we see a segregation of veridical movement classes as opposed to what we find in the proper and illusory conditions. This governing power law helps us understand how perceptual processes influence motor trajectories, as points that move along this function provide us with an index of how motor behavior is modulated by changes in internal mental states. In addition, Fig. 2.9d reports the mean ($\mu_w$) and variance ($\sigma_w^2$) for each condition and movement class. Note that the plots of the means and variances for the veridical conditions separate from the values found in the other conditions. This separation is most evident in the uninstructed automatic retractions, those that participants are unaware of. These findings also suggest that, under the veridical percept of the reverspective stimulus, tighter control of the angular rotations of the hand during the unfolding of movement is exhibited, whereas proper and illusory parameters tell a different story.
Fig. 2.9: Gamma Parameter Plane for Normalized Peak Angular Probability Distribution. 2.9a-b illustrate the Gamma probability density function that is fitted to the underlying probability distribution of normalized peak angular velocities of the hand during the goal-directed reach (Fig. 2.9a) and the uninstructed retraction of the hand back to rest (Fig. 2.9b). The illusory condition is shown in blue, the veridical in green, and the proper in red. The Gamma parameter place spanned by the shape (a) and scale (b) parameters for each empirically estimated Gamma function is shown in Fig. 2.9c. Filled diamonds designate forward goal-directed shape and scale parameters, and filled circles illustrate the supplemental retractions. 95% confidence intervals from the MLE procedure are depicted by the crosshairs. The log-log plot of the Gamma plane is also shown to characterize the Gamma parameters by the exponential fit: \[ f(x) = 0.638 \times x^{-9.92}, \] with coefficients given with 95% confidence intervals (see text for details on goodness of fit). The Gamma statistics, the mean (\( \mu_W \)) and the variance (\( \sigma^2_W \)) parameters were estimated from the shape and scale parameters and plotted in the Gamma mean-variance parameter plane (Fig. 2.9d).
Based on the mean and variance calculated from the shape and scale parameters of the Gamma fitted probability density function, Table 2.3 calculates the index of dispersion via the Fano Factor, $F = \frac{\sigma^2}{\mu}$, Note that the Fano Factors (the noise-to-signal ratio) for normalized peak angular velocities are at their lowest in the veridical condition (0.0086 in the forward reach and 0.0052 in the retraction), whereas the proper and illusory Fano Factors are comparable and almost double these values in the forward case (0.0140 and 0.0146 respectively), and at their highest in the retraction (0.0125 and 0.0137 respectively). The veridical condition gives rise to more consistent movements with a trial-by-trial lower noise-to-signal ratio. These motions are also more predictable and reliable as they fall to the far-right of the Gamma parameter plane and to the lowest scale value of all conditions. The scale value reflects the noise-to-signal ratio since the Fano Factor is the variance/mean = $b$. These retracting veridical motions are under tight motor control.
Table 2.3: Fano Factor Calculations for the Distribution of Normalized Peak Angular Velocities.

The Fano Factor $F = \frac{\sigma^2_w}{\mu_w}$ measures the level of dispersion of each estimated Gamma probability distribution of the normalized peak angular velocities in each condition. The mean is designated as $\mu_w$, and the variance as $\sigma^2_w$ for time window $w$. Note how low variance values in the veridical cases (0.0057 in the forward reach and 0.0034 in the uninstructed retraction) are responsible for smaller Fano Factors (0.0086 and 0.0052, respectively), implicating that the joint rotations underlying the linear displacements of the hand in the veridical condition are under tighter control than that found in the proper and illusory conditions. Fano Factor values for proper and illusory conditions are comparable (0.0140 and 0.0146 respectively), and almost double the Fano Factors calculated for the veridical normalized peak angular velocity distributions. These findings suggest that the veridical condition gives rise to more consistent movements as the condition produces a trial-by-trial lower noise-to-signal ratio.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Goal-Directed Reach</th>
<th>Uninstructed Retraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illusory</td>
<td>0.0096 / 0.6608 = 0.0146</td>
<td>0.0089 / 0.6496 = 0.0137</td>
</tr>
<tr>
<td>Veridical</td>
<td>0.0057 / 0.6636 = 0.0086</td>
<td>0.0034 / 0.6632 = 0.0052</td>
</tr>
<tr>
<td>Proper</td>
<td>0.0094 / 0.6695 = 0.0140</td>
<td>0.0081 / 0.6502 = 0.0125</td>
</tr>
</tbody>
</table>

2.4 Discussion

This chapter offers a new experimental paradigm and statistical platform with the potential to clarify long-debated perception and action issues in the psychological sciences. Using this novel framework, we are able to characterize interactions with the illusory percept using the motor output variability inherently present in naturalistic hand movements. We are able to unambiguously distinguish the illusory percept from its veridical counterpart, demonstrating the use of various movement biometrics to show how centrally driven top-down processes impact sensory-motor performance of the
Peripheral nervous system. These changes can be immediately read out from stochastic movement signatures as the action unfolds moment by moment.

In the spirit of psychophysical power laws relating sensation and perception (Stevens, 1957; Wolfe, 2009), here too we find a power law relation to characterize the patterns of motor output variability specific to each condition. These patterns are a form of kinesthetic sensory input that is not just passively sensed but that selectively drives the system to use the proper reach-to-grasp pattern most adequate for the illusory or physical geometry. In this sense this online, moment-by-moment information from the peripheral limbs helps anticipate the sensory consequences of impending actions and connects centrally-driven mental awareness to peripheral bodily sensations. In the spirit of the active sensing paradigm proposed long ago (Von Holst, 1954; Von Holst & Mittelstaedt, 1950) here we have shown that external sensory input from the ‘what’ ventral stream selectively penetrates the ‘where’ dorsal stream. This crosstalk permits using the motor output variability from trial to trial to statistically classify with high certainty the perceptual (mental) state of the subject. As various forms of external sensory input give rise to stable ‘disembodied’, abstract percepts, the internally experienced kinesthetic sensory input also gives rise to a stable corporeal percept. In our illusory stimulus condition, a limb percept was identifiable as each condition elicited a specific stochastic signature.

In the past, psychophysical laws pertaining to the perception of external sensory stimuli have been subjectively estimated, relying on verbal reports made by subjects of
the conscious recollection of perceptual experiences (Gazzaniga, 2012). Here, subjects internally generated movements when interacting with the illusory or veridical reverceptive stimulus. Subjects, at times, consciously experienced this continuous stream of kinesthetic sensory input during the execution of deliberate motions towards the target. However, in the uninstructed retractions supplementing the goal-directed component of the action, subjects were largely unaware of the motor output variability defining the kinesthetic sensory input. Surprisingly, these supplementary segments were by far the most informative. They could blindly tell us with high certainty, given the signatures of variability of the internal joint rotations of the moving hand, which trajectories most likely corresponded to the illusory condition. The selective feature of these transitional motions and their statistical specificity may come as a surprise to some researchers, given that they are usually discarded as noise. However, they have been identified previously as providers of rich information in the sensory-motor domain (Torres, 2011, 2012, 2013a, 2013b; Torres et al., 2014). An advantage of this new methodology over observational methods is that the power law relations objectively self-emerge, partly from segments of the behavioral stream that the subject is largely unaware of.

2.4.1 Significance of Illusion Effect

By applying new metrics to analyze the continuous behavioral stream when interacting with a visual stimulus that causes a conflict between visual top-down processes and bottom-up sensory signals, we help clarify long-debated, fundamental issues in visuomotor perception-action modeling (Goodale, 2014; Schenk, 2012;
Whitwell et al., 2014). The hollow-face illusion is another example of a DII that generates the perception of a normal, convex face although the stimulus is physically concave, implicating the role of top-down influences such as prior knowledge and convexity bias to elicit the illusory percept (Hill & Johnston, 2007; Papathomas & Bono, 2004). Despite efforts to characterize reaching behavior towards targets on the hollow-face illusion, evidence remains equivocal: one study reports an effect on goal-directed motor outputs (Hartung et al., 2005b) while another does not (Kroliczak, Heard, et al., 2006). These studies mainly rely on comparing perceptual depth estimates in relation to the hand and target, excluding the contributions of motions that supplement the goal-directed task as the movement unfolds. A distinct advantage of our project is that the automatic retracting movement was fully utilized and characterized. Since these segments are uninstructed, their statistical characterization will enable us in the future to study populations with pathologies that may prevent the subject from understanding verbal instructions.

In the present work we hypothesized that, if top-down visual processes from the ventral visual stream affect sensory-motor control, patterns of micro-movement variability under the illusory percept of the reverspective stimulus would differ from those performed under the veridical percept - even though they share the same physical stimulus. We find convincing evidence that top-down visual signals play a significant role in shaping action processes (Binkofski & Buxbaum, 2013; Ernst & Bulthoff, 2004; Franz & Gegenfurtner, 2008; Hesse et al., 2012; Hesse, Ball, & Schenk, 2014; Keane et al., 2013; Pisella et al., 2006; Schenk, 2012; Schenk & McIntosh, 2010). Interestingly,
this behavior is maintained not only in the forward, goal-directed movement, but even
more so in the uninstructed retraction of the hand. The motor-sensation paradigm
directing actions performed under the illusory percept in our study demonstrate a reliance
on the reverspective’s perceived surface orientation, highlighting the importance of the
top-down visual ventral stream processes on movement-sensing strategies. Our work
provides evidence that the sensory-motor system utilizes top-down visual information to
estimate the kinesthetic sensory consequences of the impending action and accordingly
reshapes stochastic signatures of motor output variability in both goal-directed actions
and incidental, transitional movements.
Chapter 3 Understanding The Role of Speed Instructions in Shaping Sensory-Motor Processes

3.1 Motivation

Chapter 2 demonstrates how perceptual inputs may affect kinesthetic re-afference sensing via stochastic changes in motor output variability. The work provides us with key information about patterns of physical sensory-motor behavior that enable us to blindly separate differences in mental perceptual states. We now address how the cognitive control of speed modulates motor output variability when individuals undergo changes in visual perception. Specifically, we ask how instructed speeds manifest in the postural control of the arm during reach-to-grasp movements under the illusory percept of the reverspective stimulus.

In the previous chapter, speed level was not instructed, but rather spontaneously chosen by the subject who moved automatically at his/her own comfortable pace. The instruction of speed brings an additional cognitive load to the task because movement speed is not something that one typically must think about when moving. Movement speed is the type of parameter that, once mastered, becomes automatically used beneath an individual’s awareness. Speed, however, is one of the most interesting kinematic parameters as it is comprised of the distance traveled (a spatial geometric component that can be visually monitored) and the time of the motion (a dynamic component of the movement that not necessarily emerges 100% from the interacting forces of the physical body in motion and the physical world). For the brain to solve the reach problem the external visual distance has to be transformed into an internal (physical) postural
distance. Likewise, the physical time component must be transformed into an abstract cognitive time component eventually leading the system to temporal automation under a new different context.

3.1.1 Spatial and Temporal Dynamics in Sensory-Motor Processing

A simple reach-to-grasp movement is not so “simple” when researchers attempt to computationally resolve the relationship between temporal changes of the hand, for example, with respect to its orientation in space during the execution of motor actions. A number of theories in movement research hypothesize that optimal control strategies are predetermined before we execute our actions (Elsinger & Rosenbaum, 2003; Flash & Sejnowski, 2001; Uno et al., 1989). But how do these theories account for on line motor learning when we have no prior knowledge of how to execute an action? How does proprioceptive feedback contribute to the planning and execution of natural behaviors when we are faced with new situations? The answer may lie in the fundamental differences between motor output tempo and sensory input tempo, a distinction that cannot be appreciated under the current computational paradigms or the current notions of internal models steering the empirical research in motor control.

The current computational models of motor control resolve the temporal details of the hand trajectory in full during the planning stage, before any motion is executed (Flash & Hogan, 1985; Harris & Wolpert, 1998; Todorov, 2005; Todorov & Jordan, 2002; Uno et al., 1989). Embedded in each theoretical formulation of motor control is this notion that the temporal duration of the movement execution is something that the system knows
This formulation does not leave room to differentiate situations when the system relearns this movement duration time by trial and error during adaptation to a new context. Under such learning conditions the sensory feedback times are bound to vary greatly from trial to trial. They would differ from an automated efferent motor time because under a new context, additional perceptual and cognitive loads may play a different role than when the same movement was automatic. Since motor control experiments train subjects to accomplish the goal of a task within a predefined time window (Flash & Hogan, 1985; Harris & Wolpert, 1998; Todorov, 2005; Todorov & Jordan, 2002; Uno et al., 1989), this temporal learning process is often missed. Upon familiarization with the task context, subjects are instructed to initiate the experiment and only then the recordings start. By the time that the experimental recordings begin, the subjects have already mastered the time duration of each trial to perfection, thus giving experimenters the impression that the nervous system already knew the duration of the movement and used it in the computation of the trajectory formation plan.

In a series of experiments investigating the variability of the hand trajectories’ from trial to trial in the context of subjects that were entirely naïve to a task, an interesting pattern emerged (Torres & Andersen, 2006; Torres & Zipser, 2004). We found that the duration of the trajectory is not known by the nervous system a priori. It is actually something that the system masters over minutes, trying out different movement durations from trial to trial. In stark contrast to the highly variable total movement duration, the time to complete the first impulse of the reach, from the onset of movement to the first velocity peak, was actually very stable (Torres, 2010; Torres & Zipser, 2004).
There seems to be a conservation of a symmetry related to the trajectory curvature that reveals a separation between the geometry of the space underlying the solution trajectory and the temporal coverings to travel along that spatial path (Torres & Andersen, 2006; Torres, 2010; Torres & Zipser, 2002, 2004). The subjects’ spatial path solution to the new task emerges immediately and is conserved throughout the learning. Yet the speed of the motion along that path has to be learned. This learning process occurs at a different time scale than the learning of the local spatial component. The distance traveled along the first impulse of the reach is highly variable as the system adjusts all parameters of the motion, but from trial to trial the time spent by the hand traveling along that distance is nearly constant with very small variability (Torres, 2010).

Separating the spatio-temporal components of the reach trajectory is an automatic solution that the system already has in place (Fig. 3.1a) or gradually learns when no instructions are explicitly provided about the speed of the motion (Fig. 3.1b,c). Fig. 3.1 shows outcomes in speed progression across different tasks and instruction type. When the speed is explicitly instructed, the subjects may choose different strategies than when it is implicitly chosen, so as to adjust differently the temporal duration of the reach. Despite dramatic changes in speed dynamics though, the nervous system tends to conserve certain quantities connecting the internal space of postural configurations and the external space where the hand moves to the goal (Fig. 3.2 shows different contexts where the speed varies but different geometric ratios of the transformation from posture to goal are maintained, taken from (Torres, 2010; Torres & Zipser, 2004)).
Fig. 3.1: Differential effects of speed instructions on movement output variability and trajectory formation.

Explicit instructions on speed level for orientation matching are shown in Fig 3.1a. For each speed level the hand travels a different distance along the spatial path lasting a different length of time. Both the distance and time vary across the randomly instructed speed. Yet, when gathering all trajectories each speed type is unambiguously attained by the system using a systematic strategy that conserves the ratio of distance to speed and does not significantly alter the curvature of the path. All trajectories in the top panel of A belong in the same geometry. Implicitly chosen speed during the learning of obstacle avoidance by naïve subjects (Fig. 3.1b). Spatial path conservation is achieved despite the striking changes in speed dynamics. All trajectories for the blue (learning) and automated (green) paths lie inside the tube and the mean trajectories overlap. A very different scenario from these motions emerges compared to A. The distance traveled along the first impulse of each trajectory (highlighted in yellow along the speed profiles) lasts the same amount of time (on the order of 200ms for this target location) but the variations in distance (marked by the peak values variability of the black dots) ultimately lead to the learning of stable trajectory duration. This is a very different scenario to that proposed by theoretical models of motor control where the total time of the movement is a priori needed to solve the time dependent functional that yields the trajectory. Implicitly self-modulated speed during decision making is shown in Fig. 3.1c. Here the uncertainty of deciding if a movie clip is ME vs. not ME shows up in the “change of mind routes” of the trajectories after the onset of the decision making motion. Not shown are the continuations of these trajectories as the hand spontaneously retracts from the touch of the screen, a movement segment that also
conveys information about the decision making process (even after the decision was made).

Fig. 3.2: Geometric path conservation in the face of speed changes. The shape of the trajectory during obstacle avoidance learning changes with the obstacle configuration (Fig. 3.2a). The yellow portion is the first impulse with lasts for each target a characteristic time with very low variability from trial to trial. In red are the distance traveled up to the point of first velocity peak along the trajectory. This distance is adjusted from trial to trial until the duration of the reach becomes stable. (Fig. 3.2b) The characteristic time of the first impulse forms a stable surface for each context. This surface warps differently for the same targets and starting (center) position reflected on the horizontal plane. The time length of the first impulse (ms) is a priori stable in contrast to the total duration time of the reach trajectory that changes from trial to trial. (Fig. 3.1c) Symmetric invariant from the hand trajectories conserved across different speed adaptations (methods to be explained and tested in Chapter 4).
One of the outcomes from the prior research involving the speed analyses was that the symmetry invariants in question (e.g. such as those in Fig. 3.2c) were not merely the byproduct of biomechanical constraints. They were rather under the sensory-motor cognitive control of the system. When critical areas for estimation and forward prediction of the sensory-consequences of the impending reaches were altered (due to stroke, de-afferentation and chronic illness) the symmetries in question broke down (Torres et al., 2014; Torres et al., 2011; Torres, Raymer, Gonzalez Rothi, Heilman, & Poizner, 2010). Yet using the appropriate form of sensory guidance in each patient type allowed the system to recover the symmetries and perform the task at levels comparable to those of healthy controls (Torres et al., 2014; Torres et al., 2011; Torres et al., 2010). In this sense the manipulations in speed (whether implicit in the task or explicitly instructed) were very revealing of conservation strategies in the control of movements. This theoretically driven research (Torres, 2001; Torres & Andersen, 2006; Torres & Zipser, 2002) was in line with previous empirical work (Atkeson & Hollerbach, 1985; Nishikawa, Murray, & Flanders, 1999) and fundamentally differed from the computational theories that assumed and required a pre-determined movement duration time to solve the problem of trajectory formation during the planning stages of the reach (Flash & Hogan, 1985; Harris & Wolpert, 1998; Todorov, 2005; Todorov & Jordan, 2002; Uno et al., 1989).

The previous work never examined the speed issue in light of additional perceptual loads caused by illusory percepts. How are the spatial hand-trajectories changed when the system is overloaded with the speed instructions in the face of illusory
perceptual loads? Bringing the speed level to explicit cognizance may leak into the motor output variability some of the strategies that the system uses to solve and update the reach. It may also show the increase in uncertainty as the system joggles more than one goal at a time. In this Chapter we quantified the possible crosstalk between top-down illusory percepts and bottom up movement dynamics in typical participants when the speed is explicitly instructed. Using the stochastic analyses that we introduced in the previous chapters and the same illusory paradigm we will show that cognitive overload of speed performance and perceptual overload of illusory information make a dent in the trajectory invariance and in these typical subjects increases the patterns of variability of an otherwise automated reach-to-grasp action. We will see that the speed instruction changes the stochastic signatures of spontaneous retractions into those of more deliberate ones.

3.1.2 The Posterior Parietal Cortex and Proprioception

The neural correlates of these spatio-temporal transformations primarily lie in the posterior parietal cortex (PPC), as we mentioned in Section 2.2.1. The PPC has dedicated control processes for the coordination of visually guided behaviors (Ungerleider & Mishkin, 1982). We know that the PPC is also involved in generating coordinate transformations that map visual spatial goals to changes in body position to form body-based spatial representations, serving as an interface for sensory-motor integration (Fig 3.3) (Andersen & Buneo, 2003; Buneo & Andersen, 2006; Cui & Andersen, 2011).
However, less is known about the influence of proprioceptive feedback on geometric transformations in the PPC. This is so despite known anatomical afferent pathways projecting to this multi-modal region (Prevosto, Graf, & Ugolini, 2009, 2010, 2011) that situate it as a center for forward planning and estimation (Mulliken, Musallam, & Andersen, 2008a, 2008b). Recent work in non-human primates showed that neurons in the medial intraparietal region of the posterior PPC contain information about impending speed up to a second ahead of the actual reach (Torres, Quian Quiroga, Cui, & Buneo, 2013). These neurons also selectively enhance or dampen their firing rates when postural trajectories are about to change a second later. It is this very notion of crosstalk in the cortical neurons between visual and postural aspects of the reach that gives heed to the importance of studying how kinesthetic re-afference embedded in the unfolding micro-movement output variability may contribute to central motor control of impending actions, particularly when perceptual dynamics are at play. It is unclear how the introduction of a speed instruction component to our model of perceptual inputs on sensory-motor processes modulates the flow of sensory information and how this translates into our moment-by-moment motor output fluctuations. We now describe the methods employed in this chapter to characterize the role of these spatio-temporal constraints.
Fig. 3.3: Multisensory Processing in the Posterior Parietal Cortex. It is believed that the posterior parietal cortex (PPC) is involved in the integration of multiple sensory modalities to form internal, sensory-spatial representations that are required for the anticipation, planning, and execution of our movements. Fig 3.3 demonstrates how coordinate transformations from the senses and from proprioceptive feedback are transformed to initialize motor planning. Fig. 3.3 is taken from Andersen and Buneo (2002).

3.2 Methods

3.2.1 Participants

The same 16 individuals that participated in the experimental procedure described in Chapter 2 were used for this study. The order of experimental sessions (reaching at a natural pace vs. speed instruction implementation) was counter-balanced across subjects to verify whether or not familiarity with the experimental setup and the order of experimental sessions had an influence on the outcome of our results. We discovered no such findings. Written informed consent of the Rutgers University Institutional Review Board approved protocol in compliance with the Declaration of Helsinki was obtained.
before beginning each experimental session, and compensation was provided for participation in the study.

3.2.2 Experimental Procedure

The motion capture system and stimulus apparatus implemented in Section 2.2 remained the same for this paradigm. The experimental procedure deviates from the first experiment at the start of training trials. The four training trials for each training stimulus were subdivided: two reaches were performed at a speed faster than performed in the practice trials, and two reaches were performed at a slower speed. In other words, participants were asked to use the speed of reaches previously performed during the practice trials as a reference to move faster or slower from. The MATLAB program randomized the presentation of fast/slow speed instructions.

The reverspective stimulus was presented first to determine if participants could stabilize the illusory percept of the middle building “popping out” towards them. A defocusing lens was used if participants had trouble stabilizing the percept, as described in Section 2.2.3. After the first illusory trial, the order of presentation of each stimulus was randomized. The directions were given to each participant for each stimulus condition:

**Illusory and Proper:** “View the middle building as popping out towards you…”

**Veridical:** “View the middle building as caving in away from you…”
Once the participant confirmed a stable percept, they were instructed to grab at the target using the following speed instructions:

**Fast Condition:** “Reach for the target quickly.”

**Slow Condition:** “Reach for the target slowly.”

Six trials for each stimulus-speed condition (i.e. illusory-slow, illusory-fast, proper-slow, proper-fast, veridical-slow, and veridical-fast) were performed for a total of 36 experimental trials.

### 3.2.3 Wilk’s Lambda Test Statistic

We applied the kinematic analyses described in Chapter 2 to the current paradigm. Since the number of conditions and trials has changed, we identify the correct parameters to obtain the Wilk’s lambda test statistic. Recall for the Wilk’s lambda test statistic, $\propto$ is the level of confidence, $p$ is the number of variables or dimensions, $vH = k - 1$ and $vE = k (n - 1)$ are the degrees of freedom for hypothesis and error respectively, where $k$ is the number of conditions and $n$ is the number of trials.

For the experimental design of the speed paradigm, the confidence interval $\propto = 0.05, p = 3$ for three dimensions, $vH = (6 - 1) = 5$ since the number of samples is $k = 6$ for six conditions, and $vH = 6(5 * 16 - 1) = 474$ since 5 trials per condition were analyzed for each of the 16 participants ($n = 5 * 16 = 80$). Note that although each participant completed 6 trials per condition, some trials were omitted based on the
aforementioned exclusion criteria, resulting in the analysis of 5 trials per condition for each subject. For participants that performed 6 trials per condition without error, 5 out of 6 trials were randomly selected for analysis. The values of $\Lambda^{\ast}_{\alpha,p,E,H}$ used to determine statistical significance are $\Lambda_{\text{lower}}^{\ast} = \Lambda^{\ast}_{\alpha=0.05,p=3,E=440,H=5} = 0.945$ and $\Lambda_{\text{upper}}^{\ast} = \Lambda^{\ast}_{\alpha=0.05,p=3,E=600,H=5} = 0.959$, as taken from Rencher & Christensen. These values define the range in which $\Lambda^{\ast}_{\alpha=0.05,p=3,E=474,H=5}$ lies. Therefore, values of $\Lambda > [\Lambda_{\text{lower}}^{\ast} : \Lambda_{\text{upper}}^{\ast}]$ cannot reject the null hypothesis.

### 3.2.4 Hand Orientation Angles

For stimulus-speed condition trial, normalized approach unit vectors were derived as described in detail in Chapter 2.2.5. Denoting $\hat{I}_s$ for illusory-slow, $\hat{I}_f$ for illusory-fast, $\hat{P}_s$ for proper-slow, $\hat{P}_f$ for proper-fast, $\hat{V}_s$ for veridical-slow, and $\hat{V}_f$ for veridical-fast, for each participant the following dot products in Table 3.1 are calculated, resulting in 25 angle values per comparison per subject. There are 15 angle groups formed by each hand approach unit vector condition.
Table 3.1: Hand Approach Unit Vector Dot Products.
Table 3.1 demonstrates each hand approach unit vector pair used to calculate all possible angles between each hand approach unit vector group. Each ‘X’ designates when a dot product is taken. There are 25 angle values per comparison per subject and a total of 15 angle comparison groups.

<table>
<thead>
<tr>
<th>Unit Approach Vector</th>
<th>$\hat{I}_{s1...s5}$</th>
<th>$\hat{I}_{f1...f5}$</th>
<th>$\hat{P}_{s1...s5}$</th>
<th>$\hat{P}_{f1...f5}$</th>
<th>$\hat{V}_{s1...s5}$</th>
<th>$\hat{V}_{f1...f5}$</th>
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</thead>
<tbody>
<tr>
<td>$\hat{I}_{s1...s5}$</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>$\hat{I}_{f1...f5}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\hat{P}_{s1...s5}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>$\hat{P}_{f1...f5}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>$\hat{V}_{s1...s5}$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>$\hat{V}_{f1...f5}$</td>
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</tr>
</tbody>
</table>

We then utilized the non-parametric ANOVA, the Kruskal-Wallis Test to determine whether or not each angle comparison group is statistically different from one another (Ross, 2014). We also computed the angles formed with the unit vector normal to each stimulus’s target location ($[\hat{I}_{P_{1...5}}], [\hat{I}_{R_{1...5}}]$) and compared hand approach unit vectors for each stimulus-speed condition to the target surface normal of the proper-perspective for the illusory and veridical speed mean approach unit vectors ($[\hat{I}_{s1...s5}] \cdot [\hat{I}_{P_{1...5}}], [\hat{P}_{s1...s5}] \cdot [\hat{I}_{P_{1...5}}], [\hat{I}_{f1...f5}] \cdot [\hat{P}_{f1...f5}], [\hat{P}_{f1...f5}] \cdot [\hat{R}_{1...11}]$), and the reversion perspective for the proper mean approach unit vector ($[\hat{P}_{s1...s5}] \cdot [\hat{R}_{1...11}], [\hat{P}_{f1...f5}] \cdot [\hat{R}_{1...11}]$). This allows us to determine whether or not there are similarities in hand approach under each experimental condition.
3.2.5 Speed Profiles

Next we examined the motor output variability from the trial-by-trial angular velocities in each trajectory-speed condition. Peak angular velocities were normalized as previously discussed in Section 2.2.6. Recall that normalization is attained by dividing the peak velocity between two minima by the sum of the peak velocity and the average velocity between the two minima to minimize possible allometric effects from different limb sizes across subjects (Lleonart et al., 2000). We binned the data using optimal binning procedures to examine the frequency histograms of the parameters of interest (Limpert & Stahel, 2011). We performed distributional analyses to estimate the Gamma parameters of each probability distribution as previously described in Fig. 2.6 and contrasted our results with our findings in Chapter 2.

3.3 Results

3.3.1 The Consequences of Speed Instructions on Hand Trajectory Paths

Hand path trajectory analysis using the Wilk’s Lambda Test reveal a dramatic change in the shape of all hand path trajectories performed under speed instructions in both the forward, goal-directed reach, and the automatic retraction (Fig 3.4). Recall that the values of $\Lambda*_{\propto,p,vE,vH}$ used to determine statistical significance are $\Lambda*_{lower} = \Lambda*_{\propto=0.05,p=3,vE=440,vH=5} = 0.945$ and $\Lambda*_{upper} = \Lambda*_{\propto=0.05,p=3,vE=600,vH=5} = 0.959$, defining the range in which $\Lambda*_{\propto=0.05,p=3,vE=474,vH=5}$ lies. When participants are instructed to reach quickly towards the target, reaches performed under the illusory percept are now shifted closer to reach trajectories performed under the veridical percept.
(Fig. 3.4a, b, Fig. 3.5). Recall how the signatures of movement under uninstructed natural speeds unfold, repeated in Fig. 3.4c, d (from Fig. 2.7a, b). The Wilk’s Lambda Test Statistic, \( \Lambda \leq [\Lambda_{lower} : \Lambda_{upper}] \), reveals that forward goal-directed reaches are statistically different in all pairwise comparisons (Fig. 3.4a-c). This differs from our previous findings under natural speed conditions (Fig. 2.8c), particularly in the pairwise comparison of forward path in the illusory vs. proper condition (Fig. 3.5c). When inspecting the uninstructed retractions under fast speeds, we find an increase in variance as well as changes in the curvature of path, particularly in the veridical case (Fig. 3.4b). However, Wilk’s Lambda values show that illusory and proper hand paths remain quite similar throughout the retractory movement (Fig. 3.5f). We do see a trend towards illusory and veridical retractions becoming similar as well, when compared to our analysis in Chapter 2, illustrating how these hand path trajectories are modulated by fast speed instructions. As expected, veridical and proper hand path trajectories are markedly different from one another in both movement classes (Fig. 3.4a, b, Fig. 3.5b, e).

When participants are instructed to reach slowly towards the targets on the reverspective and proper-perspective stimuli, we yet again discover changes in the shape and variance of each hand path trajectory (Fig. 3.4e, f, Fig. 3.6). Forward reaches on the reverspective stimulus under the illusory percept are now statistically different from both the veridical and proper hand path trajectory families (Fig. 3.4e, Fig. 3.6a, c). The automatic retraction under slow speed instructions (Fig. 3.4f) reveal hand path curvatures that are comparable to what we find under fast speed instructions (Fig. 3.4b) as opposed to our results in the natural speed condition (Fig. 3.4d). Wilk’s Lambda values for the
percentage of path complete in the automatic retractions of the hand under slow speed instructions are almost identical to those found under fast speed instructions (Fig. 3.6d-f, Fig. 3.5d-f, respectively). Again we obtain results indicating that illusory and proper hand path trajectories do not statistically differ from one another in this movement class. Veridical and proper hand paths, as anticipated, remained statistically different from one another in both the forward motion and uninstructed retraction (Fig. 3.4e,f, Fig. 3.6b,e).
Fig. 3.4: Hand Path Trajectory Profiles for Fast and Slow Speed Instructions. Hand path trajectory confidence intervals under the veridical percept are illustrated in green, under the illusory percept in blue, and under the proper percept in red. The mean of each trajectory family is designated in white. The y-axis denotes the direction of movement towards the target and back to rest. Fig. 3.4a,b depicts hand path trajectories for forward goal-directed movements (Fig 3.4a) and uninstructed retractions (Fig. 3.4b). Forward reaches made under slow speed instructions are found in Fig. 3.4e and the uninstructed retraction in Fig. 3.4f. Note changes in the curvature of reach under speed conditions when compared to trajectories performed under natural, uninstructed speeds (repeated in Fig. 3.4c,d from Fig. 2.7a,b). The illusory percept hand path trajectories (blue) in the forward reaches now markedly differ from both the veridical hand path trajectories (green)
and proper hand path trajectories (red) (Fig. 3.4a,e). See Fig. 3.5 and Fig. 3.6 for the statistical analyses of the hand path trajectories under speed conditions.

**Fig. 3.5:** Wilk’s Lambda Test Statistic for Fast Speed Instructions. Fig. 3.5a-c and Fig. 3.5d-f show pairwise comparisons of each condition’s hand path trajectory under fast speed instructions using calculated Wilk’s Lambda Values. Red lines found within each boxplot indicate the median Lambda value. The horizontal edges of each blue boxplot represent the 25th and 75th percentiles. Thick black dotted lines on each end of the boxplot indicate values that are not considered outliers, and red plus signs indicate any outlier values. Since the unfolding of movement is critical in determining how a participant performs each trial, the Lambda Values are calculated based on percentage of path completed (e.g. 25%, 50%, 75%, and 100%). The Wilk’s Lambda Test Statistic is given by $\Lambda_{\text{lower}} = \Lambda^{*_{\alpha=0.05,p=3,vE=440,vH=5}} = 0.945$ and $\Lambda_{\text{upper}} = \Lambda^{*_{\alpha=0.05,p=3,vE=600,vH=5}} = 0.959$, designated by the dotted lines and gray area. If $\Lambda \leq [\Lambda_{\text{lower}}, \Lambda_{\text{upper}}]$ (below the dotted lines and gray area), the trajectory families are statistically different. Fig. 3.5a and Fig. 3.5d show that veridical and illusory hand path trajectories are
statistically different from one another in both the goal-directed movement and uninstructed retraction, respectively. The same behavior is observed in the comparison of the veridical vs. proper forward hand path trajectories (Fig. 3.5b), as well as in the retraction (Fig. 3.5e). We discover a change when we compare the natural-speed (Fig. 2.8c) and the fast-speed case of Fig. 3.5c, in which illusory and proper hand paths are now statistically different from one another, as opposed to what we found when no speed instructions are given (Fig. 2.8c). However, Fig. 3.5f shows that Lambda values in the uninstructed retraction remain statistically similar for the comparison of illusory and proper hand path trajectories under fast speed conditions.

Fig. 3.6: Wilk’s Lambda Test Statistic for Slow Speed Instructions. Fig. 3.6a-c and Fig. 3.6 d-f show pairwise comparisons of each condition’s hand path trajectory under slow speed instructions using calculated Wilk’s Lambda Values. Red lines found within each boxplot indicate the median Lambda value. The horizontal edges of each blue boxplot represent the 25th and 75th percentiles. Thick black dotted lines on each end of the boxplot indicate values that are not considered outliers, and red plus signs indicate any outlier values. Since the unfolding of
movement is critical in determining how a participant performs each trial, the Lambda Values are calculated based on percentage of path completed (e.g. 25%, 50%, 75%, and 100%). The Wilk’s Lambda Test Statistic is given by \( \Lambda^{*}_{lower} = \Lambda^{*}_{\alpha=0.05,p=3,VE=440,vH=5} = 0.945 \) and \( \Lambda^{*}_{upper} = \Lambda^{*}_{\alpha=0.05,p=3,VE=600,vH=5} = 0.959 \), designated by the dotted lines and gray area. If \( \Lambda \leq [\Lambda^{*}_{lower}:\Lambda^{*}_{upper}] \) (below the dotted lines and gray area), the trajectory families are statistically different. Fig. 3.6a and Fig. 3.6d show that veridical and illusory hand path trajectories are statistically different from one another in both the goal-directed movement and uninstructed retraction, respectively. The same behavior is observed in the comparison of the veridical vs. proper forward hand path trajectories (Fig. 3.6b), as well as in the retraction (Fig. 3.6e). We discover a change when we compare the natural-speed (Fig. 2.8c) and the slow-speed case of Fig. 3.6c, in which illusory and proper hand paths are now statistically different from one another, as opposed to what we found when no speed instructions are given (Fig. 2.8c). However, Fig. 3.6f shows that Lambda values in the uninstructed retraction remain statistically similar for the comparison of illusory and proper hand path trajectories under slow speed conditions.

3.3.2 Hand Orientation Transformations under Speed Conditions

When examining the orientation of the hand as it approaches the target in each stimulus-speed condition, we find that hand-approach unit vectors, in nearly all cases, do not differ from one another when comparing all possible angles formed between each hand approach unit vector, each case displaying high levels of variability (Table 3.2). Hand orientations for representative subject VT, for example, demonstrate these results (Fig. 3.7). Each triangle represents the plane formed by sensors located on the wrist, thumb, and index finger (Fig. 2.5b). Recall that angles are determined by finding the normalized unit vector of approach (formed by the wrist sensor location and the midpoint between the thumb and index sensor positions) and taking the dot product between each unit approach vector condition. See the dramatic changes in hand posture for both the fast and slow speed instruction conditions as compared to when Subject VT was not given any speed constraints.
Fig. 3.7: Hand Orientation at the End of the Goal-Directed Reach from Representative Subject VT.
Each colored triangle represents the area formed when determining the location of sensors located on the wrist, thumb, and index finger in each condition. These triangles are representative of the orientation of the hand at the end of the goal-directed trajectory, whereby subjects complete their forward reach towards the target. See Fig. 2.5b for a detailed explanation. Hand postures under the veridical reverceptive percept are in green, illusory reverceptive in blue, and proper-perspective in red. Fig 3.7a displays hand orientations under natural speed conditions for Representative Subject VT, from the experiments described in Chapter 2. Note that the angles of approach in the veridical case (green) markedly differ from hand postures in the illusory case (blue), although both conditions share the same physical stimulus. We also find that hand orientations under the illusory percept in Fig 3.7a are similar to those performed on the proper-perspective condition (red). Fig. 3.7b illustrates what happens to these hand orientations once fast speed instructions are introduced; notice that there is a tendency for the orientations in the veridical case (green) to cluster separately from the illusory (blue) and proper (red) triangles. Fig 3.7c displays results when slow speed instructions are given. Veridical hand orientations notably change in direction, along with orientations found in the illusory and proper cases. An increase in variance is also visible from this illustration. Tables 3.1-3.5 go into the in-depth analysis of these phenomena for the group data.
Using the Kruskal-Wallis Test, we show that, for all 15 group angle assessments (which totals to 105 comparisons for each participant), only four comparisons statistically differ from one another (yellow highlighted cells in Table 3.2). We also see high levels of variability throughout each case, including in our groups that reject the null hypothesis ($p < 0.05$). This finding suggests that regardless of the physical stimulus, the family of angles formed under veridical, illusory, and proper conditions fall under the same probability distribution, thereby holding no significant difference between trials. This may be due to an increase in motor noise via the uncertainty that is introduced into the sensory-motor system once speed instructions are given.

When comparing conditions under fast speed instruction, we no longer see a significant difference $\angle$ Illusory & Proper vs. $\angle$ Veridical & Proper angle comparisons ($p = 0.142 \pm 0.329$) (Table 3.2). Hand orientations under slow speed instructions follow a similar trend ($p = 0.130 \pm 0.323$) (Table 3.2). This is inconsistent with our findings under natural speed conditions ($p = 9.5608e-10 \pm 6.8917e-14$) (Table 2.1), in which these group comparisons, as we hypothesized, would be quite different. If subjects acted on the illusory target location on the reverspective stimulus, which would be similar in nature to the physical target on the proper-perspective, then angles between illusory and proper unit hand approach vectors would differ from the angles formed between illusory and veridical unit hand approach vectors. Note the high levels of variability found in our speed measures, signifying that our key finding here is in the increased variability between hand postures, regardless of the speed condition (Table 3.2). What this tells us is
that speed constraints affect the orientation of the hand towards the targets, dampening the influence of perceptual inputs on motor trajectories.

**Table 3.2: P-values using the Kruskal-Wallis Test to Compare Angles Formed by Hand Approach Unit Vectors.**

Table 3.2 compares the angles formed (\(\angle\)) by hand unit approach vectors in each stimulus-speed condition using the Kruskal-Wallis Test. Speed comparisons were designated as follows: FF=Fast-Fast, FS=Fast-Slow, and SS=Slow-Slow (e.g. Veridical vs. Illusory FS = Veridical Fast vs. Illusory Slow). Recall that the Kruskal-Wallis Test is a non-parametric method (similar to an ANOVA) that uses median ranks to determine whether or not samples come from the same distribution. Values of \(p < 0.05\) indicate significantly different groups (indicated by red text and yellow highlight). All angle comparisons grouped by stimulus condition do not reject the null hypothesis. Across all comparisons, high levels of variability are seen. When angle group comparisons are statistically different, the variability within this metric reduces any allometric effects. This implicates that each angle comparison group belongs to the same distribution. Also notice the high levels of variability present in these metrics. These results suggest that speed instructions may introduce a form of motor noise, causing our movements to be less precise than what we find under natural speeds.

<table>
<thead>
<tr>
<th>Hand Approach Unit Vectors that Form Angle Group</th>
<th>Veridical vs. Veridical FS</th>
<th>Proper vs. Proper FS</th>
<th>Illusory vs. Veridical FF</th>
<th>Illusory vs. Proper FS</th>
<th>Illusory vs. Illusory SF</th>
<th>Illusory vs. Veridical SS</th>
<th>Illusory vs. Proper SS</th>
<th>Veridical vs. Proper FS</th>
<th>Veridical vs. Proper SS</th>
<th>Veridical vs. Proper SF</th>
<th>Veridical vs. Proper SS</th>
<th>Illusory vs. Illusory FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value</td>
<td>0.871 0.978 0.362 0.402 0.200 0.294 0.812 0.776 0.715 0.548 0.080 0.120 0.119 0.138</td>
<td>0.293 0.047 0.448 0.434 0.361 0.430 0.403 0.411 0.414 0.430 0.182 0.325 0.313 0.334</td>
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<tr>
<td>STD</td>
<td>0.260 0.470 0.484 0.436 0.471 0.389 0.456 0.427 0.453 0.266 0.266 0.402 0.366</td>
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<tr>
<td>P-value</td>
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<tr>
<td>STD</td>
<td>0.306 0.470 0.484 0.436 0.471 0.389 0.456 0.427 0.453 0.266 0.266 0.402 0.366</td>
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<tr>
<td>Proper vs. Proper FS</td>
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<tr>
<td>STD</td>
<td>0.421 0.462 0.338 0.436 0.405 0.386 0.402 0.369 0.049 0.094 0.258 0.543</td>
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<tr>
<td>Illusory vs. Veridical FF</td>
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<tr>
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<td>Angle Group</td>
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<td>Illusory vs. Veridical SS</td>
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<td>0.323</td>
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<tr>
<td>Illusory vs. Proper FF</td>
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<td>0.025</td>
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<td>0.210</td>
<td>0.853</td>
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<td>0.293</td>
<td>0.440</td>
<td>0.423</td>
<td>0.471</td>
<td>0.419</td>
<td></td>
</tr>
<tr>
<td>Illusory vs. Proper FS</td>
<td>0.783</td>
<td>0.025</td>
<td>0.705</td>
<td>0.210</td>
<td>0.293</td>
<td>0.286</td>
<td>0.293</td>
<td>0.440</td>
<td>0.423</td>
<td>0.471</td>
<td>0.419</td>
<td></td>
</tr>
<tr>
<td>Illusory vs. Proper SS</td>
<td>0.371</td>
<td>0.172</td>
<td>0.387</td>
<td>0.363</td>
<td>0.356</td>
<td>0.333</td>
<td>0.439</td>
<td>0.437</td>
<td>0.469</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veridical vs. Proper FF</td>
<td>0.933</td>
<td>0.172</td>
<td>0.187</td>
<td>0.363</td>
<td>0.158</td>
<td>0.333</td>
<td>0.284</td>
<td>0.426</td>
<td>0.447</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veridical vs. Proper FS</td>
<td>0.171</td>
<td>0.294</td>
<td>0.157</td>
<td>0.371</td>
<td>0.170</td>
<td>0.320</td>
<td>0.284</td>
<td>0.457</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veridical vs. Proper SS</td>
<td>0.090</td>
<td>0.090</td>
<td>0.846</td>
<td>0.308</td>
<td>0.688</td>
<td>0.402</td>
<td>0.845</td>
<td>0.402</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veridical vs. Proper SF</td>
<td>0.848</td>
<td>0.090</td>
<td>0.845</td>
<td>0.090</td>
<td>0.347</td>
<td>0.402</td>
<td>0.885</td>
<td>0.402</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
We next evaluated how speed affects the angle formed between mean unit approach vectors and unit vectors normal to target surface locations. With the implementation of speed instructions, the mean angles between mean hand approach unit vectors and target surface normals produce values similar to what we find under natural speed conditions (Tables 2.2, 3.3). However, the variability is significantly higher when speed instructions are introduced. Recall in our previous work that under natural speed conditions, mean illusory hand approach unit vector and the unit vector normal to the reverspective’s physical target location produced an angle close to 90 degrees (84.008º ± 13.829) (Table 2.2). We obtain a mean angle value of 76.465º ± 20.930 for the fast speed condition and a mean angle of 81.294º ± 18.441 for the slow speed condition (Table 3.3). The variance has nearly doubled in the speed cases. For the angle between the mean veridical hand approach unit vector and the target surface normal, under natural speed conditions we had obtained an angle of 46.076º ± 16.101 (Table 2.2). For the speed cases, fast speed instructions produce an angle of 54.014º ± 23.521 and slow speed instructions generate an angle value of 53.328º ± 23.075 (Table 3.3). We again demonstrate higher spreads in angle variability.

We do not find this large increase in variability when calculating the angle between the mean proper hand approach unit vectors in relation to the proper-perspective target’s surface normal (17.772º ± 8.362 under natural speed conditions (Table 2.2) vs. 16.176º ± 8.115 under fast speed instruction and 14.697º ± 7.265 under slow speed instruction (Table 3.3)). This suggests that hand orientations towards the proper-perspective stimulus remain invariant to speed constraints. Interestingly, the illusory hand
approach unit vectors formed mean angles with the proper-perspective’s target surface normal that are similar to what we find under natural speed conditions (18.377° ± 9.286 for natural speed vs. 22.390° ± 15.003 and 19.151° ± 11.571 for fast and slow, respectively.

These results suggest that although we see an increase in variance in hand postures with respect to the reverspective’s target surface location normal, mean angle values calculated from the hand approach unit vectors and target surface normals still resemble our findings under natural speed conditions. It may be that at the motor end, the introduction of speed instructions adds cognitive load to the task, as it is another higher-level goal to process before launching the movement forward. Perhaps this increase in cognitive load leaks into the motor implementation adding motor noise to the system. This can be appreciated in the highly variable hand postures manifested when reaching for targets on the reverspective stimulus. At the perceptual end, apparently, the reverse-perspective stimulus tends to confuse the motor system under speed instructions, perhaps because of its bistable perceptual nature. Hand orientations towards the proper-perspective exhibit less noise, suggesting that the type of motor noise is separable across conditions and may selectively reveal they type of percept that the system experiences.
Table 3.3: Angle between Mean Hand Approach Unit Vectors and Target Surface Normals for Speed Conditions.

Table 3.3 calculates the angles formed between the mean hand approach unit vector and the target surface normals found on each stimulus under fast speed and slow speed instructions. Under fast speed conditions, the angle between the mean illusory hand approach unit vector and the actual unit vector normal to the target’s location is $76.465^\circ \pm 20.930$, whereas the mean veridical hand approach unit vector and the target surface normal produce an angle value of $54.014^\circ \pm 23.521$. When participants are given slow speed instructions, the angle between the mean illusory hand approach unit vector and the actual unit vector normal to the target’s location is $81.294 \pm 18.441$, whereas the mean veridical hand approach unit vector and the target surface normal produce an angle value of $53.328 \pm 23.075$. Recall that the reverspective stimulus generates nearly 90-degree maximal differences between illusory and veridical perceptual states. One would expect that illusory mean hand approach unit vectors would form an angle close to $90^\circ$ if participants reach towards the illusory target. Although mean angle values are similar to what we find under natural speed conditions (Table 2.2), a high level of variability is present in the reverspective conditions. Taken together, these results suggest that speed instructions introduce a source of motor noise to the system, dampening any contributions from perceptual inputs that we previously discovered when subjects reached at natural speeds.

<table>
<thead>
<tr>
<th>Speed</th>
<th>Target Surface Normal Unit Vector Location</th>
<th>Mean Hand Approach Unit Vector</th>
<th>Mean Angle ± S.D. (degrees) Between Mean Hand Approach Unit Vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast</strong></td>
<td>Reverspective Stimulus</td>
<td>Veridical</td>
<td>54.014 ± 23.521</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Illusory</td>
<td>76.465 ± 20.930</td>
</tr>
<tr>
<td></td>
<td>Proper-Perspective Stimulus</td>
<td>Veridical</td>
<td>40.534 ± 22.585</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Illusory</td>
<td>22.390 ± 15.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proper</td>
<td>16.176 ± 8.115</td>
</tr>
<tr>
<td><strong>Slow</strong></td>
<td>Reverspective Stimulus</td>
<td>Veridical</td>
<td>53.328 ± 23.075</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Illusory</td>
<td>81.294 ± 18.441</td>
</tr>
<tr>
<td></td>
<td>Proper-Perspective Stimulus</td>
<td>Veridical</td>
<td>88.925 ± 13.569</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Illusory</td>
<td>40.067 ± 23.514</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proper</td>
<td>19.151 ± 11.571</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14.697 ± 7.265</td>
</tr>
</tbody>
</table>
3.3.3 Changes in Velocity-Dependent Kinematics: Normalized Peak Angular Velocity Distributions

We empirically estimated the underlying probability distributions of the normalized peak angular velocities for both the forward reach and uninstructed retraction to characterize possible relationships between illusory, veridical, and proper conditions under fast and slow speed instruction (Fig. 3.8, Fig. 3.9). We first present our findings for the fast speed instruction case. Fig. 3.8a demonstrates that probability distributions for the normalized peak angular velocity for the forward movement are now more similar in shape and scale, as further demonstrated in Fig. 3.8c. Please refer to Fig. 3.9 to see how each of the velocity-dependent indices contrast with our results from Chapter 2 (when participants are under natural speed conditions) and results from slow speed instruction. The shape and scale parameters of the Gamma probability distribution exposes different patterns of motor variability when compared to natural speed shape and scale parameters, illustrating a close clustering of the all normalized peak angular velocity distributions for the forward reach towards the bottom right of the Gamma plane (see blue (illusory), red (proper), and green (veridical) filled diamonds in Fig. 3.8c and colored asterisks in Fig. 3.9c). Recall that as points shift up and to the left of the Gamma plane (i.e. large scale values and small shape values near $a=1$ the memory-less Exponential distribution), the system is noisier and more random. These statistical features suggest less controllability of angular rotations of the hand represented by the probability distribution of normalized peak angular velocities. As points shift to the bottom right corner of the Gamma plane, the signatures of variability dampen the noise to signal ratio and approach the symmetric shape resembling a Gaussian distribution. A stable expected value of the rate of change of angular rotations can be predicted with higher certainty, suggesting that movements
have a higher probability of being under tight control (Fig. 3.8b, filled circles in Fig. 3.8c, and colored squares in Fig. 3.9a).

The illusory normalized peak angular velocity distribution demonstrates a slight separation from the veridical distributions in the uninstructed retraction in the Gamma plane (see blue (illusory), red (proper), and green (veridical) filled circles in Fig. 3.8a and blue square in Fig. 3.9a). We previously reported that veridical and proper shape and scale parameters are distinct from one another in the uninstructed retraction (Fig. 3.9a, filled diamonds and filled circles). Here we find the opposite, wherein the shape and scale of the estimated Gamma probability distributions for veridical, illusory, and proper normalized peak angular velocities are strikingly similar to one another (Fig. 3.8c).

The Gamma parameters also overlap with what we find in the forward reach. What this suggests is that both movement classes are under similar control strategies – it seems as though retractions are not as spontaneous as they were under implicit speed selection. Very probably, the influence of speed instructions and the load that this adds to the task leaks into the automatic retractions of the hand as it returns to rest. When we map the log of the Gamma parameters to better visualize the data (since we know it is governed by power law), we find signatures suggestive of tight control over illusory forward reaches, but we do not find this in the retraction (Fig. 3.9b). Note that control under fast speed conditions, the veridical and proper log Gamma parameters directly overlap with these values for the retraction.
Fig. 3.8: Gamma Probability Distribution under Fast Speed Instructions. Fig. 3.8a-b illustrate the Gamma probability density function that is fitted to the underlying probability distribution of normalized peak angular velocities of the hand during the goal-directed reach (Fig. 3.8a) and the uninstructed retraction of the hand back to rest (Fig. 3.8b) when fast speed instructions are given. The illusory condition is shown in blue, the veridical in green, and the proper in red. The Gamma parameter plane spanned by the shape ($a$) and scale ($b$) parameters for each empirically estimated Gamma function is shown in Fig. 3.6c. Filled diamonds designate forward goal-directed shape and scale parameters, and filled circles illustrate the supplemental retractions. 95% confidence intervals from the MLE procedure are depicted by the crosshairs. The log-log plot of the Gamma plane is also shown to characterize the Gamma parameters by the exponential fit: $f(x) = 0.7841 \times x^{-1.024}$, with coefficients (see text for details on goodness of fit and 95% confidence intervals). The Gamma statistics, the mean ($\mu_W$) and the variance ($\sigma^2_W$) parameters were estimated from the shape and scale parameters and plotted in the Gamma mean-variance parameter plane (Fig. 3.8d).
Fig. 3.9: Summary of the Normalized Peak Angular Velocity Index
Velocity-dependent kinematic parameters are mapped as an index of the normalized peak angular velocity probability distributions under natural speeds (colored diamonds and colored circles), fast speed instruction (colored asterisks and colored squares), and slow speed instruction (colored X’s and colored triangles). Motor trajectories performed under the illusory percept are marked in blue, veridical percept in green, and under the proper-perspective stimulus in red. Fig. 3.9a illustrates the Gamma plane of shape and scale parameters for both movement classes, showing overlap in the control of angular rotations of the hand in several cases. Points that shift towards the bottom right of the Gamma plane towards small scale parameter values and larger shape parameter values indicate tighter control of our movements. Recent studies show that points that tend to the opposite, left upper corner are subject to higher levels of motor noise, either due to higher levels of variability contributed by the numerator of the Fano Factor ratio, or to lower mean values in the denominator. We discover a power law governing the motor output variability in response to perceptual stimuli. The shape and scale parameters automatically separate into distinct percept classes when the log of the shape and scale parameters is taken (Fig. 3.9b). The shifts along this unit line indicate how perceptual inputs and speed control modify complex patterns of sensory-motor behavior. In Fig. 3.9c, we plot the estimated Gamma means and variances.
The power law that governs the Gamma parameters of our model of motor-sensing behavior under fast speed instruction (inset in Fig. 3.8c) is given by $f(x) = \alpha * x^\beta$ with coefficients and 95% confidence intervals in brackets, in which $\alpha = 0.7841$ [0.6128, 0.9554] for the intercept and $\beta = -1.024 [-1.074, -0.9739]$ for the slope. The goodness of fit for our model results in an $R^2$ value of 0.9989, with the Sum of Squares due to Error (SSE) at a value of $3.79 * 10^{-8}$, and the Root Mean Square Error (RMSE) at $9.734 * 10^{-5}$. Across speed condition the confidence intervals of the exponents and intercepts significantly overlap. One power law relation governs our model of perceptual influences on motor output variability and scatter of points shift along this unity line as the micro-movements signatures of variability change with different stimulus-speed condition (Fig. 3.9b). We have found an objective way to quantify changes across different behavioral contexts within the same basic task.
Table 3.4: Power Law Equations Governing Velocity-Dependent Kinematic Parameters Under Perceptual and Speed Changes.

Table 3.4 gives values for all power laws derived by speed conditions. As you can see, the confidence intervals of each coefficient $\alpha$ and $\beta$ overlap, implicating that a general power law function governs all observed behaviors within our study of perceptual inputs and speed inputs. The power law governing this phenomenon is given in the “All Conditions” column.

<table>
<thead>
<tr>
<th>Power Law Equation: $f(x) = \alpha * x^\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ (95% CI)</td>
</tr>
<tr>
<td>$\beta$ (95% CI)</td>
</tr>
<tr>
<td>SSE</td>
</tr>
<tr>
<td>$R^2$</td>
</tr>
<tr>
<td>RMSE</td>
</tr>
</tbody>
</table>

Fig. 3.8d and 3.9c report the mean ($\mu_w$) and variance ($\sigma_{w^2}$) for each condition and movement class under fast speed instruction. Under fast speed instructions, what we see is a shift towards higher mean values and less variability in the motions (Fig. 3.9c). Higher mean values of the normalized peak velocity index indicate slower rates of angular rotations on average in relation to the implicitly chosen speed. This reduction occurs because the average angular speed term drops its value in the denominator of this index. Red asterisks designate kinematic indices derived from fast goal-directed movements, and supplementary retractions are given as colored squares. Both the means and variances of the normalized peak angular velocity probability distribution contribute to these shifts (Table 3.5). The variance is much lower with the instructed speed, indicating that participants maintained speed levels in fast speed instructions. Based on these parameters, Table 3.5 calculates the Fano Factor, $F = \frac{\sigma_{w^2}}{\mu_w}$, a measure of the index of dispersion. Note that the Fano Factors for normalized peak angular velocities are now
similar in the uninstructed retractions in veridical and proper conditions (0.0114 and 0.0108 respectively), whereas the illusory Fano Factor demonstrates a lower noise-to-signal ratio (0.0085). As it turns out, motions under instructed speed conditions are much less variable in the illusory condition than what we find under natural speeds (Table 3.5). Since participants are instructed to maintain a fast pace, the drop in the value of the Fano Factors suggests that normalized peak angular velocity distributions are very likely under tighter sensory-motor control in the forward reach. Supplementary retractions of the hand back to rest are more variable under fast speed conditions (Fig. 3.8d, Fig. 3.9c). These higher levels of motor variability may account for the loss of separable percepts, as speed changes with the explicit speed instructions affect both movement classes under study.

When we empirically estimate the underlying probability distributions of normalized peak angular velocities in the slow speed condition, we again find differences between forward, goal-directed normalized peak angular velocity distributions and the uninstructed retraction (Fig. 3.9, Fig. 3.10). Normalized peak angular velocities in the veridical case are less variable than what we find in the illusory and proper conditions, implicating a tight adherence to speed instructions (colored X’s and triangles Fig. 3.9a,b, Fig 3.10c). When compared to results under natural speed conditions, again we find that the implementation of speed instructions, regardless of the instruction (fast or slow), induce less automated control of the rotations of the arm (slower and more variable motions). We also see more ambiguity in the segregation of each stimulus condition. These shifts suggest that rotational movements under the speed instruction may be under more deliberate control than when choosing speed implicitly. The implementation of these instructions brings more variability to the movements and slows them down too.
The speed instructions seem to undermine the striking differences between stimulus conditions that we previously quantified in Chapter 2.

**Table 3.5: Fano Factor Calculations for the Distribution of Normalized Peak Angular Velocities under Speed Instructions.**

The Fano Factor $F = \frac{\sigma^2_w}{\mu_w}$ measures the level of dispersion of each estimated Gamma probability distribution of the normalized peak angular velocities in each condition. The mean is designated as $\mu_w$, and the variance as $\sigma^2_w$ for time window $w$. Note that we find low variance values in all cases, implicating that the joint rotations underlying the linear displacements of the hand in each condition are under tight control. Fano Factor values for the veridical and proper conditions are comparable in the uninstructed retraction, which is markedly different from the Fano Factors calculated for under natural speed conditions (natural speed values taken from Table 2.3, Fig. 3.9). These findings suggest that speed instructions gives rise to movements with higher motor variability when acting on the physical geometry of the reverspective and proper-perspective stimuli (veridical and proper conditions respectively).

<table>
<thead>
<tr>
<th>Speed Condition</th>
<th>Goal-Directed Reach</th>
<th>Uninstructed Retraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Illusory</td>
<td>0.0096 / 0.6608 = 0.0146</td>
<td>0.0089 / 0.6496 = 0.0137</td>
</tr>
<tr>
<td></td>
<td>0.0057 / 0.6636 = 0.0086</td>
<td>0.0034 / 0.6632 = 0.0052</td>
</tr>
<tr>
<td></td>
<td>0.0094 / 0.6695 = 0.0140</td>
<td>0.0081 / 0.6502 = 0.0125</td>
</tr>
<tr>
<td>Fast Illusory</td>
<td>0.0035 / 0.6920 = 0.0050</td>
<td>0.0060 / 0.7091 = 0.0085</td>
</tr>
<tr>
<td></td>
<td>0.0046 / 0.6922 = 0.0066</td>
<td>0.0080 / 0.7038 = 0.0114</td>
</tr>
<tr>
<td></td>
<td>0.0041 / 0.7060 = 0.0059</td>
<td>0.0077 / 0.7165 = 0.0108</td>
</tr>
<tr>
<td>Slow Illusory</td>
<td>0.0028 / 0.6858 = 0.0041</td>
<td>0.0038 / 0.7155 = 0.0053</td>
</tr>
<tr>
<td></td>
<td>0.0019 / 0.6668 = 0.0028</td>
<td>0.0032 / 0.7036 = 0.0046</td>
</tr>
<tr>
<td></td>
<td>0.0026 / 0.6987 = 0.0037</td>
<td>0.0033 / 0.7146 = 0.0046</td>
</tr>
</tbody>
</table>
Fig. 3.10: Gamma Probability Distribution under Slow Speed Instructions.  
Fig. 3.10a-b illustrate the Gamma probability density function that is fitted to the underlying probability distribution of normalized peak angular velocities of the hand during the goal-directed reach (Fig. 3.10a) and the uninstructed retraction of the hand back to rest (Fig. 3.10b) when slow speed instructions are given. The illusory condition is shown in blue, the veridical in green, and the proper in red. The Gamma parameter place spanned by the shape (a) and scale (b) parameters for each empirically estimated Gamma function is shown in Fig. 3.10c. Filled diamonds designate forward goal-directed shape and scale parameters, and filled circles illustrate the supplemental retractions. 95% confidence intervals from the MLE procedure are depicted by the crosshairs. The log-log plot of the Gamma plane is also shown to characterize the Gamma parameters by the exponential fit: $f(x) = 1.185 \times x^{-1.103}$, with coefficients (see text for details on goodness of fit and 95% confidence intervals). The Gamma statistics, the mean ($\mu_W$) and the variance ($\sigma^2_W$) parameters were estimated from the shape and scale parameters and plotted in the Gamma mean-variance parameter plane (Fig. 3.10d).
We revisit the mean ($\mu_w$) and variance ($\sigma_{w^2}$) calculations for each condition and movement class under slow speed instructions (Fig. 3.9c, 3.10d, Table 3.5). The Gamma estimated mean-variance plane in goal-directed reaches under slow speed conditions shows higher mean values for normalized peak angular velocity probability distributions (this indicates slower rates of angular rotations on average). The differences we find under slow speed instruction are not as distinct as what we find under natural speed conditions (Fig. 2.8c, 2.9d). The calculated Fano Factors for the slow speed case are given in Table 3.5. Note that the Fano Factors for normalized peak angular velocities are now similar in the uninstructed retractions in veridical, illusory, and proper conditions (0.0046, 0.0053, and 0.0046 respectively). As it turns out, goal-directed motions under slow speed conditions are less variable than what we find under natural speed conditions.

Uninstructed retractions show lower Fano Factor values due to large mean values in the denominator of this ratio. Recall that the Fano Factor calculated under natural speed conditions for the veridical forward reach is 0.0086, whereas the Fano Factor for the same stimulus condition under slow speed instructions is 0.0028. Since participants are instructed to maintain a slow speed condition, the motions are more deliberate than when implicitly choosing the comfortable speed level. This reflects in the retractions as well, which under speed instruction become more systematic (less variable from trial to trial).

Under instructed speeds, we see changes in the temporal dynamics of both the forward and the backwards movement segments. These changes contribute to the
lowering of the distinction across perceptual input types. Our findings suggest that angular rotations of the hand back to rest become more deliberate than under implicit speed. The full reach loop is staged to maintain the instructed speed and as a consequence the former spontaneous retractions are under tighter cognitive control than when no instruction was provided. We have captured these phenomena in the patterns of variability of the hand trajectories as they unfold from moment to moment (Fig. 3.9c). In contrast to our results in the fast speed instruction paradigm (Table 3.4), instructed slow speed retractions are more systematic than other stimulus-speed conditions. The increase in the mean peak velocity index due to slow down in the average rate of rotation from trial to trial make these trajectories susceptible to a higher motor noise. We see that the velocity-dependent kinematic parameters of the hand’s retraction back to rest may in fact be modulated by perceptual inputs (blue triangle for illusory retraction under slow speed instructions, and blue square for fast speed instructions in Fig. 3.9b). Under the speed instruction, it is possible that there is a delay in experiencing the illusory percept so the modulation is caught in the retraction rather than in the forward reach. This scenario brings us back to Fig. 3.1c in the introduction of this Chapter when an explicit decision making process intrinsically modulated the speed of the reach loop and leaked into the retraction trajectories, making them slower, more variable and overall more deliberate than they would be otherwise. A motor decision on temporal dynamics is necessary in the instructed speed condition and the data that we present here seems to have characterized that very process.
3.4 Discussion

Our findings, taken together with the observations made in Chapter 2, indicate that the implementation of speed instructions, regardless of the temporal resolution, induces more deliberate control of the full reach loop. The movement classes under perceptual state changes are less distinct and the speed invariance that we quantify in automated reaches becomes less obvious. That being said, we discover high levels of variability in the spatial transformations of the hand when reaching for targets on each stimulus, as well in the curvature of the trajectories toward the goal and back to rest. This discovery of increased variability in the spatial domain is consistent with other studies that find evidence for fast and slow speed instructions to cause large spatial errors in reaching (Messier, Adamovich, Berkinblit, Tunik, & Poizner, 2003). Messier et al. also identified that these errors were not present when speeds were uninstructed.

The increased variability in sensory-spatial transformations under speed instructions may emerge from a decision-making process that is bound to become more obvious to the system in the presence of an illusory percept. This bi-stable percept may contribute to the increase in uncertainty about choosing the proper movement dynamics for the percept type. This in turn may increase motor noise levels. Motor trajectories under the illusory percept are now bounded by trajectories under the veridical reverperspective stimulus condition and the proper-perspective condition, statistically differing from both cases (Fig. 3.5, Fig. 3.6). We speculate that this finding is a result of perceptual inputs still contributing to the geometric transformation of the hand, adding delays with the introduction of speed instructions. This may dampen the signal, as
subjects must attend to the regulation of temporal dynamics in addition to experiencing changes in perceptual states.

The present results bring into question the validity of past work on perception-action modeling that claims that fast movements are impervious to top-down perceptual influences, while slow movements remain susceptible to them (Goodale, Gonzalez, & Króliczak, 2008; Kroliczak, Heard, et al., 2006). One cannot oversimplify patterns of sensory-motor behavior to make such assumptions: we illustrate that there are complex processes at work that integrate multiple streams of sensory information to produce our motor outputs. We show that, regardless of the speed instruction given to participants, speed in itself modulates signatures of motor output variability that are not indicative of one perceptual state over another in the sensory-spatial domain.

In light with previous work we do not find evidence for differences in postural control under the influence of instructed speeds (Nishikawa et al., 1999; Torres & Zipser, 2004). We also discovered indices of velocity-dependent kinematics that segregate each stimulus condition. These metrics are not as clearly separable as they are when subjects perform the experiment under natural speed conditions, but we do see a trend towards this separation when we explore the class of supplementary, transitional movements. The automatic retractions of the hand under speed conditions indicate that velocity-dependent kinematics under the illusory percept begin to segregate from the temporal profiles found under the veridical and proper percepts (Fig. 3.9b). Because illusory retractions are more susceptible to motor noise under speed instruction, when compared to the tight control
found in veridical and proper conditions, it may be possible that perceptual inputs influence the class of supplementary motions more so than they do in the goal-directed reach in the temporal domain.

In this chapter, we uncovered the effects that additional instructions have on the movement kinematics as their variability in temporal dynamics unfolds from moment to moment. The main result was that the entire forward and back loop turned deliberate according to the signatures of speed variability. In particular the retraction trajectories acquired features of staged forward reaches with highly systematic values in the mean and variance from trial to trial. The motions during this portion of the loop became less variable and lowered their average angular rotational speeds (as indicated by an increase in the normalized peak angular velocity index), a feature that is conducive of higher controllability. These otherwise highly automated motions turned into a perceptuo-motor decision making process, one that unfolded as the hand retracted to rest and that we were able to characterize as they changed with respect to the implicitly chosen speeds of Chapter 2. We next explore these malleable retracting motions as they seem to broadcast rather accurately perceptual states with different levels of intent and mental awareness. How do they manifest in patients with mental illness where the borderline between physical and imaginary realities may be blurred?
Chapter 4 Translating our Basic Science Research Tool into Clinical Applications

4.1 Motivation

We now shift gears and focus our attention to the clinical arena. In Chapters 2 and 3, we demonstrated the utility of our statistical framework and continuous motor paradigm in clarifying longstanding issues within the psychological sciences. We discovered methods to objectively track changes in visual perceptual states by assessing the continuous flow of motor output variability in deliberate and automatic motions. Here we discuss a critical need in the behavioral neurosciences for objective metrics to gain a better understanding of the etiology of complex psychiatric disorders and to help pave the way for improved diagnostics and clinical treatments.

4.1.1 Issues Surrounding the Current Scope of Practices in Psychiatry

Recent technological advances have revolutionized our abilities to analyze human behaviors in the natural environment. On the contrary, psychiatry has remained stagnant in refining its current scope of practices, seemingly unwilling to adopt new methodologies that can transform our understanding of disorders of the brain (and body) (Kapur, Phillips, & Insel, 2012). The American Psychiatric Association has recently been under fire during the development of the current Diagnostic and Statistical Manual of Mental Disorders (DSM-V), as there is little to no scientific evidence cited in the DSM-V to back the descriptions and diagnostic criteria for mental disorders (Belluck & Carey, 2013; de Leon, 2013; Menand, 2010). Even the National Institutes of Mental Health...
(NIMH) recognize these issues, as they publicly withdrew support before the release of the DSM-V.

4.1.2 The Mind-Body Disconnect

So what explains psychiatry’s departure from a neurologically based, scientific approach to a framework that mainly relies on theoretical descriptors and observed symptomatology? Interestingly, studies dating back to the late 1800’s first characterized conditions (that we now believe to be hallmarks of schizophrenia (SZ)) as disorders of the motor system. Before the influential works of Sigmund Freud, Eugen Bleuler, and Emil Kraepelin shaped our current views on SZ, psychiatrist Karl Ludwig Kahlbaum defined catatonia (which according to the DSM-V is a subtype of SZ) motorically (D. M. Rogers, 1992). Kahlbaum described abnormalities in the posturing of the body, as well as the presence of muscle rigidity, spasms, jerking, and decreased responsiveness in patients with catatonia (Kahlbaum, 1973).

It was not until Kraepelin founded the theory of dementia praecox that we started to see the categorization of the psyche as a separate entity from the body (Kraepelin, Barclay, & Robertson, 1919). In addition, Bleuler went even further to claim that sensation and perception were unaffected by SZ, stating that there was no demonstrable evidence for sensory-motor issues (1950). Influenced by these conjectures, researchers focused their efforts on understanding high-level cognitive processes rather than on exploring the body’s role in embodying these mental states, widening the gap in knowledge on mind-body relationships and severely impeding the full characterization of
mental disorders from a physiologically-relevant lens (Rogers, 1985). Fortunately, in recent years, theories of embodied cognition have gained traction, reestablishing the link between the mind and the body to recognize the contributions of sensory-motor processes on shaping high-level executive functions (Caramazza, Anzellotti, Strnad, & Lingnau, 2014; Koziol, Budding, & Chidekel, 2012).

4.1.3 Motor Disturbances in Neurological and Mental Disorders

Although the literature reports motor abnormalities in many neurological and psychiatric disorders, clinical rating scales predominantly serve as the main assessment tool for analyzing these disturbances (Baker, Lane, Angley, & Young, 2008; Diederich et al., 2009; Lerner & Miodownik, 2011; Montero-Odasso & Hachinski, 2014; Parker, Lamichhane, Caetano, & Narayanan, 2013; Putzhammer & Klein, 2006). Steps have been made to objectively characterize these anomalies, but there is an absence of a unifying framework to collectively understand the causes of motor control dysfunction and how they relate to the perceptual abnormalities that coexist with these features. We therefore stress the critical need for the translation of basic science research tools in this domain.

Recent works highlight the importance of characterizing patterns of kinesthetic reaффerence through micro-movements in neurological disorders such as Parkinson’s disease and Autism Spectrum Disorders (ASD). This work has uncovered objective biomarkers that blindly identify sublevels of severity in different pathologies of the nervous system (Torres, 2012; Torres, Brincker, et al., 2013; Torres et al., 2014; Torres et al., 2011). These studies motivated us to apply our statistical framework to SZ. Moreover,
since visual perceptual abnormalities persist in the SZ population, this further influenced our decision to transition from the study of visual perceptual processes in the normative system to understanding the underlying sensory-motor issues in a system that is highly disrupted (Dima et al., 2012; Keane et al., 2012; Keane et al., 2013; Schneider et al., 2002; Silverstein & Keane, 2011a; S. M. Silverstein et al., 2013; Silverstein, Moghaddam, & Wykes, 2013; Silverstein, Spaulding, & Menditto, 2006; Uhlhaas & Mishara, 2007; Uhlhaas, Phillips, Mitchell, & Silverstein, 2006).

4.1.4 Schizophrenia: Insights from Vision Research

Traditionally, SZ has been defined as a disorder of cognitive impairment, with disruptions in functions such as memory, executive function, and attention (Silverstein & Keane, 2011b; Silverstein et al., 2013; Silverstein et al., 2006; Uhlhaas & Mishara, 2007). SZ is characterized by positive, negative, and disorganized symptoms that can range from the presentation of delusions and hallucinations, to avolition (the attenuation of willful behaviors), anhedonia (the inability to experience pleasure), and disorganized behaviors. The underlying pathophysiological mechanisms that cause these dysfunctions remain unclear.

However, evidence of visual perceptual issues in SZ clarifies the possible underpinnings of this debilitating disorder. Examples of impairments in visual perception include deficits in perceptual organization (PO). Recent studies find PO deficits in contour integration, form and motion perception, as well as in low spatial frequency processing, which typically signals information about global form (Fig. 4.1) (Dima,
Evidence of PO deficits suggests that visual dorsal stream connections that lead to the posterior parietal cortex (PPC) may in fact be compromised. As we discussed in Chapters 2 and 3, the PPC makes significant contributions to kinesthetic sensing, motor planning, and motor execution, serving as a possible epicenter for the integration of multiple sensory modalities (Andersen & Buneo, 2003; Buneo & Andersen, 2006; Cui & Andersen, 2011). PO impairments in SZ give us even more of a reason to characterize sensory-motor disruptions that may clue us into neurological underpinnings of the disorder. Our previous findings demonstrate our ability to track perceptual changes by objectively analyzing movement kinematics in goal-directed movements and supplementary motions. We now investigate how patterns of sensory-motor behavior are modulated within this disorder, as researchers are faced with many challenges when attempting to deconstruct and quantify the presentation of perceptual abnormalities.

**Fig. 4.1: Examples of Visual Stimuli in the Study of Perceptual Organization Deficits in Schizophrenia.**

Fig. 4.1a gives examples of a simple contour integration task given to patients with SZ to investigate perceptual organization deficits that are related to early visual processing. Figure adapted from Silverstein (2011). Fig. 4.1b illustrates the use of depth inversion illusions (DIIs) in SZ vision research, with the stimulus in the upper left panel in Fig. 4.1b being identical to the reverspective stimulus used in Chapters 2 and 3 (adapted from Keane et al. 2013).
4.1.5 Motor Variability in Schizophrenia: Symptoms vs. Side Effects

Recent works aim to identify motor disturbances attributed to SZ. Researchers have found evidence for motor disturbances in spatial and temporal domains when analyzing postural sway, gait disturbances, as well as in a number of goal-directed behaviors such as grip force and finger tapping (Ahlgren-Rimpilainen et al., 2010; Kappenman et al., 2015; Kent et al., 2012; Lallart et al., 2014; Mattheyse, Levy, Wu, Rubin, & Holzman, 1999; Putzhammer & Klein, 2006; Reuter et al., 2007; Teremetz et al., 2014; Walther, Vanbellingen, Muri, Strik, & Bohlhalter, 2013). But to our knowledge, the newly defined class of supplementary movements has not been studied within the SZ population, as the focus remains on measuring volitional control (and sometimes the lack thereof) (Barch & Dowd, 2010; Bender et al., 2013; Reuter et al., 2007; Tremeau, Nolan, Malaspina, & Javitt, 2012). Without the analysis of the important supplementary movement component to the continuous stream of natural behaviors, we cannot get a clear picture of what is inherently happening to the system.

Another issue that concerns the validity of these studies is how motor tasks are analyzed. Many of these studies assume that the underlying probability distribution of their datasets is Gaussian, and therefore apply statistical methods without knowledge of whether or not this holds true. We take a radically difference approach to the analyses of movement variability. Instead of smoothing out the minute fluctuations that the movement output has from moment to moment, we statistically characterize these micro-movements and empirically estimate the probability distributions that they most likely give rise to. By doing so in the typical population first and then in the various pathologies
of the nervous system, we find that normative statistics no longer apply. Performing the traditional hypothesis testing under the assumption of homogeneous variance is not a valid approach across these disorders. It is not that there is a shift in the mean of the distributions. It is rather that each patient has a different probability distribution. Any similarity across the population self-emerges and automatically subtypes the disorders according to the stochastic signatures of the micro-motions of different kinematics levels. This enables us to examine various population types as a function of other parameters (e.g. medications, clinical scores, etc.). The continuous family of Gamma probability distributions has been amenable to characterize both the typical and the atypical cases (Torres, 2012; Torres, Brincker, et al., 2013; Torres et al., 2014; Torres et al., 2011). By assuming that the behavioral data follows the theoretical Gaussian distribution, researchers may be unintentionally skewing results (Limpert & Stahel, 2011). Although these studies contribute to our understanding of SZ, the characterization of this disorder is still missing a unifying framework that can describe motor dysfunction in SZ reliably and objectively in relation to controls and also in relation to other pathologies of the nervous system.

Moreover, the debate surrounding motor control research in SZ revolves around the question as to whether or not these disturbances are features of the disorder, attributable to medication effects, or a combination of both (Frank et al., 2014; Keedy, Reilly, Bishop, Weiden, & Sweeney, 2015; Matsuda et al., 2014; Nowak, Connemann, Alan, & Spitzer, 2006; Tandon, 2011). A list of medications is provided in Appendix 1 to highlight the medication profiles of subjects in our study. Appendix 1 also brings our
attention to the presence of motor side effects associated with each drug (see red face font in Appendix 1). It is unclear as to whether or not motor disturbances are physical manifestations of SZ, if they are attributed to medication side effects, and/or if medications amplify/dampen the presentation of abnormal motor control. Regardless of the case, the presence of motor noise and the quantification of its properties may be a key factor in understanding how perceptual abnormalities attributed to the disorder arise. Since we look at stochastic signatures of movement on an individual level, we may be able to tease apart the nuances associated with the symptom vs. side effect debate. Here we present the application of our motor paradigm and statistical platform to objectively characterize patterns of sensory-motor behavior in SZ during a simple baseline-pointing task.

4.2 Methods
4.2.1 Participants

Written informed consent of the Rutgers University Institutional Review Board approved protocol in compliance with the Declaration of Helsinki was obtained before beginning the experimental session and after explaining the nature of the study and its implications. Compensation was provided to participants. Our subject sample consisted of 24 neurotypical controls (20 males, 4 female) and 23 schizophrenia patients (18 males, 5 females) (**Table 4.1**).

For all subjects, the inclusion/exclusion criteria included the following:

- Normal stereoscopic vision
- Normal or corrected-to-normal visual acuity
- Age 18–65 years
- No clinically significant head injury or loss of consciousness
- No diagnosis of neurological disease
- No diagnosis of mental retardation or pervasive developmental disorder
- No substance dependence in the past six months

Additional criteria for control group:
- No Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM–IV–TR) diagnosis of schizophrenia or any other psychotic or mood disorder (APA, 2000)
- No current psychotropic or cognition enhancing medication

Additional criteria for patient population:
- DSM–IV diagnosis of schizophrenia (SZ) or diagnosis of schizoaffective disorder (SA)

Note that out of the 23 patients, only one patient was not taking antipsychotic medication at the time of testing. We included this patient in our analysis since we determine stochastic signatures of sensory-motor behavior on an individual basis and would like to see how his results unfold in contrast to patients that are on antipsychotic medication. We also included patients with a diagnosis of schizoaffective disorder (SA) to see how their motor variability patterns compare to patients diagnosed with SZ with no co-morbidities.
Table 4.1: Demographic Information for Patients and Controls. Table 4.1 displays means and variances for patient and control demographics. Patients ranged from ages 22-57 (median age 47), whereas controls ranged from ages 18-64 (median age 45). Controls were recruited to match subjects as closely as possible to patients based on the demographic parameters listed in Table 4.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients</th>
<th>S.D.</th>
<th>Controls</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.83</td>
<td>11.99</td>
<td>44.04</td>
<td>12.68</td>
</tr>
<tr>
<td>Years of Education (Self)</td>
<td>12.26</td>
<td>2.32</td>
<td>13.41</td>
<td>1.56</td>
</tr>
<tr>
<td>Years of Education (Father)</td>
<td>10.82</td>
<td>3.85</td>
<td>11.35</td>
<td>3.32</td>
</tr>
<tr>
<td>Years of Education (Mother)</td>
<td>11.18</td>
<td>3.89</td>
<td>10.75</td>
<td>3.53</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>39.13%</td>
<td>N/A</td>
<td>54.17%</td>
<td>N/A</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>78.26%</td>
<td>N/A</td>
<td>79.17%</td>
<td>N/A</td>
</tr>
<tr>
<td>Handedness (% Right Handed)</td>
<td>78.26%</td>
<td>N/A</td>
<td>87.5%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Patients were recruited from the Rutgers University Behavioral HealthCare System. Patients were either enrolled in the extended partial hospital program (PHP) or were outpatients that only required biweekly or monthly visits to healthcare providers. The extended PHP provides patients that are still going through the stabilization process (from the stabilization to the stable phase) with continual structured daily living support before they are ready to graduate to outpatient status. There were 13 patients enrolled in the extended PHP and 10 were considered outpatient. Of the 23 patients, 18 participants had a diagnosis of SZ, while the remaining 5 were diagnosed as SA.

Table 4.2 provides a list of medications prescribed to patients enrolled in the study. It is important to note whether or not these drugs are known to have motor side effects, as this must be taken into account for our assessment of motor variability within the clinical population. Appendix 1 lists common and severe side effects associated with each drug listed in Table 4.2.
To assess whether patients exhibited executive dysfunction at the time of the experiment, the Frontal Systems Behavior Scale (FrSBE™) Self-Rating Form is administered (Grace & Malloy, 2001). The FrSBE aims to identify and quantify disordered natural behavior both retrospectively and at the present time. Patients are given a series of phrases, such as “I feel confused,” and are asked to rate from a scale of 1-5 (1 being “Almost Never” and 5 being “Almost Always”) on how this phrase pertains to them before illness and at the present time. Patients were asked to rate the phrases that were relevant to the assessment of executive dysfunction unbeknownst to them.
Table 4.2: List of Drugs Prescribed to Patients Enrolled in the Current Study.

Table 4.2 lists the current medications prescribed to patients within our study, along with their drug classifications. For more detail on the side effects associated with each drug, see Appendix 1.

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine (Symadine, Symmetrel)</td>
<td>anti-parkinsonian</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Benztropine Mesylate Oral (Cogentin)</td>
<td>anticholinergic</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>benzodiazepine</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>selective serotonin and norepinephrine reuptake inhibitors (SNRIs)</td>
</tr>
<tr>
<td>Fluphenazine (Prolixin, Permitil)</td>
<td>typical antipsychotic</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>anticonvulsant</td>
</tr>
<tr>
<td>Lithium (Eskalith, Lithobid)</td>
<td>antimanic agent</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Paliperidone (Invega, Invega Sustenna)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>atypical antipsychotic</td>
</tr>
<tr>
<td>Trazodone (Desyrel, Oleptro, Trialodine)</td>
<td>serotonin modulator</td>
</tr>
<tr>
<td>Valproic Acid (Depakote)</td>
<td>anticonvulsant</td>
</tr>
</tbody>
</table>

4.2.2 Motion Capture

We used the same motion capture system (Polhemus, Liberty, Colchester, VT) and motion-tracking software (The Motion Monitor, Innovative Sports Training, Inc., Chicago, IL) used in our previous studies involving the visual illusion in Chapters 2 and 3. Sensor assignments also remained constant for this paradigm (Fig. 2.2a). Since there is only one stimulus apparatus in this study (the touchscreen display), we placed one sensor on the backside of the display screen behind the approximate location of where the target appears during the experiment. We recorded the full motor response of each participant in
real time both in the forward motion (from initiation of hand movement up to the touch of the target), and in the non-instructed, automatic retraction of the arm back to the table during the baseline-pointing task.

4.2.3 Stimulus Apparatus and Experimental Procedure

Once all sensors have been donned and calibrated, subjects were seated at a table facing a touchscreen display. A MATLAB program controls the presentation the targets on the display. Each target consists of a filled yellow circle located in the middle of the display screen (Fig. 4.2). Participants were instructed to place their dominant hand at the edge of the table before the start of each trial. The experimenter instructed subjects to touch the target as quickly and as accurately as possible, returning to the table before initiating the next goal-directed reach. Upon touching the target, the yellow circle disappears briefly (for 300 ms) and then reappears. The location of the target does not change. Participants were told to continuously reach for targets once the experimenter says to begin. They were instructed to stop once they hear a beep. The auditory cue signifies the end of a 15s recording interval. Participants repeated the same procedure for each trial until at least 100 successful touches are recorded via the MATLAB program.
Fig. 4.2: Baseline-pointing Task Illustration. Participants reached for yellow circular targets on a touchscreen display. The goal-directed reach is designated in red. We also record the spontaneous retraction of the arm back to the table (blue dotted line arrow). The top graph illustrates a representative speed profile associated with the goal-directed reach. The peak velocity is marked by the green dot on both the forward trajectory and the representative speed profile. The peak velocity (black dot) in the retraction (blue) is also shown on the trajectory path. Black arrows mark the time to peak velocities.

Motor trajectories were decomposed into movement classes for analysis (the forward, goal-directed reach and the spontaneous, supplemental retraction). Trials were excluded from analyses for the following reasons: (1) if data capture did not record the entire motor loop due to equipment malfunctioning and (2) if the touchscreen did not respond to the participant’s reach.
4.2.4 Speed Profile Analysis

We assessed the motor output variability from the angular velocities in each movement class for each subject. To avoid allometric effects due to different anatomical sizes across different subjects, the peak angular velocities were normalized by dividing the peak velocity between two minima by the sum of the peak velocity and the average velocity between the two minima attains the normalization. We apply the same statistical framework that is described in Chapters 2 and 3 (Fig. 2.6) to empirically estimate the underlying probability distribution for normalized peak angular velocities in the forward reach and in the uninstructed retraction when participants performed the baseline-pointing task.

Fig. 4.3: Normalized Peak Angular Velocity Calculation Example

In Fig. 4.3, we graphically illustrate how normalized peak angular velocities are calculated for our study. Each maxima, designated by blue points, are divided by the sum of the peak velocity and the average velocity between the two minima it falls between (green points). Fig. 4.3b zooms in on one peak to demonstrate how each calculation is determined.

In addition to calculating the shape ($\alpha$) and scale ($\beta$) parameters, means ($\mu_W$), and variances ($\sigma_W^2$) for each participant and window W (forward or retraction), we determine the line that best fits the log of the Gamma parameters in each movement class for each
subject pool. We previously found power laws distributions in the hand linear and angular velocities that characterize the micro-movements variability. We here calculate the error estimate, delta (Δ), i.e. the normal distance from the point (for each participant) to the unit line of the power fit to the log-log of the Gamma plane empirically estimated parameters. We do this for each subject in each movement class. Delta is an estimate of the standard deviation of the error in predicting a future observation at each point with respect to the empirically estimated coefficients of the fitted polynomial function. The slope of this line is the exponent of the power relation that we uncovered between the shape and scale Gamma parameters describing the probability distribution of the angular trajectory parameters. The delta error gives a sense of departure of each subject data from the theoretical power law relation. We then take delta values for each participant and map them against Fano Factor (FF) calculations. Recall that the Fano Factor is another measure of noise (i.e. noise-to-signal ratio given by the empirically estimated Gamma variance divided by the mean). The Fano factor provides an index of dispersion for each movement class.

We employ the Wilcoxon Rank Sum test to determine if velocity-dependent parameters derived from each movement class are independent from one another in our control and patient groups. The Wilcoxon Rank Sum Test is a nonparametric test that assesses whether or not population medians ranks differ (Ross, 2014). We apply the Wilcoxon Rank Sum Test to the Fano Factor calculations and the delta values associated with each condition.
It is important to note that we apply these techniques to calculate each participant’s stochastic signature of micro-movement variability. Since SZ is a spectrum disorder, our characterization of each individual subject may help us identify whether or not patients blindly separate from one another to form sub-groups. These sub-groups may identify levels of severity or symptomology when we compare our findings to the clinical profile of each patient. We may also discover that certain sub-groups may be indicative of medication side effects (see Appendix 1), as motor disturbances are common side effects in the drugs prescribed to patients. We must also acknowledge that the literature reports certain motor dysfunctions in patients who have not taken anti-psychotic medications (Kent et al., 2012; Koethe et al., 2006; Mori et al., 2012; Pappa & Dazzan, 2009). Moreover, as we discussed in Section 4.1.2, early descriptions of SZ in the late 1800’s and early 1900’s characterized the presence of motor disturbances (Kahlbaum, 1973; Kraepelin et al., 1919; Rogers, 1985; D. M. Rogers, 1992) when none of the present days drugs were in use. Our current study aims not only to characterize the population in juxtaposition to controls, but also to improve our understanding of the phenomenology of SZ and possible medication effects as a spectrum disorder through objective quantification.

Because each patient is on a number of different medications that may have an effect on sensory-motor function, we approach the issue of medication effects by looking at the number of drugs prescribed to each patient. The variability inherently present in the micro-movements that we examine is sensitive enough to drug’s type and/or to drug combination effects (work in progress in the autism program of Dr. Torres’ lab) that we
could use this motor output information to tease apart a variety of issues regarding drug treatments. However, this question is beyond the scope of this thesis. Here we just want to assess whether, with or without the presence of the drugs, the signatures of motor output variability in patients with a diagnosis of schizophrenia differ from those of controls.

It is difficult to tease out how the combination of drugs that make up each patient’s medical profile affects the variability of micro-motions because we have no information about the drug dosage and/or the patient’s longitudinal usage of each drug before visiting our lab. Our goal here is to understand how the unmedicated patient’s signatures of motor variability compare to the rest of the patient population, and determine if the number of medications taken impacts the moment-by-moment micro-movements signatures. These signatures along a continuum are bound to impact the reaference sensory feedback from self-produced motions and impact as well kinesthetic sensing. In this sense it is not the magnitude of the micro-movements’ fluctuations that are relevant to us, but rather the degree of randomness and noise that they accumulate over time in the patients.

To address these issues, we empirically estimated the cumulative density function (CDF) associated with patients grouped by the number of drugs prescribed to them. We then used the Kolmogorov–Smirnov two-sample Test to determine if each CDF is drawn from the same distribution (Ross, 2014). The Kolmogorov-Smirnov Test is a non-parametric test of the equality that can be applied in pairwise comparisons of the
empirical CDFs, using the maximum absolute difference between the two samples. It can be used to test samples that are of uneven size, making it appropriate for our analysis of the breakdown of medication effects. The Kolmogorov-Smirnov Test statistic is given by $D^* = \max_x \{|\hat{F}_1(x) - \hat{F}_2(x)|\}$, in which $\hat{F}_1(x)$ and $\hat{F}_2(x)$ are the empirically estimated CDFs under comparison. Using the MATLAB function $kstest2$ gives us a $p$-value representative of the probability of observing the test statistic $D^*$ as extreme as, or more extreme than, the observed value under the null hypothesis. If $p < 0.05$ for pairwise comparisons of each empirically estimated normalized peak angular velocity CDF, we reject the null hypothesis, confirming that CDFs are not drawn from the same distribution.

Whether the micro-movements’ variability that we quantify is due to drug use or inherent to the system with this pathology is irrelevant to the argument that we pose here. What we argue is that corrupted micro-movements output variability (unpredictable, random, noisy and with narrow signal bandwidth) is problematic and must be addressed across mental illnesses if one truly seeks to help alleviate the burden of the mental disorder on the affected person. This type of corrupted motor output is objectively quantifiable. It re-enters the system as a form of kinesthetic reafference through the mechanoreceptors. It must be integrated for predictive and anticipatory control of the sensory consequences of our impending actions along with information from thermoreceptors and nociceptors across the peripheral nervous system. In order to be able to provide the central controllers with proper internally generated sensory feedback this information must be tracked, quantified and properly characterized across all mental
disorders that are now defined subjectively and through a psychological interpretation of what the clinician’s opinion may be.

### 4.2.5 Area-Perimeter Ratio Error Triangulation

Previous works highlight an invariant symmetry of intended curved reaches, in which the spatial transformations of goal-directed reaches remain invariant to changes in temporal dynamics (Torres, 2010; Torres et al., 2011). What this means is that although high levels of motor variability occur during motor learning processes, the geometric sensory-motor transformation of our movements are impervious to these changes. For example one such a transformation could be from an external spatial goal (such as the orientation and position of an object to be grasped) to the sets of postural configurations and their rates of change to attain that target with the hand in the appropriate position and orientation. Since the arm has so many degrees of freedom, the hand could be positioned and oriented in a very large number of ways. Yet the system has a unique way to do it within a given context, manifesting minute fluctuations around that solution (micromovements) that typically maintains invariant the original transformation in the face of complex dynamics required coordinating all those degrees of freedom in a systematic way. How this coordinate-transformation invariance breaks down or is altered in various patients’ populations is specific to the disorder in question (e.g. PD vs. stroke (Torres et al., 2011; Torres et al., 2010)) but it has not been tested in patients with SZ. We assess how these transformations are modulated in individuals with SZ, as we reiterate how little is known about sensory-motor disturbances in this population.
Hand trajectories in the goal-directed reaches and automatic retractions for each subject were resampled to 4x the number of points in each trajectory in order to generate a large number of equally spaced intervals. This was done with in-house developed geometric methods that preserve the geometric path of the curve. This is important to accurately estimate the area enclosed between the curved reaching trajectory and the straight line joining its two ending points (i.e. starting hand location and the target). This relation is determined for each trial (Fig. 4.4a). Fig. 4.4a graphically illustrates the Euclidean straight line from the initial hand position (blue star) to the baseline target location (yellow circle). Each point in the resampled trajectory is then projected onto each corresponding point on the straight line. The partial area enclosed between the curve and the straight line is obtained up to the point of maximum bending ($\kappa_{max}$), denoted $A_{partial}$. We also obtain the total area, $A_{total}$ between the full curve and the line and their partial to total ratio is calculated. When the coordinate transformation is distance metric preserving this ratio is $\frac{1}{2}$ (Torres, 2010)

The perimeter ratio was determined in a similar fashion, by the quotient between the partial perimeter ($P_{partial}$) and the total perimeter. The partial perimeter is the sum of the path lengths of the hand path from the initial hand position and the baseline target up to the point of maximum bending, and the perimeter of the curve traced by the hand. The total perimeter, $P_{total}$ is given by the sum of the lengths along the entire hand path and the straight line, ($P_{ratio} = P_{partial}/P_{total}$) (Fig. 4.4a).
A theoretical result analytically established that when a lower dimensional manifold is locally embedded in a higher dimensional manifold under isometric transformation (metric-distance preserving transformation) there is a symmetry that emerges in the geodesic trajectories of the lower dimensional manifold under non-Euclidean metric. When these trajectories are projected on Euclidean geodesics between the two points of interest the point of maximal curvature (maximal bending of the line) reveals this interesting symmetry. In our case the points are the starting location of the hand and the target location in three dimensions (Fig. 4.4a). The higher dimensional manifolds are representing postures of the arm and the lower dimensional manifolds the three-dimensional configurations of the hand. The tangent spaces to these two manifolds are our manifolds of interest as the coordinate transformations are studied according to their geometric properties. The theoretical considerations behind these ratios are beyond the scope of this thesis and have been published elsewhere (Torres, 2001, 2010; Torres et al., 2011). Using these ratios, we have been able to identify proper sources of sensory guidance to help the injured system recover this symmetry (Torres et al., 2014; Torres et al., 2011). In other words, the symmetry that also manifests in the neurotypical primate system (both humans and non-humans) is not merely a byproduct of the arm’s biomechanics. It is rather under cognitive control, as it breaks down selectively different with different brain injuries. More important yet, the symmetry can be recovered in the injured system under specific forms of sensory guidance (e.g. egocentrically guided in PD vs. allocentrically guided in patient with a stroke localized to the left posterior parietal lobe).
Previous work has established that in stable automated motions the area-perimeter ratios remain close to $\frac{1}{2}$ and invariant to changes in temporal dynamics in neurotypical controls. That work has also established that the symmetry breaks down when there is a disconnect between the mentally intended motion and its physical execution under control, implying lack of volitional control (Torres, 2010; Torres et al., 2011; Torres et al., 2010). Motivated by these results and the issues with avolition in SZ, we here assess the error from the ideal $\frac{1}{2}$ associated with the variance of area-perimeter ratios in the patients with mental illness diagnosis. This enables us to quantify the motor output variability representative of each individual subject in this cohort (Fig. 4.4b). In Fig. 4.4b, we illustrate sample area-perimeter ratios for forward reaches in red and uninstructed retractions in blue. Ideally, the geometric transformation of the area-perimeter ratio should fall on a straight line with a slope of 1, signifying that the balance between both spatial parameters is equal ($P_{ratio} = A_{ratio}$). We calculate the error of each area-perimeter ratio value by determining the shortest normal distance to the line $y = mx$, in which $y$ is the $P_{ratio}$, $x$ is the $A_{ratio}$, and $m = 1$. Since we now introduce a third dimension to our data, the error $E$, we can generate a 3D surface representation of all three variables to perform topological and geometric queries (Fig. 4.4c,d). We built a matrix with values for all $A_{ratio}, P_{ratio}$, and $E$ for each subject and movement class, and created a Delaunay triangulation surface.

Delaunay triangulation creates a surface representation of a matrix $P$ out of triangles connected by points $[x, y, z]$ in each row of matrix $P$, each point serving as a vertex, such that the circumsphere associated with each triangle formed contains no other
points in matrix $P$ in its interior (Delaunay, 1934). Fig. 4.4c demonstrates an example of how Delaunay triangles are constructed in 2D, and Fig. 4.4d-e illustrates the surfaces formed from the sample data found in Fig. 4.4b, in which Fig. 4.4d represents the surface generated by forward goal-directed reaches and Fig. 4.4e represents the surface generated by the spontaneous retractions of the hand.

We then calculate the areas of the triangles (Fig. 4.4d-e) that make up each 3D surface, and find the underlying probability distribution for each movement class. We can now apply the statistical framework presented throughout this dissertation on these new kinematic spatial metrics to understand how they unfold in the forward goal-directed reach and the spontaneous, uninstructed retraction. The Gamma parameters were estimated based on the Gamma probability density function fitted to each participant’s probability distribution of triangle areas. We then took the log of the shape ($a$) and scale ($b$) parameters and found the first-degree polynomial function that best fits in a least-squares sense the grouped data. We calculated delta for each group and mapped delta values against the Fano Factor calculations.

**Fig. 4.4: Overview of Methods for Area-Perimeter Error Triangulation Model**
Fig. 4.4 provides a graphical representation of the analysis of sensory-spatial kinematic parameters. To perform the area-perimeter error analysis, we must first calculate the perimeter and area under each trajectory path in each movement class (Fig. 4.4a). To obtain the perimeter ratio, we first calculate the Euclidean line that connects the initial hand position to the target. We then take the sum of the path lengths from the initial hand position and to the baseline target up until the point of maximum bending and the perimeter of the curve traced by the hand. The total perimeter, \( P_{total} \) is given by the sum of the lengths along the entire hand path and the straight line, \( P_{ratio} = P_{partial} / P_{total} \). The area is calculated in a similar fashion. We then plot the area-perimeter ration (Fig. 4.4b) to look at the conservation of each spatial parameter. The error is found by determining the distance between each area-perimeter ratio point to a straight line with the slope equal to 1. With our three spatial parameters, we can now generate a surface representation of each index using the Delaunay triangulation method (Fig. 4.4c). For every 3D point in the plane, a triangle is formed under the condition that no other vertices lie in the circumcircle of each generated triangle. The resulting surface triangulation can be seen in the examples in Fig. 4.4d,e. These triangulation surfaces correspond to the sample data in Fig. 4.4b: Fig. 4.4d corresponds to the forward reaches (red points) and Fig. 4.4e is representative of the blue points in Fig. 4.4b (blue points). Note that Fig. 4.4a is adapted from Torres (2011).
4.3 Results

4.3.1 Assessment of Executive Dysfunction in Patients with SZ

The average FrSBE Score for executive dysfunction was 59.5 +/- 17.14 for the entire clinical population (Table 4.3). Scores between 65 and 130 are considered in the clinical range, whereas any scores between 60 and 64 are considered borderline. Note that we see high variance in scores, as approximately half of the patient group (n=11) scored as exhibiting executive dysfunction, while others did not. We therefore find evidence for heterogeneity in the population under study. It should be noted that, if we included individuals from the inpatient unit and acute PHP, we may see higher levels of executive dysfunction when compared to the existing cohort.
Table 4.3: FrSBE Test Scores for Executive Dysfunction.
Table 4.3 lists the average scores for executive dysfunction using the FrSBE Self Rating Form. Patients were asked to rate each statement presented in the FrSBE form from a scale of 1-5 on how the given phrase, such as “I feel confused” applies to oneself, with 1=”Almost Never” and 5=”Almost Always”. Patients were asked to score themselves “Before Illness” and “At the Present Time”. A score of 65<=130 is determined to be in the clinical range. Scores between 60-64 are considered borderline.

<table>
<thead>
<tr>
<th>FrSBE Score for Executive Dysfunction (Clinical Range: 65&lt;=130, Borderline: 60-64)</th>
<th>Before Illness</th>
<th>Present Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>SZ Group (n = 18)</td>
<td>72.39 +/- 20.89</td>
<td>64.11 +/- 20.89</td>
</tr>
<tr>
<td>SA Group (n = 5)</td>
<td>54.25 +/- 22.70</td>
<td>59.5 +/- 17.14</td>
</tr>
<tr>
<td>All Patients (n = 23)</td>
<td>69.09 +/- 21.86</td>
<td>63.27 +/- 14.20</td>
</tr>
</tbody>
</table>

4.3.2 Changes in Temporal Dynamics: Normalized Peak Angular Velocities

We first present our results for the analysis of velocity-dependent kinematic parameters in our baseline-pointing task. Fig. 4.5 depicts the Gamma parameters for the normalized peak angular velocity distributions for controls (red for goal-directed reach and blue for the supplementary retraction in Fig. 4.5a, c) and patients (green for goal-directed reach and black supplementary retraction in Fig. 4.5b, d). As you can see, the shape and scale parameters for the normalized peak angular velocity probability distributions in the forward reach and uninstructed retraction in controls cluster together more tightly (Fig. 4.5a), than the patient group, which exhibits a larger spread in Gamma values (Fig. 4.5b). Again we find a power law governing the Gamma shape and scale empirically estimated parameters using velocity dependent micro-movements.

When plotting the log of the shape and scale parameters, we find the line that best fits the data by subject and by movement class (Fig. 4.5c-d). Table 4.4 lists the coefficients of each line equation and the goodness of fit characteristics, $p1$ and $p2$, in
which \( f(x) = p_1 \times x + p_2 \). All fitted first-degree polynomial functions have an adjusted \( R^2 \) value of close to 1: 0.9958 and 0.9955 for goal-directed movements and supplementary motions in controls, respectively (conditions are also abbreviated as CTRL FWD and CTRL BWD, correspondingly), and 0.9971 and 0.998 for goal-directed and supplementary motions in patients (SZ FWD and SZ BWD, respectively). **Fig. 4.5e,f** shows the means and variances associated with each Gamma probability distribution. Note how levels of variance in the SZ group are quite high, notably in the goal-directed segment of the motor action (marked by green diamonds in **Fig. 4.5f**). We then calculated the delta values according to each condition and mapped them to our Fano Factor calculations (**Fig. 4.6**). Recall that the scale parameter \( b \) is also the Fano Factor, as

\[
F = \frac{\sigma_W^2}{\mu_W} \quad \text{(where } \sigma_W^2 = a \cdot b^2 \text{ and } \mu_W = a \cdot b \text{)} \quad \text{reduces to } F = b.
\]

**Table 4.4: Coefficients of the First-Degree Least-Squares Polynomial Function and Goodness of Fit Statistics.**

Table 4.4 illustrates the parameters associated with the line of best fit for the log Gamma plane (**Fig. 4.5c,d**). The log Gamma plane helps us determine how movements along a continuum are subject to random motor noise, or if they are under tight control.
Fig. 4.5: Normalized peak velocity indices for neurotypical controls and SZ patients performing the baseline-pointing task.

Fig. 4.5 illustrates the Gamma parameters associated with each subject pool. Signatures of motor output variability in controls (Fig. 4.5a,c,e) and patients with SZ (Fig. 4.5 b, d, f) show differences in the angular rotations of the hand during the
unfolding of movement. We find a power law governing the control of micro-movement variability (Fig. 4.5a, b). When taking the log of the Gamma parameters, we can find the line of best fit (Fig. 4.5c, d). We see that subjects in the SZ group exhibit higher levels of motor noise, as they tend to have high scale parameters and low shape values in Fig. 4.5b. This can be attributed to higher levels of micro-movement variability in the probability distribution of normalized angular peak velocities in patients (Fig. 4.5f) vs. controls (Fig. 4.5e).

We find striking differences between patients and control groups in our error analysis (Fig. 4.5). As seen on the Gamma plane in Fig. 4.5, the scale parameter, which is also the Fano Factor, displays a higher spread of values in patients with SZ in both movement classes vs. controls. Their motions have higher noise-to-signal ratio in the maximum speed values. Specifically, in the forward segment of the motor trajectory, the Fano Factor is attenuated by the fact that patients with SZ exhibit higher levels of motor variability in the angular rotations of the hand as they reach towards the baseline target (Fig. 4.5f), but the value of the mean normalized velocity index increases to the left in the patients. This indicates that their average speed (in the denominator of this index) is lower than controls, thus impacting the numerator to a higher value. The decrease in the mean paired with the increase in the variance contribute to the higher Fano Factor in the patients. The sensory-motor control in SZ is primarily disrupted by high levels of variability in within the execution of both goal-directed and spontaneous motor acts. Note that there is a reduction in the overall motor noise in the SZ scatter dispersion corresponding to the spontaneous hand retraction (denoted as SCHIZ BWD and yellow triangles in Fig. 4.5f).

When the delta parameter is plotted against these values, we find a relationship within each subject group’s movement class, in which lower Fano Factors indicate higher
delta values (Fig. 4.6a,c). As the index of dispersion (Fano Factor) dampens, levels of delta increase, pulling the point away from the power relation. Two important results emerge here: the magnitude of the FF is higher in the patients than in controls, but also the rate of change of this parameter differs between the two cohorts. This can be seen in the different slopes and intercepts of the lines that emerge when we fit a polynomial to each spread. The coefficients and goodness-of-fit calculations for this signature of motor-output variability are found in Table 4.5. Tighter control of temporal dynamics are conserved in controls, whereas patients exhibit a much higher spread of temporal sensory-motor transformations due to increased variability within their movements, particularly more so in the forward reach than in the supplementary motion (Fig. 4.5f).

We applied the demographic information from each patient to the delta-Fano Factor mapping to look for any possible clusters indicative of these parameters (e.g. age, illness onset, longitude of illness, etc.). We do not find any group differences related to age, gender, race, or years of education (for self as well as parental) when we map these individuals unto the Gamm plane. The unmedicated outpatient included in our study is specified in Fig. 4.6 by orange arrows. It is important to track where this subject falls in our analyses to clarify whether or not signatures of motor output variability are due to medication effects or are related to the motor sensory phenomenology of SZ. Fig. 4.6 suggests that, as motor noise decreases there is a higher deviation from the power law relation. Since in the SZ patients the decrease in Fano Factor is in part contributed by a decrease in average speed (bradikynetic) retracting motions that are typically fast and automatic, it is safe to conclude that these movements are more deliberate than normal.
Indeed, they align with the signatures of forward motions of the controls. This motions are under tight motor control as they are deliberately guided towards the visual goal.

The delta value is indicative of how close the Gamma parameters fit our governing power law. As indicated by the orange arrows in Fig. 4.6a, the unmedicated patient exhibited much higher delta values, meaning that the temporal dynamics of sensory-motor behavior deviate from the power law governing the velocity-dependent kinematics of our model. A small cluster of patients with SA self-emerged on the Gamma plane that also deviate from the power relation with higher delta values. These speed at which these patients performed the baseline-pointing task is also significantly slower than controls, suggesting other factors at play. Their decrease in the FF is contributed in part by the increase in the mean normalized peak velocity, which indicates lower values of their speed on average. This could be due to some medication type or inappropriate sensory-motor feedback, among other factors. When we mapped FrSBE executive dysfunction scores onto our delta-FF map, we did not see any significant clusterings of patients in the clinical, borderline, and stable ranges. Outpatients did not cluster differently from PHP patients. More testing of unmedicated patients, SA patients, and acute subjects is warranted to get a better picture of how sensory-motor patterns forming tight clusters in the data relate to other physiological metrics like temperature, heartbeat variability, and breathing patterns.
Fig. 4.6: Mapping of Delta vs. Fano Factor Values for the Normalized Peak Angular Velocity Distributions of the Hand.

The Fano Factor (y-axis) is mapped against delta values (x-axis) for the forward, goal-directed movement in controls (red circles) and the supplementary retraction (blue triangles) (Fig. 4.6a). Goal directed movements in the patient group are shown in comparison (green circles and black triangles, respectively). Box plots against each axis designate median values. The horizontal edges of each boxplot represent the 25th and 75th percentiles of each subject group. Thick dotted lines on each end of the boxplot indicate values that are not considered outliers, and red plus signs indicate any outlier values. The range of values for both the Fano Factor and delta are much higher in the SZ group than in controls for both movement classes. Orange arrows point to the unmedicated participant in the SZ group.
Table 4.5: Coefficients of Fitted Power Laws Governing Delta-Fano Factor Relationships for Normalized Peak Angular Velocity Distributions.

Table 4.5 gives values for all power laws derived from each subject group and movement class. A general power law function can represent both patients and controls, as the confidence intervals overlap for each equation. Movement along the power law function may be indicative of differences between each subject group and movement class.

Power Law Equation: \( f(x) = \alpha x^\beta \)

<table>
<thead>
<tr>
<th></th>
<th>Neurotypical Controls</th>
<th>Schizophrenia Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Goal-Directed</td>
<td>Supplementary</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>1.15e-05 (9.038e-06, 1.395e-05)</td>
<td>1.395e-05 (1.239e-05, 1.55e-05)</td>
</tr>
<tr>
<td>( \beta )</td>
<td>-1.177 (-1.236, -1.118)</td>
<td>-1.005 (-1.033, -0.9766)</td>
</tr>
<tr>
<td>SSE</td>
<td>1.63E-08</td>
<td>4.62E-09</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.987982986</td>
<td>0.99604049</td>
</tr>
<tr>
<td>( Adj. R^2 )</td>
<td>0.987436758</td>
<td>0.995860512</td>
</tr>
<tr>
<td>RMSE</td>
<td>2.73E-05</td>
<td>1.45E-05</td>
</tr>
</tbody>
</table>

Using the Wilcoxon Rank Sum Test, we find the \( p \)-values associated with each condition comparison in Table 4.6. Note that the Fano Factors for the normalized peak angular velocity distributions are statistically different from one another when comparing the forward reaches in controls and patients, as well as in the rejections between our two subject pools. This finding translates to the delta comparisons, as delta values for the goal-directed control condition differ from patients’ goal-directed movements. This separation between subject groups holds true in the retraction as well. Delta values are statistically different for every group and movement class comparison, except for the comparison of goal directed patient reaches (SZ FWD) and supplemental patient motions (SZ BWD). This signifies that movement classes for patients with SZ are indistinguishable from one another in this velocity-dependent component.
Table 4.6: Wilcoxon Rank Sum Test for Velocity-Dependent Kinematic Parameters. P-values for the Wilcoxon Rank Sum Test for velocity-dependent kinematic parameters (Fano Factor and delta) are given in Table 4.6. An asterisk * indicates that $p < 0.05$, resulting in a significant difference between groups.

<table>
<thead>
<tr>
<th>Wilcoxon Rank Sum Test P-Values</th>
<th>Fano Factor</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRL FWD CTRL BWD</td>
<td>0.1245</td>
<td>0.0081*</td>
</tr>
<tr>
<td>CTRL FWD SCHIZ FWD</td>
<td>1.4344e-04*</td>
<td>0.0013*</td>
</tr>
<tr>
<td>SCHIZ BWD</td>
<td>0.0541</td>
<td>8.6219e-05*</td>
</tr>
<tr>
<td>CTRL BWD SCHIZ FWD</td>
<td>1.9819e-05*</td>
<td>3.6796e-06*</td>
</tr>
<tr>
<td>SCHIZ BWD</td>
<td>0.0051*</td>
<td>1.0391e-06*</td>
</tr>
</tbody>
</table>

To understand how similar each normalized peak angular velocity index is for the number of medications each patient is on, we explored the dynamics governing the cumulative density function (CDF) of each for each medication group contrasted with our control group (Fig. 4.7). The empirical CDF is estimated and then compared using the Kolmogorov-Smirnov Test. P-values are plotted as a heat map to indicate whether or not comparisons of CDFs for each probability distribution are significantly different. Values of $p < 0.05$ indicate statistical differences and are marked by white asterisks. Corresponding p-values are listed in Table 4.7 and Table 4.8. As seen in Fig. 4.7c,d, CDFs for the unmedicated patient in both movement classes belong to the same distribution as those taking 1-4 drugs. What this signifies is that the signatures of motor output variability for the patient population are comparable (Fig. 4.7, Table 4.47, Table 4.8). The control group is different from all subgroups of patients. Differences in patients taking one medication vs. those that are taking between 2-4 are seen. Since this raises the issue of the contributions each type of medication has on our population, further investigation into these dynamics is required, but this is beyond the scope of this work. It is also important to note that when grouping all patients in comparison to controls, some of these effects wash out as expected from interaction effects across strikingly different
probability distributions (data not shown). We stress the importance of treating the SZ population as individuals, just as we did in our analyses, as the grouping of all patient data cancels out effects that are informative of each individual’s sensory-motor profile.

Fig. 4.7 Cumulative Probability Density Function for Number of Medications
Analysis using the Kolmogorov-Smirnov Test
Cumulative Probability Distributions are empirically estimated for each movement class and medication group compared to controls in Fig. 3.10a,b. To determine whether or not each CDF comes from the same family of distributions, we used the Kolmogorov Test Statistic to compare each group in the forward, goal directed action (Fig. 3.10c) and in the uninstructed, supplementary retraction (Fig. 3.10d). The color bar denotes the $p$-value scale in which $p<0.05$ rejects the null hypothesis (red). No significant differences are found within each group, implicating that
normalized peak angular velocity indices belong to the same probability distribution family.

Table 4.7 Corresponding P-Values Calculated Using the Kolmogorov-Smirnov Test for Forward, Goal Directed Movements. The $p$-values used to visualize the Kolmogorov-Smirnov Test for effects of the number of medications taken by patients (Fig. 4.7c) are listed in below for motions in the goal-directed movement class. Values less than 0.05 indicate that groups are significantly different from one another. Each number in the first column and first row designates the number of medications the participant was taking during the time of the experiment.

<table>
<thead>
<tr>
<th>Number of Medications Taken</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0000</td>
<td>0.2036</td>
<td>1.0000</td>
<td>0.6927</td>
<td>1.0000</td>
<td>0.0008</td>
</tr>
<tr>
<td>1</td>
<td>0.2036</td>
<td>1.0000</td>
<td>0.0010</td>
<td>0.0289</td>
<td>0.0329</td>
<td>0.0000</td>
</tr>
<tr>
<td>2</td>
<td>1.0000</td>
<td>0.0010</td>
<td>1.0000</td>
<td>0.0821</td>
<td>1.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>3</td>
<td>0.6927</td>
<td>0.0289</td>
<td>0.0821</td>
<td>1.0000</td>
<td>0.3795</td>
<td>0.0000</td>
</tr>
<tr>
<td>4</td>
<td>1.0000</td>
<td>0.0329</td>
<td>1.0000</td>
<td>0.3795</td>
<td>1.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Controls</td>
<td>0.0008</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Table 4.8 Corresponding P-Values Calculated Using the Kolmogorov-Smirnov Test for Supplementary, Uninstructed Retractory Movements. The $p$-values used to visualize the Kolmogorov-Smirnov Test for effects of the number of medications taken by patients (Fig. 4.7d) are listed in below for the supplementary movement class. Values less than 0.05 indicate that groups are significantly different from one another.

<table>
<thead>
<tr>
<th>Number of Medications Taken</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0000</td>
<td>0.2948</td>
<td>1.0000</td>
<td>0.8416</td>
<td>1.0000</td>
<td>0.0001</td>
</tr>
<tr>
<td>1</td>
<td>0.2948</td>
<td>1.0000</td>
<td>0.0035</td>
<td>0.2642</td>
<td>0.0417</td>
<td>0.0000</td>
</tr>
<tr>
<td>2</td>
<td>1.0000</td>
<td>0.0035</td>
<td>1.0000</td>
<td>0.1642</td>
<td>1.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>3</td>
<td>0.8416</td>
<td>0.2642</td>
<td>0.1642</td>
<td>1.0000</td>
<td>0.4553</td>
<td>0.0000</td>
</tr>
<tr>
<td>4</td>
<td>1.0000</td>
<td>0.0417</td>
<td>1.0000</td>
<td>0.4553</td>
<td>1.0000</td>
<td>0.0000</td>
</tr>
<tr>
<td>Controls</td>
<td>0.0001</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
4.3.3 Spatial Sensory-Motor Transformations: Area-Perimeter Ratio Error Triangulation

The area-perimeter ratio error triangulation uncover salient differences in spatial sensory-motor transformations (Fig. 4.8). We discover that goal-directed movements in the patient population (green circles) are more similar to spontaneous retractions in our control group (blue triangles) (Fig. 4.8a). In contrast, the spontaneous retractions of the arm in patients (black triangles) produce spatial transformations that are closely related to those found in goal-directed movements in controls (red circles). This suggests that the spatial kinematics of supplementary, spontaneous movements in the SZ population are under tighter control than in the goal-directed movement (Fig. 4.8c). The variability in Fano Factor calculations are lower in controls for both movement classes than they are in the patient population (Fig. 4.8b). This result is consistent with our findings on velocity-dependent parameters, where we also find a wider distribution of normalized peak angular velocity measurements.
Fig. 4.8: Mapping of Delta vs. Fano Factor Values for Spatial Sensory-Motor Kinematics Associated with the Area-Perimeter Transformation of the Arm.

Fig. 4.9a illustrates the mapping of the delta against the Fano Factor for the areas of the triangles that make up the error surface. Box plots against each axis designate median values. The horizontal edges of each boxplot represent the 25th and 75th percentiles of each subject group. Thick dotted lines on each end of the boxplot indicate values that are not considered outliers, and red plus signs indicate any outlier values. A striking phenomenon is observed in which SZ supplementary motions map closer to the forward motions of the control group in the spatial domain (black and red, respectively). Goal-directed movements in the spatial domain resemble the spatial parameters of automatic retractions of the control population (green and blue, respectively). The unmedicated patient is noted by the orange arrow. In this representation of spatial transformations of the hand in space, we do not see a clustering of patients with SA as we did in Fig. 4.9.
The Wilcoxon Rank Sum Test on the delta-Fano Factor values for spatial kinematic parameters reveals that the Fano Factor for the area-perimeter ratio error triangulation surface are similar in all cases except within patient movement classeses and between control and patient supplementary movements (Table 4.9). As we see in Fig. 4.9, the automatic retractions of SZ patients are closely related to the goal-directed actions in controls, indicating that control in the this movement domain is under more control than in the goal-directed segment of motion.

Table 4.9: Wilcoxon Rank Sum Test for Spatial Kinematic Parameters.
P-values for the Wilcoxon Rank Sum Test for spatial kinematic parameters (Fano Factor and delta) are given in Table 4.9. An asterisk * indicates that \( p < 0.05 \), indicating a significant difference between groups.

<table>
<thead>
<tr>
<th></th>
<th>Fano Factor (p-values)</th>
<th>Delta (p-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRL FWD</td>
<td>CTRL BWD</td>
<td>0.1768</td>
</tr>
<tr>
<td>CTRL FWD</td>
<td>SCHIZ FWD</td>
<td>0.8565</td>
</tr>
<tr>
<td></td>
<td>SCHIZ BWD</td>
<td>0.0788</td>
</tr>
<tr>
<td>CTRL BWD</td>
<td>SCHIZ FWD</td>
<td>0.1979</td>
</tr>
<tr>
<td></td>
<td>SCHIZ BWD</td>
<td>5.4374e-04*</td>
</tr>
<tr>
<td>SCHIZ FWD</td>
<td>SCHIZ BWD</td>
<td>3.0637e-09*</td>
</tr>
</tbody>
</table>

These results, taken together with our findings in speed-dependent micromovements variability, point to disturbances in sensory-motor control in patients with SZ. We find evidence for differences in both spatial and temporal representations of micro-movements output variability. This form of motor output variability is also a form of kinesthetic reafference that we find very distinguishable in controls between instructed-deliberate and uninstructed-spontaneously performed movements. In marked constrast to controls, the patients’s velocity-dependent stochastic signatures of the micro-movements are indistinguishable between levels of volitional control. Furthermore, the coordinate transformation metric shows an inversion of the control schema whereby
motions that are otherwise spontaneously occurring in controls, largely beneath the person awareness, are here showing signatures of deliberate control in all of these patients.

4.4 Discussion

Our data demonstrates the utility of quantifying the continuous flow of micro-movement output variability to help characterize disruptions of the sensory-motor system present in individuals with SZ. Our investigation into the sensory-motor patterns of patients with SZ indicates a high level of micro-motor variability in the temporal domain, particularly in the goal-directed segment of the motor action loop (Fig. 4.5f, Fig. 4.8). We identify the source of variability to be in the angular rotation of the hand as it reaches towards the target and returns back to rest. This coincides with other works that account for higher levels of variability in motor-related tasks (Kappenman et al., 2015; Kent et al., 2012; Lallart et al., 2014; Teremetz et al., 2014). Here we specify that motor variability is due to less control of motions undergoing the angular rotations of the arm, as the estimated Gamma probability density function for normalized peak angular velocities in the patient group contains higher scale values than what we see in controls.

In addition to our findings on velocity-dependent kinematic parameters, we discover that geometric transformations of the hand present in such a manner that motor trajectories in the goal-directed reach of the patient group now mirror the behaviors of neurotypical controls in the retraction motion (Fig. 4.9). This result could possibly serve as an index representative of the state of disorganization the individual is currently in, as
the balance between both movement classes is markedly disrupted. Our discovery that goal-directed movements are subject to more noise and randomness in patients may contribute to our understanding of negative symptoms such as avolition (Barch & Dowd, 2010; Foussias & Remington, 2010; Tremeau et al., 2012). Because supplementary motions are slower and exhibit signatures of characteristic of deliberateness in controls, they seem to be under more awareness. This could explain some of the perceptual phenomena experienced by these individuals, as the control of these segments of movement are inconsistent with what we find in neurotypical controls.

We also show that stochastic signatures of micro-movement variability for the patients, grouped by number of medications, are mostly similar to the patient who was not under the influence of any medication during the time of the experiment. The fact that noise and randomness in the movements prevail with and without medications may indicate that we have captured an endophenotypic feature of this spectrum of disorders. Currently, we are unable to tease out any medication effects based on a specific drug. The patients in the study were taking a combination of drugs, making it more difficult to classify how drug interactions modulate the motor noise signal. Past studies point to the effects of certain atypical antipsychotics in exacerbating motor features of SZ, (Berle, Loberg, & Fasmer, 2013; Coesmans et al., 2014; Frank et al., 2014; Keedy et al., 2015; Tandon, 2011). It is also important to address the possibility that our results on meds may be skewed due to the inclusion of PHP patients and outpatients. The spectrum of SZ may hold other implications as severity worsens or we may see differences in the development of these complex patterns over the longitude of illness. Now that we have a basic
understanding of sensory-motor issues in both movement classes, we can investigate these issues more thoroughly and accurately.

4.4.1 Future Work: Perception-Action Modeling in Schizophrenia

In Section 4.1.4, we briefly discussed the use of perceptual stimuli to uncover differences in visual processing in patients with SZ. One study that can extend our model of perception and action would be to run patients with SZ on the experiments conducted in Chapters 2 and 3. It is known that a reduction in binocular depth perception occurs in patients with SZ (Dima et al., 2009; Keane et al., 2013; Koethe et al., 2009; Schneider et al., 2002), but how this translates motorically is still up to debate. Now that we’ve established metrics that characterize SZ in a simple baseline-pointing task, we can progress to the exploration of perceptual tasks that are more complex. Utilizing the established framework of our study, we can make further advances in our knowledge of the underlying mechanisms that contribute to SZ as well as to other neurological disorders.

In closing, these stochastic signatures of micro-movement variability seen in our work adds great value to our current understanding of SZ, highlighting the significant contributions of the peripheral nervous system to our mental states and vice versa. We see the presentation of disorganized sensory-motor behavior, consistent with theories of disorganized behavior. Our findings allude to disruptions not only in the brain, but in the peripheral nervous system as well. We propose that perceptual abnormalities arise from a failure to sense the environment properly: the integration of multiple sensory modalities
may be compromised in SZ, leading to cognitive dysfunctions characteristic of the disorder. We introduce new concepts on the balance of movement classes within the SZ population to show the value in assessing both goal-directed and goal-less movements with unprecedented level of statistical precision. What had been traditionally treated as motor noise and thrown away or smoothed out as a nuisance in data capture, turned out to be a very rich signal in our approach. Nikolai Bernstein pointed out that “The movements of the body are as complex as the human… [They] are too fast and fleeting to be caught by the ordinary eye” (1948). In light of the works Bernstein pioneered nearly a century ago, we have offered a new unifying statistical framework to examine micro-movements that are invisible to the human eye, but can today be capture with advanced instrumentation.
Chapter 5 Concluding Remarks and Future Work

5.1 Implications of Our Work

Collectively, we demonstrate the value in assessing natural behaviors over a continuum using physical, quantifiable measures. We identify physiologically relevant signals from the peripheral nervous system that inform us of internal mental states. Our work discovers a methodical approach to blindly and objectively separate changes in visual perception by studying the unfolding of movement, stressing the importance of treating behavior as a continuum of motions. We also uncover effects of speed instructions on perceptual tasks, implicating that instructed speed maintenance may require a high cognitive load that in turn dampens our responses to perceptual inputs in order to execute motor tasks as instructed.

When we apply our statistical framework to a clinical population that exhibits a number of cognitive abnormalities, we see a disorganization of sensory-motor processing in the deliberate control of actions and in the automatic retractions of the arm, suggesting that the presence of disorganized high-level mental processes is closely related to kinesthetic sensing. By reestablishing the relationship between the brain and body, we establish a transformative approach to research practices that can help advance our understanding of basic scientific principles. Ultimately, we can translate these findings into clinically relevant tools to better diagnose and treat patients suffering from brain disorders. In fact, calling schizophrenia a disorder of the brain is in itself incomplete and inaccurate, as we demonstrate that abnormalities exist throughout the body. Taken together, we set out to redefine the way in which research is conducted in the
psychological and psychiatric sciences to better understand the underlying processes that make up our natural behaviors through a new, objective, statistical lens.

5.2 Future Directions

The utility of our research platform is in our ability to translate it across different scientific disciplines. With advances in wearable sensing technology growing at an exponential rate, the scope of our research applications expands as the quantification of human movement becomes more reliable and accessible to the public domain. Although this dissertation addresses the needs of the psychological and psychiatric sciences, we highlight that our framework is also applicable to fields outside of the neural sciences.

For example, an objective behavioral tool may transform the methods used to assess stages of clinical trials, potentially saving time, cost, and effort in the drug development pipeline. It is estimated that pharmaceutical companies may spend close to $350 million before a drug is ready for the market (Herper, 2013), with some estimates as high as $2.6 billion ("Drug development costs jump to $2.6 billion," 2015). This poses a major concern as to where to concentrate efforts in drug discovery, especially when we see high failure rates (Fig. 5.1) (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014). As we have demonstrated in past works as well as in this dissertation, it is invalid to assume and apply normative statistics to the analysis of behavioral data from clinical populations (Torres, 2012; Torres et al., 2014; Torres et al., 2011). The use of normative statistics in clinical trials may contribute to the pitfalls of pharmaceutical research
(Pocock, Hughes, & Lee, 1987), thereby calling for the need for an objective statistical platform that is appropriate for these areas of research.

Fig. 5.1: Examples of Success Rates in Clinical Drug Trials for the Pharmaceutical Industry. Fig. 5.1a,b illustrate the probability of success rate between clinical trial phases for lead indications (black bars) as well as all indications (blue bars). Note that LOA = Likelihood of Approval, NDA = New Drug Application, BLA = Biologic License Agreement. Fig. 5.1c shows how these success rates are modulated when based on disease type. The bars in Fig. 5.1c represent Phase 2 and Phase 3 success rates and the line represents LOA from Phase 1.

In addition to supplementing clinical trial research, we also see the therapeutic value of our current methodology. Through the National Science Foundation Innovation Corps (I-Corps) Program (see Appendix 2), we discovered a lack of objective metrics for evaluating functional improvements in neurological disorders such as Autism Spectrum Disorders (ASD), particularly in the field of occupational therapy (OT). Qualitative
measures such as the Sensory Integration and Praxis Test (SIPT) and the Beery-Buktenica Developmental Test of Visual-Motor Integration (BEERY VMI) proved to be insufficient tools to quantify disruptions in sensory-motor behavior. Moreover, the frustrations felt by the OT community extend to affecting the lives of families with children with ASD, as insurance companies will only cover therapies that can report overall functional improvements. To our astonishment, occupational therapists informed us that sometimes the only way to rate improvement was to count the number of times a child smiled or made eye contact with them. How can these rudimentary, subjective measures still exist when technological advances can easily detect changes in sensory-motor behavior that serve as better indicators for functional improvement?

These observations fuel our research, as it is important for us to develop our metrics into practical applications to benefit society as a whole. We have proven that micro-movement analyses can inform us of brain-body relationships that typically have been difficult to characterize. By measuring movement along a continuum, we offer a window into the brain to understand the interplay between sensory-motor processes and cognitive abilities, providing a unifying framework that will transform the way in which we conduct scientific research.
## Appendix 1: Patient Medications and Side Effects

Prescription information is adapted from the Medline Plus online database ("AHFS Consumer Medication Information," 2008). Select motor disturbances are in red font.

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Classification</th>
<th>Common Side Effects</th>
<th>Severe Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine (Symadine, Symmetrel)</td>
<td>anti-parkinsonian</td>
<td>blurred vision; dizziness; lightheadedness; faintness; trouble sleeping</td>
<td>depression or anxiety; swelling of the hands, legs, or feet; difficulty urinating; shortness of breath; rash</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>atypical antipsychotic</td>
<td>headache; nervousness; drowsiness; dizziness; heartburn; constipation; diarrhea; stomach pain; weight gain; increased appetite; increased salivation; pain, especially in the arms, legs, or joints</td>
<td>seizures; slow, fast, or irregular heartbeat; chest pain; changes in vision; unusual movements of your body or face that you cannot control; high fever; muscle stiffness; confusion; sweating; rash; hives; itching; swelling of the eyes, face, mouth, lips, tongue, throat, hands, feet, ankles, or lower legs; difficulty breathing or swallowing; tightening of the neck muscles; tightness in the throat</td>
</tr>
<tr>
<td>Benztropine Mesylate Oral (Cogentin)</td>
<td>anticholinergic</td>
<td>drowsiness; dry mouth; difficulty urinating; constipation</td>
<td>skin rash; fast, irregular, or pounding heartbeat; fever; confusion; depression; delusions or hallucinations; eye pain</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>tricyclic antidepressant</td>
<td>drowsiness; dry mouth; nausea; vomiting; diarrhea; constipation; nervousness; decreased sexual ability; decreased memory or concentration; headache; stuffy nose; change in appetite or weight</td>
<td>uncontrollable shaking of a part of the body; seizures; fast, irregular, or pounding heartbeat; difficulty urinating or loss of bladder control; believing things that are not true; hallucinations (seeing things or hearing voices that do not exist); shakiness; difficulty breathing or fast breathing; severe muscle stiffness; unusual tiredness or weakness; sore throat, fever, and other signs of infection</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>benzodiazepine</td>
<td>drowsiness; dizziness; unsteadiness; problems with coordination; difficulty thinking or remembering; increased saliva; muscle or joint pain; frequent urination; blurred vision; changes in sex drive or ability</td>
<td>rash; hives; swelling of the eyes, face, lips, tongue, or throat; difficulty breathing or swallowing; hoarseness; difficulty breathing</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>atypical antipsychotic</td>
<td>drowsiness; dizziness; increased salivation; constipation; dry mouth; restlessness; headache</td>
<td>shaking hands that you cannot control; seizures; fainting; difficulty urinating or loss of bladder control; confusion; changes in vision; shakiness; fever; severe muscle stiffness; sweating; confusion; changes in behavior; sore throat; unusual bleeding or bruising; loss of appetite; upset stomach</td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Common Side Effects</td>
<td></td>
</tr>
<tr>
<td>------</td>
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<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>Selective serotonin and norepinephrine reuptake inhibitors (SNRIs)</td>
<td>Nausea; vomiting; constipation; diarrhea; heartburn; stomach pain; decreased appetite; dry mouth; increased urination; difficulty urinating; sweating or night sweats; dizziness; headache; tiredness; weakness; drowsiness; muscle pain or cramps; changes in sexual desire or ability; uncontrollable shaking of a part of the body</td>
<td>Unusual bruising or bleeding; pain in the upper right part of the stomach; swelling of the abdomen; itching; yellowing of the skin or eyes; dark colored urine; loss of appetite; extreme tiredness or weakness; confusion; flu-like symptoms; fever; sweating, confusion, fast or irregular heartbeat, and severe muscle stiffness; fever; blisters or peeling skin; rash; hives; difficulty breathing or swallowing; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs; hoarseness</td>
</tr>
<tr>
<td>Fluoxetine (Prozac, Sarafem, Rapiflux, Selfemra)</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Nervousness; nausea; dry mouth; sore throat; drowsiness; weakness; uncontrollable shaking of a part of the body; loss of appetite; weight loss; changes in sex drive or ability; excessive sweating</td>
<td>Rash; hives; fever; joint pain; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs; difficulty breathing or swallowing; fever; sweating, confusion, fast or irregular heartbeat, and severe muscle stiffness; seeing things or hearing voices that do not exist (hallucinating); seizures</td>
</tr>
<tr>
<td>Fluphenazine (Prolixin, Permitil)</td>
<td>Typical antipsychotic</td>
<td>Upset stomach; drowsiness; weakness or tiredness; excitement or anxiety; insomnia; nightmares; dry mouth; skin more sensitive to sunlight than usual; changes in appetite or weight</td>
<td>Constipation; difficulty urinating; frequent urination; blurred vision; changes in sex drive or ability; excessive sweating; jaw, neck, and back muscle spasms; slow or difficult speech; shuffling walk; persistent fine tremor or inability to sit still; fever, chills, sore throat, or flu-like symptoms; difficulty breathing or swallowing; severe skin rash; yellowing of the skin or eyes; irregular heartbeat</td>
</tr>
<tr>
<td>Gabapentin (Neurontin, Horizant)</td>
<td>Anticonvulsant</td>
<td>Drowsiness; tiredness or weakness; dizziness; headache; uncontrollable shaking of a part of your body; double or blurred vision; unsteadiness; anxiety; memory problems; strange or unusual thoughts; unwanted eye movements; nausea; vomiting; heartburn; diarrhea; dry mouth; constipation; increased appetite; weight gain; swelling of the hands, feet, ankles, or lower legs; back or joint pain; fever; runny nose, sneezing, cough, sore throat, or flu-like symptoms; ear pain; red, itchy eyes (sometimes with swelling or discharge)</td>
<td>Rash; itching; swelling of the face, throat, tongue, lips, or eyes; hoarseness; difficulty swallowing or breathing; seizures</td>
</tr>
<tr>
<td><strong>Haloperidol</strong> (Haldol)</td>
<td>conventional antipsychotic</td>
<td>drowsiness; dry mouth; increased saliva; blurred vision; loss of appetite; constipation; diarrhea; heartburn; nausea; vomiting; difficulty falling asleep or staying asleep; blank facial expression; uncontrollable eye movements; unusual, slowed, or uncontrollable movements of any part of the body; restlessness; agitation; nervousness; mood changes; dizziness; headache; breast enlargement or pain; breast milk production; missed menstrual periods; decreased sexual ability in men; increased sexual desire; difficulty urinating</td>
<td>fever; muscle stiffness; confusion; fast or irregular heartbeat; sweating; decreased thirst; neck cramps; tongue that sticks out of the mouth; tightness in the throat; difficulty breathing or swallowing; fine, worm-like tongue movements; uncontrollable, rhythmic face, mouth, or jaw movements; seizures; eye pain or discoloration; decreased vision, especially at night; seeing everything with a brown tint; rash; yellowing of the skin or eyes; erection that lasts for hours</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong> (Lamictal)</td>
<td>anticonvulsant</td>
<td>loss of balance or coordination; double vision; blurred vision; uncontrollable movements of the eyes; difficulty thinking or concentrating; difficulty speaking; drowsiness; dizziness; diarrhea; constipation; loss of appetite; weight loss; stomach, back, or joint pain; missed or painful menstrual periods; swelling, itching, or irritation of the vagina; uncontrollable shaking of a part of the body</td>
<td>seizures that happen more often, last longer, or are different than the seizures you had in the past; chest pain; swelling of the hands, feet, ankles, or lower legs; headache; stiff neck; sensitivity to light; loss of consciousness</td>
</tr>
<tr>
<td><strong>Lithium</strong> (Eskalith, Lithobid)</td>
<td>antimanic agent</td>
<td>restlessness; fine hand movements that are difficult to control; mild thirst; loss of appetite; stomach pain; gas; indigestion; weight gain or loss; dry mouth; excessive saliva in the mouth; change in the ability to taste food; swollen lips; acne; hair loss; unusual discomfort in cold temperatures; constipation; depression; joint or muscle pain; paleness; thin, brittle fingernails or hair; itching; rash</td>
<td>unusual tiredness or weakness; excessive thirst; frequent urination; slow, jerky movements; movements that are unusual or difficult to control; blackouts; seizures; fainting; dizziness or lightheadedness; fast, slow, irregular, or pounding heartbeat; shortness of breath; chest tightness; confusion; hallucinations (seeing things or hearing voices that do not exist); crossed eyes; painful, cold, or discolored fingers and toes; headache; pounding noises inside the head; swelling of the feet, ankles, or lower legs</td>
</tr>
<tr>
<td><strong>Lurasidone</strong> (Latuda)</td>
<td>atypical antipsychotic</td>
<td>drowsiness; anxiety; agitation; weakness; tiredness; restlessness; uncontrollable shaking of a part of the body; slow movements or shuffling walk; difficulty falling asleep or staying asleep; nausea; vomiting; increased saliva; breast enlargement or discharge; late or missed menstrual period; decreased sexual ability</td>
<td>seizures; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs; hoarseness; difficulty swallowing or breathing; shortness of breath; abnormal heartbeat; sore throat, fever, cough, chills, and other signs of infection; fever, sweating, confusion, fast or irregular heartbeat, and severe muscle stiffness; unusual movements of your face or body that you cannot control</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Drug Type</td>
<td>Side Effects</td>
<td>Additional Symptoms</td>
</tr>
<tr>
<td>-----------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>Antidepressant</td>
<td>Drowsiness; dizziness; anxiousness; confusion; increased weight and appetite; dry mouth; constipation; nausea; vomiting</td>
<td>Flu-like symptoms, fever, chills, sore throat, mouth sores, or other signs of infection; chest pain; fast heartbeat; seizures</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Atypical Antipsychotic</td>
<td>Drowsiness; dizziness; restlessness; unusual behavior; depression; difficulty falling asleep or staying asleep; weakness; difficulty walking; constipation; weight gain; dry mouth; pain in arms, legs, back, or joints; breast enlargement or discharge; late or missed menstrual periods; decreased sexual ability</td>
<td>Seizures; changes in vision; swelling of the arms, hands, feet, ankles, or lower legs; unusual movements of your face or body that you cannot control; sore throat, fever, chills, and other signs of infection; very stiff muscles; excess sweating; fast or irregular heartbeat; rash; hives; difficulty breathing or swallowing</td>
</tr>
<tr>
<td>Paliperidone (Invega, Invega Sustenna)</td>
<td>Atypical Antipsychotic</td>
<td>Dizziness; extreme tiredness; weakness; headache; dry mouth; increased saliva; weight gain; stomach pain</td>
<td>Fever; muscle pain or stiffness; confusion; fast, pounding, or irregular heartbeat; sweating; unusual movements of your face or body that you cannot control; slow or stiff movements; restlessness; painful erection of the penis that lasts for hours</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Atypical Antipsychotic</td>
<td>Drowsiness; dizziness; pain in the joints, back, neck, or ears; weakness; dry mouth; vomiting; indigestion; constipation; gas; stomach pain or swelling; increased appetite; excessive weight gain; stuffy nose; headache; pain; irritability; difficulty thinking or concentrating; difficulty speaking or using language; loss of coordination; unusual dreams; numbness, burning, or tingling in the arms or legs; missed menstrual periods; breast enlargement in males; discharge from the breasts; decreased sexual desire or ability</td>
<td>Fainting; seizures; changes in vision; uncontrollable movements of your arms, legs, tongue, face, or lips; painful erection of the penis that lasts for hours; fever; muscle stiffness, pain, or weakness; excess sweating; fast or irregular heartbeat; confusion; unusual bleeding or bruising; sore throat, fever, chills, difficult or painful urination and other signs of infection; hives; rash; blisters; tightening of the neck muscles or the throat; tongue sticking out; difficulty breathing or swallowing</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Atypical Antipsychotic</td>
<td>Drowsiness; dizziness; nausea; vomiting; diarrhea; constipation; heartburn; dry mouth; increased saliva; increased appetite; weight gain; stomach pain; anxiety; agitation; restlessness; dreaming more than usual; difficulty falling asleep or staying asleep; decreased sexual interest or ability; breastmilk production; vision problems; muscle or joint pain; dry or discolored skin; difficulty urinating</td>
<td>Fever; muscle stiffness; confusion; fast or irregular pulse; sweating; unusual movements of your face or body that you cannot control; faintness; seizures; slow movements or shuffling walk; rash; hives; itching; difficulty breathing or swallowing; painful erection of the penis that lasts for hours</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Common Side Effects</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Trazodone (Desyrel, Oleptro, Trialodine)</td>
<td>Serotonin modulator</td>
<td>Headache; nausea; vomiting; bad taste in mouth; diarrhea; constipation; changes in appetite or weight; weakness or tiredness; nervousness; dizziness or lightheadedness; feeling unsteady when walking; decreased ability to concentrate or remember things; confusion; nightmares; muscle pain; dry mouth; rash; sweating; changes in sexual desire or ability; uncontrollable shaking of a part of the body; numbness, burning, or tingling in the arms, legs, hands, or feet; decreased coordination; tired, red, or itchy eyes; ringing in ears.</td>
<td></td>
</tr>
<tr>
<td>Valproic Acid (Depakote)</td>
<td>Anticonvulsant</td>
<td>Drowsiness; dizziness; headache; diarrhea; constipation; changes in appetite; weight changes; back pain; agitation; mood swings; abnormal thinking; uncontrollable shaking of a part of the body; loss of coordination; uncontrollable movements of the eyes; blurred or double vision; ringing in the ears; hair loss; unusual bruising or bleeding; tiny purple or red spots on the skin; fever; blisters or rash; bruising; hives; difficulty breathing or swallowing; confusion; tiredness; vomiting; drop in body temperature; weakness in the joints.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: Out of the Lab and Into the Market: Lessons Learned in the NSF I-Corps Program

Theoretically speaking, we can apply our methodology to a broad range of areas. But how does one transition from a basic science research tool and into the actual marketplace? As scientists, our training is often limited to our research endeavors, lacking formal instruction on business practices and in understanding the dynamics needed to bring a potential product to market. This is discouraging, as many discoveries in the lab end up staying there. Here we provide reflections on the lessons learned from the National Science Foundation Innovation Corps, an initiative that enables NSF-funded researchers to explore the potential commercial impact of technologies discovered in the lab, as well as endow young scientists with an entrepreneurial skillset to help bridge the gap between the basic sciences and real-world applications.

In addition to conducting research to satisfy requirements for a doctoral degree in the Graduate Program in Neuroscience here at Rutgers, I was afforded the opportunity to participate in the National Science Foundation Innovation Corps (I-Corps) Program. The NSF I-Corps’s mission is “to foster entrepreneurship that will lead to the commercialization of technology that has been supported previously by NSF-funded research” ("NSF Innovation Corps: About I-Corps," 2015). The NSF I-Corps platform can be thought of as an entrepreneurship incubator that is fast-paced and demanding.

A total of 23 Venture Teams participated in the NSF I-Corps Program that was held from July 14th to August 26th, 2014 at the University of Michigan. Venture Team
341 consisted of the dissertation chair, Dr. Elizabeth B. Torres, industry mentor Dr. Sathapana Kongsamut, and myself as the Entrepreneurial Lead. The objective was to validate the commercial impact of our technology to determine if there is product-market fit and substantial market potential to pursue the venture. During the intensive 7-week program based out of the University of Michigan I-Corps Node, we conducted 116 customer discovery interviews (70 in-person) using Lean Startup Methodology to construct and refine our business model, identifying potential revenue streams, understanding purchase decision-making processes, creating distribution models, and estimating cost structure.

As we learned, transitioning from the lab to the market is no easy feat. We started our discovery process based on assumptions that practically every market segment we explored would find utility in our statistical platform. To our dismay, our confirmation bias blinded us from understanding the true needs of the greater public. The NSF I-Corps experience taught us to objectively investigate the ecosystem that makes up each market segment we pursued. As a result, we identified the autism community as our main target, as existing diagnostic and therapeutic tools are incapable of capturing the sensory-motor processing issues that we see in the lab.

We identified disturbing accounts from families who spoke of the constant fight to obtain proper medical coverage for children with ASD. We learned that the very source of these issues lies in the metrics used to assess functional improvements in therapeutic interventions. Evaluations were subjectively based, with very few advances
made in the clinic to record data other than by paper and pencil. These discoveries have fostered ongoing collaborations to translate our methodology to clinically relevant applications that address the needs of the ASD population. Our hope is that we can shed light onto these issues so that researchers can begin to strengthen relationships beyond the scientific community to improve upon the lives of individuals within the autism ecosystem and beyond.
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