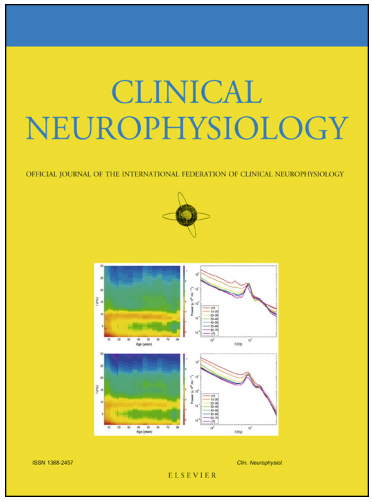

Review

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Lucio Marinelli, Angelo Quartarone, Mark Hallett, Giuseppe Frazzitta, Maria Felice Ghilardi

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The many facets of motor learning and their relevance for Parkinson's disease

Lucio Marinelli[1,*], Angelo Quartarone[2,3], Mark Hallett[4], Giuseppe Frazzitta[5], Maria Felice Ghilardi[6,3,*]

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Italy

[2] IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Department of Neuroscience, University of Messina, Italy

[3] The Fresco Institute for Parkinson's & Movement Disorders, NYU-Langone School of Medicine, New York, NY, USA

[4] Human Motor Control Section, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

[5] Department of Parkinson's disease and Brain Injury Rehabilitation, "Moriggia-Pelascini" Hospital, Gravedona ed Uniti, Como, Italy

[6] Department of Physiology, Pharmacology & Neuroscience, CUNY School of Medicine, New York, NY, USA

*** Corresponding author:**

M. Felice Ghilardi

Department of Physiology, Pharmacology & Neuroscience, CUNY Medical School, 138th Street and Convent Avenue, New York, NY 10031, USA

E-mail: lice.mg79@gmail.com

Highlights

- Retention of motor skills is impaired in Parkinson's Disease, despite preserved on-line learning.
- Declarative learning is impaired even in the early stage of Parkinson's Disease.
- Exercise, but not levodopa can improve motor learning and plasticity in Parkinson's Disease.

Abstract

The final goal of motor learning, a complex process that includes both implicit and explicit (or declarative) components, is the optimization and automatization of motor skills. Motor learning involves different neural networks and neurotransmitters systems depending on the type of task and on the stage of learning. After the first phase of acquisition, a motor skill goes through consolidation (i.e., becoming resistant to interference) and retention, processes in which sleep and long-term potentiation seem to play important roles. The studies of motor learning in Parkinson's disease have yielded controversial results that likely stem from the use of different experimental paradigms. When a task's characteristics, instructions, context, learning phase and type of measures are taken into consideration, it is apparent that, in general, only learning that relies on attentional resources and cognitive strategies is affected by PD, in agreement with the finding of a fronto-striatal deficit in this disease. Levodopa administration does not seem to reverse the learning deficits in PD, while deep brain stimulation of either globus pallidus or subthalamic nucleus appears to be beneficial. Finally and most importantly, patients with PD often show a decrease in retention of newly learned skill, a problem that is present even in the early stages of the disease. A thorough dissection and understanding of the processes involved in motor learning is warranted to provide solid bases for effective medical, surgical and rehabilitative approaches in PD.

Keywords: exercise; plasticity; implicit learning; declarative learning; dopamine; levodopa.

Introduction

Motor learning in Parkinson's disease (PD), defined as the ability to learn and refine skills, has been the subject of investigations and debate for more than two decades. In fact, studies have produced controversial results, as whether or not motor skill formation is impaired in PD. Confounding factors are many, starting from the use of a variety of tasks that tap into different cognitive and motor aspects to the influence of drugs and therapies used in PD. Another important problem in deciphering those results is the range of terminology used in defining the type of learning involved in the different motor tasks. The study of motor learning, a special category in the field of learning and memory, is a relatively recent, but rapidly growing field that has borrowed, sometimes inaccurately, nomenclature and definitions from neuropsychology. Briefly, neuropsychological research has proposed a major distinction between *explicit* and *implicit* learning (Tulving 1985; Squire and Zola-Morgan 1991). Explicit (or *declarative*, *noetic*) learning is the capacity for *conscious*, declarative learning and memory about facts and events that can be expressed through recollection, and constitutes a sort of memory register for facts and notions, be they general or autobiographical. Implicit (or *non-declarative, procedural*, *anoetic*) learning, on the other hand, refers to a heterogeneous collection of *unconscious*, non-declarative memory abilities, which includes procedural learning and thus, all motor skill and habit formation. From an operational point of view, while implicit processes are usually measured by continuous variables, explicit learning is more likely to involve discrete changes and variables. Moreover, factors such as instructions, selection of performance measures, contextual cues as well as motivation might be implicit or explicit in nature and differentially influence the use of implicit or explicit “channels” and attentional resources. One must not assume that all the processes that occur during motor learning are *implicit*; in fact, motor learning is a multistep operation, involving both declarative and procedural mechanisms, usually at different stages (Moisello et al. 2009). In the

following review, we will first address general concepts and ideas about motor learning; we will then summarize the results of motor learning studies in PD focusing on the type of tasks used and the effect of drugs and other therapeutic interventions. Finally, we will review the few studies that have investigated retention of motor skills in PD. Dissecting motor learning is highly relevant in PD: as illustrated in this review, motor learning encompasses the formation and retention of motor skills and, in particular, the achievement and the use of automaticity in daily routines, which are both impaired in PD. Detailed knowledge of the learning processes in this context is important to enhance and maximize the effects of rehabilitation and compensation strategies to overcome the motor deficits and the disabilities imposed by PD.

Different stages of motor learning: Explicit and Implicit processes are both present

Explicit or declarative processes are important for most motor skill learning. In fact, many of the actions that we learn or we perform daily can be described, to some extent, verbally and the initial stages of learning new motor routines, the *what to do*, often rely on verbal and visual information. An example is when volleyball players first learn to hit the ball: following the coach's instructions, they learn to take three steps, jump, raise the arm and then hit the ball. However, despite as much detail one can provide in a verbal or visual description, this does not guarantee that performance will be flawless and effective: extensive hands-on practice needs to follow to obtain winning actions. Thus, explicit information and actual performance must coexist in variable degrees at different stages of practice, depending on the task, on the instructions and also on individual differences such as genetic predisposition, age, experience, motivation and personality.

The classic view on the development of motor skills (Fitts 1964; Anderson 1982; Logan 1988; Anderson 1995) posits that motor learning generally occurs in three main phases: *cognitive*, *associative* and *autonomous* phases (Figure 1). In the first, the *cognitive* phase, the learner is usually new to a task

and the primary concern is to understand *what* needs to be done mostly through the interpretation of verbal instructions, a declarative process (Anderson 1982). In this phase, performance is usually effortful, tentative, slow and inaccurate, but dramatic gains in proficiency, generally larger than at any other time, are noted. Declarative and attentional processes as well as cognitive strategies mediate most of the improvement, with major advances in terms of *what to do*, rather than in the refinement of motor patterns themselves (*how to do*). The duration of this "verbal-motor" stage (Adams 1971) usually depends on the clarity of the instructions (see also the end of this part) and on the complexity of the task. Indeed, very simple tasks, like the repetitive flexion of the index finger, have a very short *cognitive* phase that can be captured only focusing on the first few movements. The second phase of learning, also known as *slow learning stage*, or *motor stage* (Adams 1971), starts when subtle performance adjustments, imperceptible to the subject, occur: movements become more consistent and improvements more gradual. In this phase, which might persist for days or weeks, performance becomes more accurate and automatic with small changes in the motor patterns, as the declarative aspects have completely or largely dropped out and *implicit* mechanisms have taken over. Finally, after a longer time of practice, perhaps as long as months or years, in the third phase, the skill becomes largely automatic, as it can be performed with little deployment of attentional resources and less interference from other simultaneous activities. In this "automatization" phase, extended practice establishes a direct condition-action association: the result is that performance is faster, effortless, and more precise with movement details unavailable to awareness. An important change contributing to the increased efficiency is that, in this phase, movements are planned in a motor-center coordinate system rather than using a vision-center coordinate system as in the earlier learning stages (Figure 2; see also: Ghilardi et al. 1995). As a consequence, at this stage the transfer of the skill becomes effector-specific. Declarative processes are ousted by implicit mechanisms and optimization and automatization are

achieved: attending to a particular stimulus is sufficient to retrieve rapidly an associated, specific solution from memory. Indeed, the more represented the experience, the faster and the more efficient the retrieval (Logan 1988). Importantly, this depends not just on the amount of practice but also on its specificity: performance improves more and faster with practice in consistent environment for the specific stimulus and the mapping rules experienced during training. An important advantage of automatization and optimization is that attentional resources can be freed for other necessities, such as deploying them to higher order aspects of the task, performing simultaneous tasks or simply resting neural substrates to prevent fatigue. The most fitting description of the processes linked to motor learning is through the power law that proposes that the learning of a motor skill is complete when the parameters describing optimization, after an exponential increase, reach an asymptote (Logan 1988). Needless to say, investigations on the automatization processes in motor learning, which are of crucial importance for understanding high levels skills, are rare because of the difficulty of reproducing such long time intervals in an experimental context. Therefore, the majority of studies on learning and PD have mostly focused on the first and second phases of learning. Indeed, automaticity and its mechanisms are abnormal in PD and have great role in the genesis of motor dysfunction (Wu and Hallett 2005; Wu et al. 2010), as also detailed in a recent review (Wu et al. 2015).

Explicit and Implicit processes in motor sequence learning and their neural substrate

The progression through different learning stages has been studied with imaging mostly using motor sequence learning tasks with explicit instructions. The pattern of activation that emerges from these studies assigns an important role to cortico-striato-thalamo-cortical loops, in particular to the "*visual*" and "*motor*" loops (Alexander et al. 1986; Nakahara et al. 2001). A schematic representation is given in Figure 2. The *visual* or "*cognitive*" cortico-striatal loop links the dorsolateral prefrontal cortex (DLPFC), the inferior parietal cortex and the anterior part of the striatum (caudate nucleus and

anterior putamen) and is involved in the initial stages of learning, when visuo-spatial abilities and working memory are crucial. The *motor* loop connects motor, premotor, somatosensory and supplementary motor areas (SMA) to the posterior part of striatum (posterior putamen) and is involved in performance optimization. The pre-SMA likely coordinates the activities of these two loops (Nakahara et al. 2001). In the early stages of motor learning, there is a prominent involvement of the *cognitive* loop, followed by a gradual reduction in favour of the motor loop activity, thus with a transition of cortical activation from DLPFC to central regions (Toni et al. 1998; Hikosaka et al. 1999, 2002). The earlier activity of DLPFC reflects the engagements of attentional and executive functions that are needed to acquire the sequence order in the first learning phases. The pre-SMA is also active in the early phase, but its activity increases in intermediate phases, possibly to facilitate the transition of activation to the *motor* loop (Shima and Tanji 2000). The precuneus, which is also active in intermediate phases, might help retrieving the sequence order from memory; since its activity wanes later on, its activity has a *declarative* function. Finally, the latest phases are characterized by activity in the context of the motor loop, with no relation to conscious perception (Sakai et al. 1998), when optimization processes are engaged and the need of attention greatly diminished. In summary, there is a smooth transition from the visual-cognitive to the motor loop, with a switch from anterior to posterior circuits, from declarative learning to optimization networks. The participation of cerebellum in this process is discussed in the following paragraphs. Finally, the transition from the visual-cognitive to the motor loop not only corresponds to a switch from controlled to automatic processes but also to a change of the coordinate system used to program the movement, from vision-centered to motor-centered (Figure 2), with significant gains in efficiency.

Cerebro-cerebellar interactions also are important in sequence learning processes, although their role has not fully been elucidated. Activation of cerebellar cortex and dentate nucleus occurs at

the beginning of the motor phase of sequence learning (Carbon et al. 2003; Penhune and Doyon 2005); during successful sequence learning, activation of the cerebellar cortex co-varies with those of lateral and medial premotor cortices (Carbon et al. 2003). Also during learning, cerebello-thalamo-cortical pathways seem to have effects on the sensorimotor (Molinari et al. 2002; Daskalakis et al. 2004) and medial premotor cortices (Carbon et al. 2003). While at the beginning of the motor phase of sequence learning there is also a linear dependence between the activity of the sensorimotor cortex and of the spinal cord. This dependence fades away in the course of learning, whereas functional connectivity between spinal activity and cerebellum measured in fMRI experiments gains strength (Vahdat et al. 2015). While the nature of these interactions is not well understood, during learning such interactions might produce distinct inhibitory and facilitatory effects on the motor cortex, which are different from those present when simple movements are used (Torriero et al. 2011).

The joint contribution of the cerebellum and the basal ganglia on motor learning has been increasingly emphasized. In particular, recent work has challenged the traditional view about the connections between basal ganglia and cerebellum by hinting that both structures integrate inputs from widespread cortical areas in the prefrontal, parietal and temporal lobes funneling information to the primary motor cortex via the thalamus. According to this new vision, the cerebellum and basal ganglia might exchange neural information thanks to an extensive multi-synaptic sub-cortical network bypassing the thalamus. Indeed, animal studies in monkeys have demonstrated topographically organized di- or tri-synaptic projections running from both motor and non-motor domains of dentate nucleus, passing through the thalamus and reaching the putamen or the external segment of globus pallidus. This system was paralleled by a di-synaptic afferent pathway from sensorimotor, associative, and limbic territories of the subthalamic nucleus to the posterior aspects of Crus II and the hemispheric lobule VIIB of the cerebellar cortex, passing through the pontine nuclei (Hoshi et al. 2005; Bostan et

al. 2010). Importantly, recent work with diffusion tensor imaging and tractography reconstruction has confirmed, *in vivo,* in humans, the presence of extensive connections between the basal ganglia and cerebellum, including the existence of sub-cortical pathways running between the subthalamic nucleus and the cerebellar cortex via the pons (Cacciola et al. 2016), with a **possible** direct route linking the dentate nucleus to the globus pallidum and the substantia nigra (Cacciola et al. 2016). The existence of direct cerebellum-pallidal and cerebellum-nigral pathways may provide, in humans, a short-latency route for fast interaction between the cerebellum and the basal ganglia to harmonize their outputs in real-time (Cacciola et al. 2017) and thus to provide the bases for their co-activation, which has been shown in motor learning studies with fMRI.

Several evidences also suggest a compensatory role of the cerebellum in PD which is crucial in maintaining a relatively normal motor and non-motor function at early stage of the disease (Wu and Hallett 2013). However this compensatory effect may diminish or eventually fail as pathological damages become more severe at the advanced stage (Jankovic 2005). Finally, cerebellar plasticity may become maladaptive and contribute to the appearance of levodopa-induced dyskinesias (Kishore et al. 2014).

Interference and sleep affect retention and consolidation

Importantly, the latest phases of learning depend not only on the amount of practice, but also on interposed activities and sleep. In fact, while performance on a specific motor task is usually better the day following the first acquisition training (Brashers-Krug et al. 1996; Shadmehr and Holcomb 1997), interposed activities that engage the same neural loops might prevent its retention and improvement (Brashers-Krug et al. 1996; Shadmehr and Holcomb 1997; Krakauer et al. 1999, 2005; Ghilardi et al. 2009). Therefore, if, after learning to perform movements in a first viscous force field, subjects immediately after learn to move in a second force field of opposite direction, retention of the first skill

does not occur (Shadmehr and Holcomb 1997). Similar phenomena occur also for visuo-motor adaptation to clockwise rotation followed by training with counterclockwise rotation (Krakauer et al. 1999, 2005), for speed and accuracy in tasks of finger movement sequences (Karni et al. 1998; Walker et al. 2003) and of reaching movements (Ghilardi et al. 2009). Importantly, the second task no longer interferes with the retention of the first task if sufficient time (i.e., from five to twenty-four hours) elapses between the two tasks. Moreover, performance in the first task becomes more resistant to interference from a second one even if practiced a few minutes later, if the amount of practice in the first task is substantially increased (Krakauer et al. 2005; Ghilardi et al. 2009). Resistance to interference by a similar task is defined as "consolidation". It should be noted that, in the literature, the terms "skill retention" and "consolidation" have been used as synonyms, although sometimes inappropriately. It is also possible to produce interference by using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS). For example, 1 Hz-rTMS can disrupt the consolidation of a ballistic pinch task (Muellbacher et al. 2002). However, both the timing and the location of the stimulation are crucial to obtain the desired result: the effect is present only for stimulation of the contralateral M1 applied just after the task. Enhancement of retention can also be obtained using high frequency rTMS (Moisello et al. 2015a) and by anodal tDCS applied over the motor cortex (Cantarero et al. 2013; Leow et al. 2014).

Another important aspect that affects retention of motor skills is sleep. The idea that sleep plays a crucial role in any type of learning and memory has a long history (Jenkins and Dallenbach 1924). Over the past several decades, careful experimental studies have provided strong evidence that sleep can enhance performance of tasks learned during prior wakefulness. This enhancement is not merely time-dependent, but specifically requires sleep, and is independent of circadian factors. By now, evidence of sleep-dependent memory enhancement has been found in human and nonhuman primates,

cats, rats, mice, and zebrafish, using a variety of behavioral paradigms (Peigneux et al. 2001; Smith 2001). While initial studies focused on a role for REM sleep (Karni et al. 1994), more recent studies have emphasized the importance of NREM sleep (Gais and Born 2004; Peigneux et al. 2004), of specific components within NREM sleep such as spindles (Gais et al. 2002) and slow waves (Huber et al. 2004), and of a combination of NREM and REM sleep (Mednick et al. 2003). Perhaps the most consistent evidence of sleep-dependent enhancement has been in skill formation and for implicit learning, although examples of sleep-dependent enhancement of explicit memory have also been forthcoming. Over the past ten years, several studies have shown a beneficial effect of sleep after motor, visual, and auditory tasks that are learned implicitly - without explicit awareness of what is being learned (Karni et al. 1994; Gais et al. 2000; Stickgold et al. 2000), auditory (Atienza et al. 2004; Gaab et al. 2004), and motor systems (Smith and MacNeill 1994; Fischer et al. 2002; Korman et al. 2003; Walker et al. 2003; Walker and Stickgold 2004). Importantly, a night of sleep can trigger significant performance improvements in speed and accuracy on a sequential finger-tapping task, while equivalent periods of time during wake provide no significant benefit (Walker et al. 2003). Sleep is also important to improve retention on both explicit and implicit aspects of motor learning captured with a motor sequence learning task (Kvint et al. 2011). An important development regards the search for specific aspects of sleep EEG activity, such as spindles and slow waves that predict post-sleep performance improvement. It should be noted that spindle activity is closely associated with cortical slow oscillations and slow wave activity (Steriade and Timofeev 2003). For instance, it has been found that NREM spindle density increased after a task that involved learning to walk in a city maze (Meier-Koll et al. 1999). In addition, we have shown that a visuo-motor rotation adaptation task, an implicit learning task, compared to a control non-learning task, produced an increase in slow wave activity that is localized to right parietal cortex, a brain region known to be involved in learning the task (Huber et

al. 2004). Most importantly, this local increase in slow wave activity is highly correlated with the improvement in performance that is observed the next day (Huber et al. 2004). Taken as a whole, these studies leave little doubt that sleep, and slow wave activity in particular, plays a critical role in post-training motor memory formation.

The effects of instructions: Explicit, Implicit and Incidental Learning

In many motor tasks, instructions about what to learn are very explicit. This occurs, for instance, when subjects are explicitly requested either to learn a sequence of events and actions or to apply rules and strategies to accomplish a goal such to make a movement to a target with an opposite direction from the presented target. However, there are instances where subjects are not informed about being tested about learning and instructions do not contemplate any learning aspects. In these cases, learning of some sort can occur *incidentally*. A striking case of *incidental* learning is the serial reaction time (SRT) paradigm (Nissen and Bullemer 1987), a widely used task to test the learning of a sequence's order including in PD, where the learning is not intentional because it is not stated in the task's instructions. Indeed, In this task, subjects are usually required to press as fast as possible one out of four buttons when the corresponding target on a screen lights up. Unbeknownst to them, targets appear in a series of blocks of a fixed, repeating sequence interspersed with blocks of random sequences. The median of the response time (i.e., the time required to press the corresponding button), which is measured for each block, progressively decreases across sequence blocks and increases in random blocks introduced after several sequence blocks. These differences between sequence and random blocks have been interpreted as evidence of unaware acquisition of the sequence order, that is, a type of *implicit* "sequence learning", as subjects are not allegedly aware of the entire sequence order (Willingham et al. 1989). However, it is unlikely that this is a pure measure of implicit learning, as detailed in Figures 3 and 4. Briefly, first, subjects with significant changes in this measure most of the

times have a declarative knowledge, although partial, of the sequence order. In the classical SRT tasks, declarative knowledge (which is defined at knowledge of at least 50% of the sequence) is tested only "a posteriori" and is subjected to temporal decay and to interference from many sources, including the interposition of random blocks. Second, experiments dissecting this task with different kinematic measures have shown that, during SRT paradigms, two processes strictly related to a motor sequence learning occur: the most effective process in terms of decrease in response time is the development of the knowledge of sequence order, a *declarative* process, which is also followed by kinematic optimization, an *implicit* learning process (Ghilardi et al. 2009; Moisello et al. 2009). The response time, used as the sole learning outcome for SRT tasks, represents a combination of the two learning processes (which sometimes have cancelling effects) and results from two measures, reaction time and movement duration (Pascual-Leone et al. 1993; Moisello et al. 2009). The two measures are differentially affected by the development of explicit learning (mostly expressed by changes in reaction time) and of implicit learning (with which mostly affect movement duration) (Figures 3 and 4, see also Moisello et al. 2009). As illustrated in Figures 3 and 4, acquisition of the sequence order is a declarative type of learning, which is faster, measurable directly with discrete variables and indirectly, with changes in reaction time. Kinematic optimization, that is the ability to perform the sequence of movements smoothly and efficiently in that specific context, usually follows with practice, when the entire sequence is known, and it is measurable with continuous kinematics and biomechanics variables (Figure 4) (Ghilardi et al. 2008, 2009; Moisello et al. 2009).

Finally, neuroimaging studies (Schendan et al. 2003) have shown that performance in an SRT task involves a significant activation of dorsolateral prefrontal cortex and medio-temporal areas, which are essential substrates of the declarative memory system (Squire and Zola 1996) and are mostly active during conscious learning (Grafton et al. 1992; McIntosh et al. 1999). For these reasons, the results of

studies with the classical SRT task are difficult to interpret in terms of explicit and implicit learning. However, variants of the classical SRT tasks strictly controlling for these factors have been successfully used to determine the functional and anatomical bases of implicit and explicit learning (Pascual-Leone et al. 1994; Honda et al. 1998), as also discussed other parts of this paper.

In summary, when instructions are specific and the learning intentional, attention is focused on the objective. On the other hand, when the instructions do not address the subjects' attention toward the specific aim (in the case of the SRT task, the sequence order), explicit knowledge can be achieved *incidentally* only when the subjects are able to shift or broaden the temporal or spatial focus of their attention.

Learning may occur with and without cognitive strategy

The effectiveness of using explicit or cognitive strategies (or a trial-and-error approach) depends a great extent on the type of feedback provided. When the feedback of the performance is constituted of "discrete" information and is available at the completion of each response, the use of explicit, cognitive strategies is usually very effective, while its absence might delay learning. However, when the feedback provided is in the form of "continuous" stream information during the learning itself (such as visual and proprioceptive information during the learning of sensorimotor transformations or proprioceptive information during fast index extensions), the use of explicit strategies might be less efficient. In fact, subjects may learn a transformation rule, but the implementation of the rule in each single instance will require longer time and after effects will be virtually non-existent (Mazzoni and Krakauer 2006). The mere execution of the motor task, without the use of a cognitive strategy, will be very efficient and will speed up the learning process (Mazzoni and Krakauer 2006). This is the case of tasks in which subjects progressively adapt their movement to visually rotated path displays (Huber et al. 2004; Landsness et al. 2009; Marinelli et al. 2009;

Landsness et al. 2011; Perfetti et al. 2011; Moisello et al. 2015a). Usually, the instructions are to make a movement as soon, as accurate, and as fast as possible without attempting any corrections. If the imposed rotation is below or close to the threshold of a perceived "rotation", i.e., around 20° (Marinelli and Ghilardi, unpublished data), gradual adaptation, measured as a decrease in direction error measured at the peak velocity, occur without the subjects' awareness of either the rotation or the adaptation itself. For this reason, the learning occurring during this task can be considered *implicit*. Conversely, if the imposed rotation or visuo-motor transformation is highly noticeable, subjects usually employ a cognitive strategy with a trial-and-error approach that is reflected in a step-wise decrease of the directional error and an initial substantial increase in reaction time. Furthermore, they can perfectly describe the strategy used and the nature of visuo-motor distortion. Therefore, this type of adaptation heavily relies on attentional and spatial working memory mechanisms and requires the engagement of neural substrates that are part of the declarative memory system (Squire and Zola 1996) active during conscious learning (Grafton et al. 1992; McIntosh et al. 1999).

Reward and learning

Motivation and reward are intermingled and drive actions and projects throughout people's lifetime. Motivational processes may effectively influence human performance and specifically motor learning (Balleine and Dickinson 1998). Both animal and human studies confirmed the role of dopamine in learning processes associated with a reward. Dopamine neurons in the substantia nigra pars compacta and the ventral tegmental area show a phasic activation associated with positive reward and induce D1- and D2-mediated long-term potentiation processes (Matsumoto 2015). Specific brain regions contribute to reward-based memory, including ventral striatum (Wächter et al. 2009), ventral tegmental area, nucleus accumbens, and hippocampus (Wittmann et al. 2005; Adcock et al. 2006; Kuhl et al. 2010). Functional MRI studies however showed that brain activity related to reward is ubiquitous

and involves many structures along mesocortical and mesolimbic dopaminergic pathways (Vickery et al. 2011). Indeed, ventromedial and orbitofrontal prefrontal cortex, amygdala, anterior insula and mediodorsal thalamus are also strongly engaged in brain reward mechanisms (Sescousse et al. 2013). The role of these brain structures in motor learning and consolidation was investigated using behavioral tasks often in association with volumetric and functional MR studies. In normal humans, grey-matter volume of the lateral prefrontal cortex predicted the degree of reward-dependence during a sequential explicit visuomotor acquisition task (Dayan et al. 2014). Functional MRI brain connectivity evaluation associated with a visuomotor force pinching task confirmed that connectivity in the frontostriatal-limbic network is related to the consolidation of motor skills only when the training is rewarded (Hamann et al. 2014). Increased dopaminergic function in the midbrain and striatum was associated with reward and triggered long term potentiation that gradually developed in the hours following the training process (Jay 2003). Rewarded training determined greater consolidation and long term retention compared to neutral or punished training (Abe et al. 2011).

PD is an ideal model to understand the role of dopamine when reward and motivation interact with motor control and learning processes. In the recent years, research studies tackled the complex interplay between cognition, motivation and movement in the parkinsonian model. Among the motor features of PD, bradykinesia is specifically modulated by motivation. When experiencing physical or emotional stress, PD patients may show transient increase of movement speed (Schlesinger et al. 2007; Bonanni et al. 2010). Strong motivation can therefore temporarily reduce bradikinesia, hypothetically involving noradrenergic transmission, visual cueing and activation of compensatory circuitry. In experimental conditions, movement time decreased in a rewarded context both in off and on conditions when PD patients were tested using a simple reaction time paradigm (Kojovic et al. 2014). Notably, the improvement was more efficient during the on state. Dopamine increased the

propensity to invest more effort in energy-demanding tasks, exerting a motivating influence on choice behavior (Chong et al. 2015). Dopamine depletion made PD patients less willing to invest effort compared to controls (Chong et al. 2015), implicitly affecting estimation of movement energy cost and therefore movement speed (Mazzoni et al. 2007; Moisello et al. 2011b). Movement variability is reduced in PD, probably because of impaired sensitivity to negative outcomes (with preserved sensitivity to positive outcomes), determining less exploratory variation in motor performance (Pekny et al. 2015).

The knowledge about how motivation influences learning processes in normal subjects and motor control in PD patients provides the basis for future studies aimed at understanding how reward and motivation influence learning and consolidation of motor memories in PD.

Motor learning in PD: implicit learning and retention in visuomotor adaptation tasks

The first studies that investigated procedural or implicit learning in PD used a variety of experimental paradigms in which subjects adapted their performance to novel situations without a cognitive strategy. These included mirror-reversed tracking (Frith et al. 1986), word-fragment priming (Taylor et al. 1990), mirror-reversed reading and pursuit-rotor tracking (Bondi and Kaszniak 1991). All these studies found that *implicit* learning in non-demented PD patients was unaffected. Conversely, with a reaching motor task in which the direction of the movements was rotated by 90° on the screen, patients with PD showed both slower and reduced adaptation compared to controls (Contreras-Vidal and Buch 2003). As described in the previous paragraphs, such a large amount of rotation engages attentional and cognitive strategies similar to those involved in mental rotation tasks that are impaired in PD (Yamadori et al. 1996; Amick et al. 2006). Similarly, motor adaptation to prism displacement in PD can be impaired (Canavan et al. 1990) or normal (Weiner et al. 1983; Stern et al. 1988) depending upon the magnitude of prism displacement.

Indeed, experimental paradigms with visuomotor transformations that do not require the use of cognitive strategy provide a good way to assess implicit motor learning, as they decrease the amount of declarative processes involved. For example, this is the case of learning to scale movement amplitudes, a task in which the performance of patients with PD and age-matched control subjects is rather similar (Smiley-Oyen et al. 2003). In a reaching task where the movements of the upper limb that were shown on a screen as rotated by 90°, PD patients showed both slower and reduced adaptation compared to controls (Contreras-Vidal and Buch 2003). Indeed, effective adaption to such amount of rotation triggers the use of cognitive strategies and explicit mechanisms (Marinelli et al. 2009) similar to those involved in mental rotation tasks, where the performance of patients with PD is invariably impaired (Yamadori et al. 1996; Amick et al. 2006). Reducing the amount of rotation to 30° or lower values make the learning occur implicitly, without awareness and thus, without the use of cognitive strategy. In such conditions, patients with PD adapt similarly to controls (Marinelli et al. 2009; Bédard and Sanes 2011; Isaias et al. 2011; Moisello et al. 2015a), independently of their disease severity and the use of dopaminergic treatment.

Retention of motor skills in PD has been assessed in a limited number of studies, mostly with tasks testing implicit learning. Differently from the studies evaluating the first phase of learning, those studies have unequivocally reported impaired retention, despite intact initial learning (Stern et al. 1988; Smiley-Oyen et al. 2003; Cohen and Pourcher 2007; Marinelli et al. 2009; Mochizuki-Kawai et al. 2010; Bédard and Sanes 2011; Isaias et al. 2011; Terpening et al. 2013). The most controlled studies were performed with adaptation to small rotations of the visual display. Briefly, these studies showed that that the deficit in retention was present already in the early stages of the disease in treated and untreated patients (Marinelli et al. 2009), when tested either immediately after training or 24 and 48 hours later (Marinelli et al. 2009; Bédard and Sanes 2011) and even when the initial training was

substantially increased (Bédard and Sanes 2011). Confirming this deficit, studies have also shown that the transfer of the learned skill to the other hand was diminished in patients with PD compared to controls (Isaias et al. 2011). The reason for impaired retention of new skills in PD is likely to be that the formation of motor memories (that is, the mechanisms that produce new internal models or that modify pre-existing models) is impaired due to a deficit of induction of long-term potentiation (LTP)-related phenomena (Marinelli et al. 2009). In fact, many studies have now shown that there are deficits of cortical potentiation, which reflect LTP-like phenomena, in the primary motor cortex of patients with PD (Morgante et al. 2006; Ueki et al. 2006; Suppa et al. 2011; Kishore et al. 2012; Kojovic et al. 2012). This deficit might extend to other cortical areas, including those involved in rotation learning and retention, that is, the right posterior parietal areas (Ghilardi et al. 2000; Huber et al. 2004; Landsness et al. 2011; Perfetti et al. 2011). In other words, the neural activity resulting from training might induce a weak neural activity not sufficient to trigger efficient LTP cascade signaling, but enough to produce a priming effect, that is a neural trace can be further boosted. In fact we recently (Moisello et al. 2015a) found that retention in patients with PD improved with the stimulation of the right parietal areas with 5 Hz repetitive transcranial magnetic stimulation (rTMS), a treatment that enhances LTP-like phenomena in vivo (Quartarone et al. 2005; Esser et al. 2006; Huber et al. 2007; Wang et al. 2011). The results of that study suggest that using rTMS in close temporal proximity with a task that activates specific neural pathways is a possible approach to enhance plasticity in PD. Further evidence of altered cortical plasticity comes from a recent study on prolonged motor practice and modulation of EEG activity in the beta band (Moisello et al. 2015b). In agreement with previous TMS work showing that local power changes in the beta frequency range likely reflect cortical plasticity modification (McAllister et al. 2013), that study showed a practice-related increase in the amplitude of event-related synchronization and desynchronization in normal subjects but not in patients with PD

(Moisello et al. 2015b).

Another important factor in determining a deficient retention of new skills in PD could be related to the role of sleep in retention. In fact, sleep disturbances are frequent complaints already in the early stages of PD, with a very high prevalence varying from 40 to 98% (Dhawan et al. 2006). Importantly, a study has shown a selective decrease in slow wave activity in both drug-naïve and treated patients compared to age-matched controls (Brunner et al. 2002). According to the *sleep synaptic homeostasis hypothesis* (Tononi and Cirelli 2014), decreased plasticity phenomena and sleep alterations could be strictly linked: a reduced sleep efficiency, particularly slow wave sleep, might reflect impaired long-term potentiation (LTP) mechanisms. In fact, that hypothesis posits that learning and its molecular counterpart, LTP, during wakefulness, result in local increases in synaptic strength, which in turn, promote slow wave activity during sleep. The net effect of these processes at the behavioral level is retention and potentiation of specific memory. A deficit in LTP-like mechanisms such as that present in PD might fail to trigger the appropriate mechanisms to promote slow wave activity during sleep, resulting in poor skill retention. Supporting this scenario is the recent finding that the production of nitric oxide, which is involved in LTP mechanisms, is abnormally modulated in patients with PD during sleep, thus producing an imbalance between REM and N-REM sleep (Wu et al. 2014).

PD and sequence learning with the SRT task

Ferraro et al (Ferraro et al. 1993) tested patients with PD with an SRT paradigm as described in the previous paragraphs. They maintained that this task measured implicit learning. They found no significant changes between the response time of sequence and random blocks and thus concluded that *implicit* learning was impaired in PD. Despite the claimed "*implicit*" nature of the task used, they further speculated that the results were due to the fact that the task required important attentional

resources, which can be impaired in PD. Other SRT studies reported conflicting results. In fact, some showed impaired (Westwater et al. 1998; Smith and McDowall 2004; Deroost et al. 2006; Siegert et al. 2006; Smith and McDowall 2006; Wilkinson and Jahanshahi 2007) and other preserved (Pascual-Leone et al. 1993; Jackson et al. 1995; Smith et al. 2001; Kelly et al. 2004; Seidler et al. 2007) SRT learning in PD. The results of these studies are difficult to interpret. First, as discussed in the previous paragraphs, SRT tasks involve both declarative and non-declarative learning components (Moisello et al. 2009) that cannot be merely measured with the difference of the response time between random and sequence blocks. In fact, the response time in SRT tasks partly depends on movement speed (Moisello et al. 2009), which in PD can be impaired simply due to bradykinesia, a clinical hallmark of the disease. In addition, the deployment of attentional resources needed for successful *incidental* learning (Dominey et al. 1997; Kelly et al. 2004) must be internally or self-driven, due to the absence of explicit learning instructions. This is an important point in PD, as these patients heavily rely on external drives and cues and typically exhibit a decrement of self-drive, that can at least partially explain the non-significant difference between response times of SRT sequence and random blocks. Therefore, the "abnormal" lack of change in response time in SRT tasks could reflect a motor deficit (Westwater et al. 1998; Deroost et al. 2006; Seidler et al. 2007) as well as a decreased self-drive and not an actual impairment in motor learning.

PD and sequence learning in motor tasks with declarative components

Deficits in the spontaneous generation of efficient strategies (Taylor et al. 1986, 1990) as well as problems with dual tasking (Soliveri et al. 1992; Canning et al. 2008; Nieuwboer et al. 2009) are present in PD. Patients with PD show great benefit from external cueing and visual feedback (Verschueren et al. 1997; Rochester et al. 2010), with important consequences on rehabilitative strategies (Lim et al. 2005; Abbruzzese et al. 2009; Nieuwboer et al. 2009). As previously discussed,

directing the attentional resources with specific, explicit instructions leads to a faster and more efficient learning of the order of motor sequences in normal subjects (Moisello et al. 2009). Nevertheless, even when tested with sequence learning tasks with such characteristics, patients with PD have unequivocally demonstrated slower learning and impaired performance (Ghilardi et al. 2003; Smiley-Oyen et al. 2006; Nagy et al. 2007; Marinelli et al. 2010; Mochizuki-Kawai et al. 2010). The likely cause is a decrease of awareness and attentional resources (including spatial memory and spatial working memory), which present already in the early stages of PD, also in the absence of dementia (Owen et al. 1993, 1997; Postle et al. 1997; Pillon et al. 2000; Kemps et al. 2005) and which are due to alteration of striato-frontal pathways. With disease progression, acquisition of sequence learning further deteriorates (Carbon et al. 2010).

Functional neuroimaging studies have been useful to characterize the neural bases of sequence learning in patients with PD. In studies with motor sequence learning and explicit instructions, which is among the most used experimental paradigms in PD, the area that activates more clearly is the DLPFC (Nakamura et al. 2001; Carbon et al. 2003; Feigin et al. 2003; Mentis et al. 2003; Carbon et al. 2004; Carbon and Eidelberg 2006; Rounis et al. 2006), a crucial region for attention and working memory (Goldman-Rakic 1996; Arnsten 1997). The studies in PD have shown that the learning performance directly correlates not only with the activation of DLPFC (Feigin et al. 2003; Carbon et al. 2004), but also with that of the premotor cortex, posterior parietal cortex and occipital association areas (Nakamura et al. 2001; Feigin et al. 2003). When compared to normal age-matched controls, patients with PD show an increased activation of such areas with additional recruitment of homologous cortical regions and bilateral lateral cerebellum, possibly in the effort to compensate and to improve the outcome (Nakamura et al. 2001; Mentis et al. 2003). As discussed in previous sessions, the pattern of activation reflects the role of the "*visual*" and "*motor*" loops (Alexander et al. 1986; Nakahara et al.

2001). Interestingly, in sequence learning tested over two years (Carbon et al. 2010), activation in PD declined in most of these areas, including the parietal, occipital and DLPFC, while increases were found in the anterior cingulate cortex, pre-SMA and the hippocampus. These changes in activation were accompanied by worsening of the performance, indicating that, the compensation through a more extended task-specific activation becomes less efficient with the disease progression.

Levodopa effect on motor learning

Levodopa is considered the gold standard for the symptomatic treatment of PD. Although its effects on motor symptoms are well defined, those on cognitive aspects and learning are not as clear. Only few studies have assessed the effects of L-Dopa on motor sequence learning. However, since the 1970s, many studies have been reporting conflicting results about its effects on frontal cognitive performance, which are altered by PD. Whereas verbal fluency and set-shifting (Gotham et al. 1986, 1988) improve, levodopa may impair high speed memory scanning, associative conditional learning, visual learning, reversal, subject-ordered pointing and highly demanding executive tasks (Cools 2006; Ghilardi et al. 2007). Indeed, the results of human and animal studies (Murphy et al. 1996; Zahrt et al. 1997; Müller et al. 1998; Mehta et al. 1999; Adriani et al. 2000) point out that levodopa may have adverse effects on attention and working memory, cognitive aspects that are of great importance for successful performance in sequence learning tasks (Nakamura et al. 2001; Ghilardi et al. 2003). In fact, animal studies have shown that both excessive and insufficient stimulation of dopamine receptors in the DLPFC may disrupt attentional and working memory function, in a sort of inverse U function (Murphy et al. 1996; Zahrt et al. 1997). Therefore, it is possible that the levels of dopamine that are necessary to improve motor performance and UPDRS scores through the motor loop might produce over stimulation of the dopamine receptors in the DLPFC, thus causing attentional and working memory deficits. This view is also supported by studies that have shown that Levodopa does not

influence the performance during demanding executive tasks in clinically-stable patients without motor complications, but it has detrimental effects in patients with wearing-off (Kulisevsky et al. 1996). This might explain the results of a study where levodopa infusion was individually titrated to obtain a stable, maximal improvement in the motor UPRDS scores (Feigin et al. 2003; Ghilardi et al. 2007). This study demonstrated that motor sequence learning with explicit instructions was slowed down in the declarative aspects during such treatment compared to the off-drug state (Ghilardi et al. 2007). Nevertheless, tasks testing pure motor functions showed a significant performance improvement during levodopa infusion (Ghilardi et al. 2007). The differential effects of levodopa on motor tasks and on working memory attentional performance were confirmed by other studies (Jubault et al. 2009). A corresponding PET study showed that this slowing in learning was associated with impaired activation of occipital association cortex (Feigin et al. 2003). Moreover, the learning-related deactivation present in the ventromedial prefrontal cortex in normal subjects and in OFF-drug patients, was absent during the levodopa infusion treatment (Argyelan et al. 2008), in agreement with studies reporting that levodopa reduces cortical over-activity in DLPFC (Cools et al. 2002; Mattay et al. 2002). Treatment-mediated changes in deactivation correlated with the OFF-drug performance and with the val(158)met catechol-O-methyltransferase genotype. The authors concluded that levodopa has an influence on prefrontal deactivation during motor sequence learning, but these effects are also related to the performance at baseline and to the genotype. The negative effects of levodopa on attention and working memory have been confirmed also with a mirror-drawing learning task, where cognitive strategies and executive functions are significantly involved, with learning occurring more easily while patients are off levodopa (Anderson et al. 2014). That same study has shown that subsequent retention is independent from dopaminergic treatment (Anderson et al. 2014). A recent study assessing brain function with 18F-DOPA PET on untreated patients in the early stages of PD underlines the role of

mesocortical dopamine and possibly other catecolamines in the attentional processes related to learning and movement preparation (Marinelli et al. 2015).

Despite their common use already in the early stages of the disease, there are no studies on the effect of dopaminergic agonists on motor learning performance of patients with PD. However, a single study in a group of young healthy subjects has shown that stimulus-response learning with abstract images is decrease after one dose of 0.5 mg of pramipexole (Gallant et al. 2016). Thus, although more studies are needed, it is possible that dopaminergic agonists might interfere with learning also in patients with PD like levodopa.

Finally, no studies have addressed the effects of other neurotransmitter deficits, such as noradrenergic, serotoninergic and cholinergic deficiency, that might be present in PD. It is important to recognize that they play a role in some of the cognitive deficits observed in PD (Dubois and Pillon 1997) and thus, they could affect learning.

Deep brain stimulation effect on motor learning

Deep brain stimulation of the subthalamic nucleus (STN DBS) has been widely used with a significant benefit/risk ratio on the treatment of motor signs in PD. The effects on cognition have been less studied with controversial results. Most studies investigated the effect of DBS on working memory and other cognitive domains with neuropsychological testing: some showed absence of negative effect or presence of beneficial effect (Ardouin et al. 1999; Pillon et al. 2000; Gironell et al. 2003; Witt et al. 2004), but other stressed a mild but significant detrimental effect on cognitive functions, more evident with disorder progression and in aged patients (Saint-Cyr et al. 2000; Alegret et al. 2001; Parsons et al. 2006; Alberts et al. 2008; Witt et al. 2008). It must be noted that motor learning has not been specifically addressed in most of the cases; studies involving patients with internal globus pallidus deep brain stimulation (GPi DBS) and with STN DBS demonstrated an acute beneficial effect of both

types of stimulations (Fukuda et al. 2002; Feigin et al. 2003; Carbon et al. 2004; Argyelan et al. 2008), on motor sequence learning paradigms with a declarative component. The beneficial effect of STN DBS was also demonstrated acutely comparing STN DBS OFF, DBS ON and levodopa administration (Carbon et al. 2004; Argyelan et al. 2008). GPi DBS has been less used than STN DBS, but the effect on cognitive function appeared to be similar (Ardouin et al. 1999; Pillon et al. 2000). A more recent study underlines some differences between STN and GPi DBS: learning requiring mental control and cognitive flexibility is decreased in patients with GPi DBS compared to those with STN DBS (Rothlind et al. 2015). In addition, a longitudinal study comparing patients treated with either medical therapy or DBS showed that measures of processing speed and working memory have a greater decay in patients with DBS on a 6-month follow-up (Rothlind et al. 2015). DBS to the pedunculopontine nucleus seems to speed up working memory, possibly modulating attentional resources (Costa et al. 2010).

Exercise in PD: Implications from motor learning studies

The considerations about motor learning deficits in PD and in particular, the deficiency of retention of new skills, have important implications for the implementation of rehabilitation and exercise protocols in PD. For instance, a crucial point is that rehabilitation protocols should take into account that in PD there is a reduced cortical plasticity with consequence on retention of new skills: a treatment should address both the specific motor deficit and the decreased plasticity in order to maximize the positive effects and their duration. Indeed, in the last decade, an increasing number of papers has demonstrated that exercise exerts a positive effect on the parkinsonian symptoms that do not respond well to either pharmacological or surgical treatment, namely, gait, posture and balance (Bloem et al. 2015). However, not all types of exercise produce the same positive effect: to be effective, exercise should have appropriate intensity and repetition (the best results can be achieved with daily

treatments), difficulty, complexity and specificity (that is, it should be designed to target specific skills, such as gait) (Mehrholz et al. 2015). The effectiveness of motor rehabilitation interventions may further improve by adding sensory stimulation, cueing, and music in pleasant social contexts and environment that increase task enjoyment (Volpe et al. 2013). These approaches are now gaining more attention: each factor that makes motor training more attractive and improves motivation during the tasks can increase the patients' compliance and prevents the worsening of motor performance (for a review: Zemankova et al. 2016). Relevant is also the application of strategies during the exercise itself, which include the use of feedback, external cues, reward and motivation; this type of approach produce good results probably by allowing the execution of correct movements under attention-volitional control, with a direct access to cortical resources and limiting the use of automaticity mechanisms that are affected by PD (Nieuwboer et al. 2009). Importantly, as stated earlier, for good and lasting results neuroplasticity and thus, the retention of the re-acquired skills should be enhanced, since both are decreased in PD (Stern et al. 1988; Smiley-Oyen et al. 2003; Cohen and Pourcher 2007; Marinelli et al. 2009; Mochizuki-Kawai et al. 2010; Bédard and Sanes 2011; Isaias et al. 2011; Terpening et al. 2013). Some rehabilitation treatments might have these effects (Petzinger et al. 2013; Hirsch et al. 2016) and in particular, the aerobic exercises enhancing blood flow and have appropriate intensity and repetition. Indeed, the application of intensive rehabilitation treatments with these characteristics (Ferrazzoli et al. 2016) not only produces long lasting effects (Frazzitta et al. 2012) but also enhances BDNF levels and BDNF-TrkB activity (Frazzitta et al. 2014; Fontanesi et al. 2016). Other mechanisms by which exercise leads to beneficial effects include the decrease of the pathological hyperexcitability in the basal ganglia-cortical circuits and the induction of compensatory changes in dopamine handling and neurotransmission, in particular in the dorsolateral striatum (Petzinger et al. 2007). Finally, rTMS and neurofeedback are promising add-on treatments that may increase the persistence of the exercise-

related benefits (Yang et al. 2013; Subramanian et al. 2016).

Conclusions

In summary, motor learning cannot be simply labelled as "procedural" or "implicit", but must be defined by its characteristics, instructions, external or internal drive, cues, context, phase of learning and type of measures used. This is of great importance overall in PD, where movement execution is usually altered by motor problems such as akinesia and bradykinesia. When this is taken into account, motor learning that occurs without awareness or cognitive strategies is normal in PD. Conversely, learning that relies on attentional resources and cognitive strategies is usually slower in PD. An important problem in PD is the deficit in retention of new skill, which is present already in the early stages of PD and does not improve with treatment. Unlike DBS, dopaminergic medications do not improve learning. A better understanding of motor learning processes may provide solid bases for more effective medical, surgical and rehabilitative approaches.

Conflict of interest

The authors report no financial interests or potential conflicts of interest.

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Figure legends

Figure 1. The development of motor skills.

The cognitive stage (top) represents the first step of learning a motor task and encompasses the interpretation of verbal instructions (a declarative process), which should be then transformed into an expert motor act. This stage, usually with high performance variability, is fast and, depending on the task and the ability of the subject (born athletes might have a shorter cognitive stage), may last from minutes to hours. The second phase of learning (center), or motor stage, is mostly implicit with small performance improvements and might persist for days up to years, depending upon the intensity and frequency of training. This stage is complete when implicit mechanisms have taken over. In the third stage, autonomous (bottom) the skill has become automatic, as it can be performed automatically, with little attentional resources and less interference from other simultaneous activities. In this stage, a direct condition-action association is established and can be triggered by cues, implicitly. Performance is faster, effortless, precise, effector-specific with details unavailable to awareness.

Figure 2. Schematic representation of the neural bases of visuo-motor sequence learning*: from the visuo-cognitive (left panel, white background) to the motor stage (right panel, gray background).*

A. On the left, the visuo-cognitive stage, the first step of sequence learning, includes declarative learning for the acquisition and transformation of visual information in a motor act. This requires the planning of movements as a controlled process based on a vision-centered coordinate system. With practice, there is a switch to the motor stage (right) that implies implicit mechanisms and automatic processes and the change of the coordinate system for motor planning from vision- to motor-centered. In this stage, the performance becomes efficient and effector-specific.

B. Following the visual input, in the visuo-cognitive stage, the frontal and parietal associative cortices are involved and their action is linked with the associative regions of the basal ganglia and the cerebellum. The passage to the motor stage is mediated by the activity of the pre-SMA, SMA and pre-motor areas. In the motor stage, the motor cortices operate with a link to the motor areas of the basal ganglia and the cerebellum. Dopamine-based reward systems enhance learning in all stages.

Figure 3. The task determines the characteristics of a movement.

In the two arm reaching tasks presented in A. and B., the out-and-back movements are directed to the same targets and are "as fast and as accurate as possible with overlapping strokes". Moreover, the interval between two consecutive targets is the same (1 s). However, the tasks differ in other instructions and characteristics of target presentation.

In **A.**, the time of target presentation is predictable, but not its location. Subjects are instructed to move to the target as soon as it appeared, minimizing reaction time but avoiding anticipation. Thus, movement planning occurs after target presentation (vertical solid line), during the reaction or onset time. Response time is the sum of onset time and movement duration. The temporal profile of the movement's velocity is usually bell-shaped with the peak occurring around 50% of the movement time. The inset a. illustrates an index of spatial accuracy, the hand path area, which reflects adherence to the instructions of "overlapping strokes" and is computed as the area enclosed between the out and back strokes normalized by the squared path length (Moisello et al. 2008).

In **B.**, the target location and its appearance time are known in advance. Instructions are to reach the target at the precise time of its appearance, so that movements must be initiated before it.

C. Movements performed in the two tasks differ not only in terms of onset (a.) and response times (dotted thick line in b.), but also in terms of movement duration (b.), peak velocity (e.), spatial

errors (c.) and hand path area (d.). In summary, *movements performed in the unpredictable condition are faster* (duration: ~100 ms less than in the predictable condition) *and less accurate: all this in order to save time*. However, *when target is known in advance, movements are slower and more accurate, allowing for energy saving*. Sequence learning implies not only changes in the reaction or onset time but also in movement characteristics (duration, velocity and spatial accuracy), going from unpredictable to predictable condition (adapted from Moisello et al., 2009).

Figure 4. Sequence learning SRT task with arm-reaching tasks.

We adopted the R-S-S-S-S-R-R-S-R, which is the same structure used in the classical SRT key-press tasks of "implicit learning" where subjects are not informed about the presence of a sequence. The order of target appearance is random in four blocks (R) and a fixed sequence of 16 elements (=eight complete repetitions) in five blocks (S). Instructions are to move as soon and as fast as possible after the stimulus appearance in all the blocks. The main outcome measure of the classical SRT task is based on the response time (the sum of reaction or onset time and movement time) and is computed as the delta between the response time of the last S and R blocks. The arm reaching task was used to parcel out the changes in onset time from those in movement time (Moisello et al. 2009). The results were replicated with finger movements.

1. In the *Intentional Sequence Learning*, subjects are informed of the presence of a 16-element repeating sequence in the S blocks, they are instructed to learn the order and at the end of each block, they report the sequence order and a verbal score is computed (Moisello et al. 2009).

A. Average onset times in S blocks fell toward negative values and were significantly lower (more than 300 ms) than in R blocks.

B. Average Movement time increased in the S blocks. In particular, movement time of the

correct anticipatory movements increased by more than 50 ms and was significantly higher than those of R blocks.

C. The correct anticipatory movements increased to almost 90% across S blocks.

Interestingly, at the end of the first S block all subjects correctly report the entire sequence, while anticipatory movements are only 30% and mean onset time decrement is ~100 ms shorter. This suggests that decreases in onset time, the main drive of response time changes, usually follow and do not precede the development of declarative knowledge of the sequence order.

2. In the *Incidental Sequence Learning* with arm-reaching movements, the presence of a sequence is not mentioned, like the classical SRT tasks with the key-pressing responses.

A. Like in the key-pressing tasks, response time decreases by ~30 ms within the four first "S" blocks with a rebound of ~20 ms in the subsequent two "R" blocks. Interestingly, the response time changes are not equally reflected in onset and movement time.

B. Onset time is constant in the first five blocks but increases by an average of 15 ms in R6 compared to S5. These changes were confined to three of the 16 elements (varying from 25 to 40 ms, data not shown, see Moisello et al., 2009), suggesting that a partial order of the sequence might have been identified.

C. Movement time continuously decreases across all blocks, with significant difference (~ 50 ms) between the first and the blocks starting from S4. Therefore, the reduction in response time over the first five blocks is mostly due to a reduction in movement time, while its change in the R blocks is mostly due to increase in onset time.

D. The number of anticipatory movements increases across S blocks, reaching 5.7% in S8 (~8 out of 128 movements). When such movements are excluded from the analysis, R-S differences in onset time almost vanished (B: gray filled circles). These results, which were replicated with a finger

press task (Moisello et al. 2011a), suggest that the response time changes during the so-called "implicit" SRT tasks reflects the development of a declarative, although fragmentary, knowledge of the sequence order.

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Figure 1

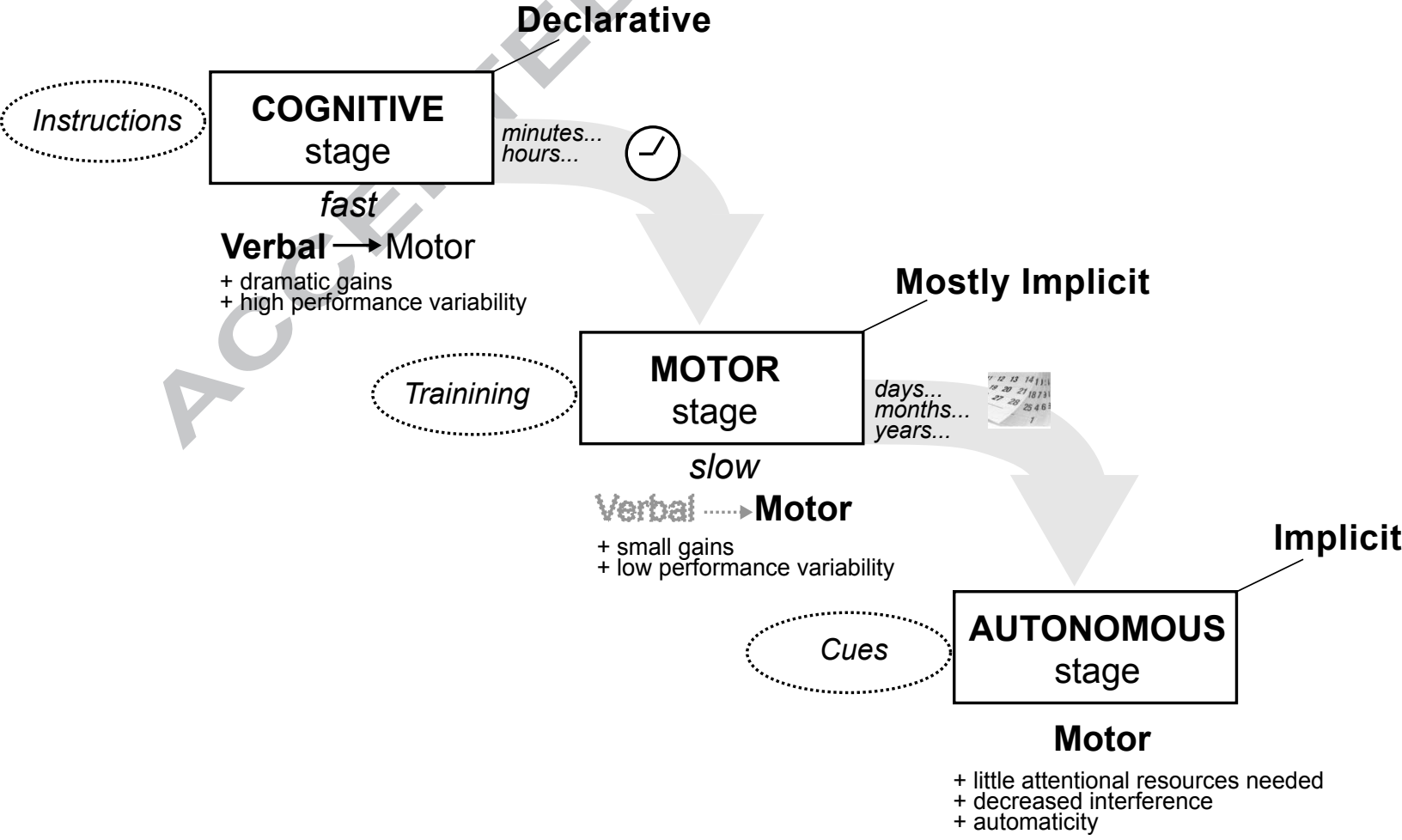


Figure 2

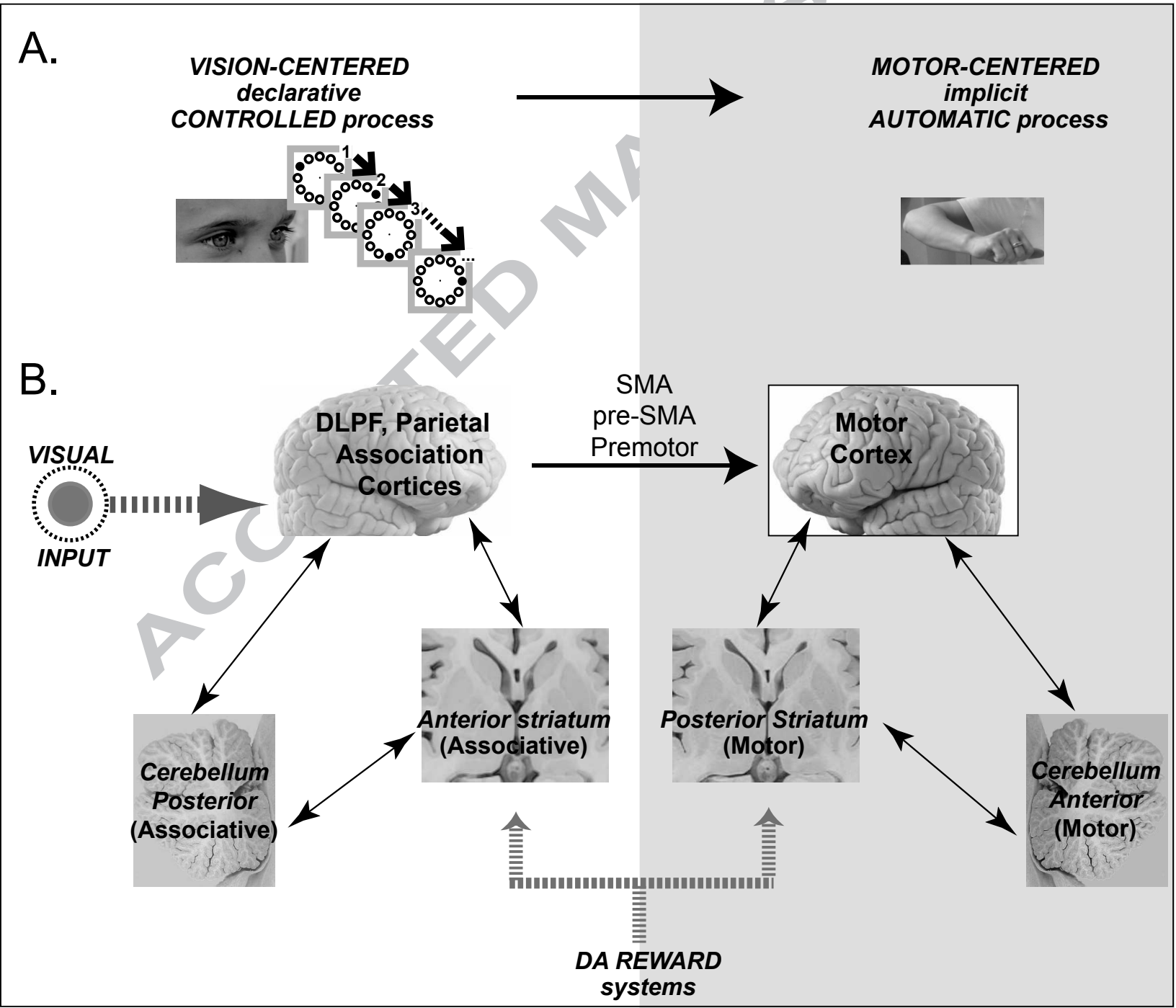


Figure 3

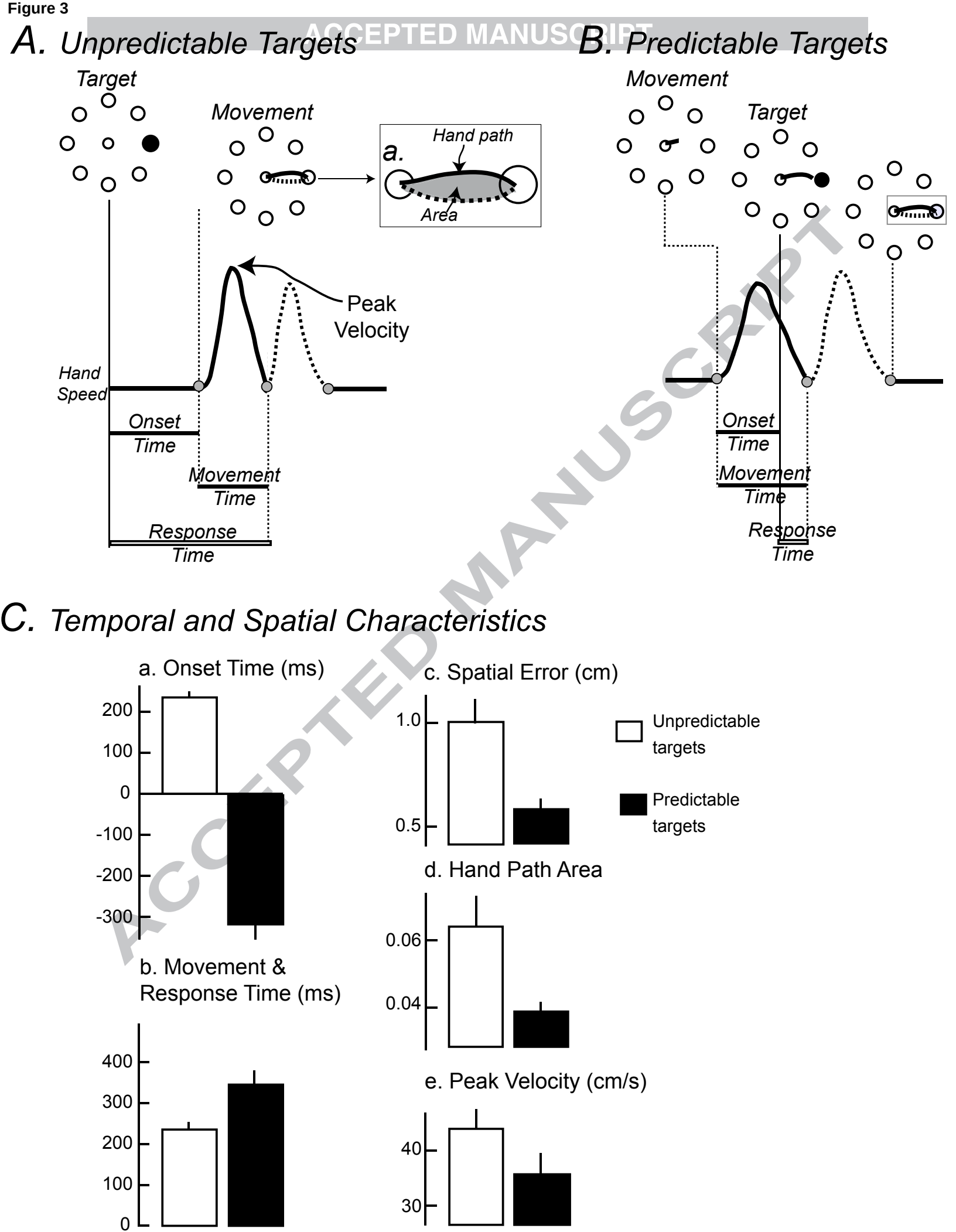
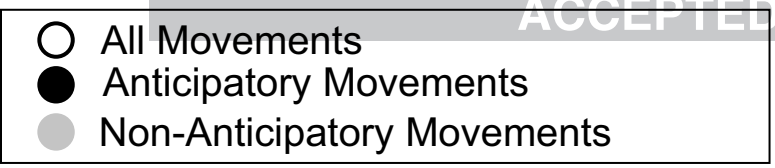
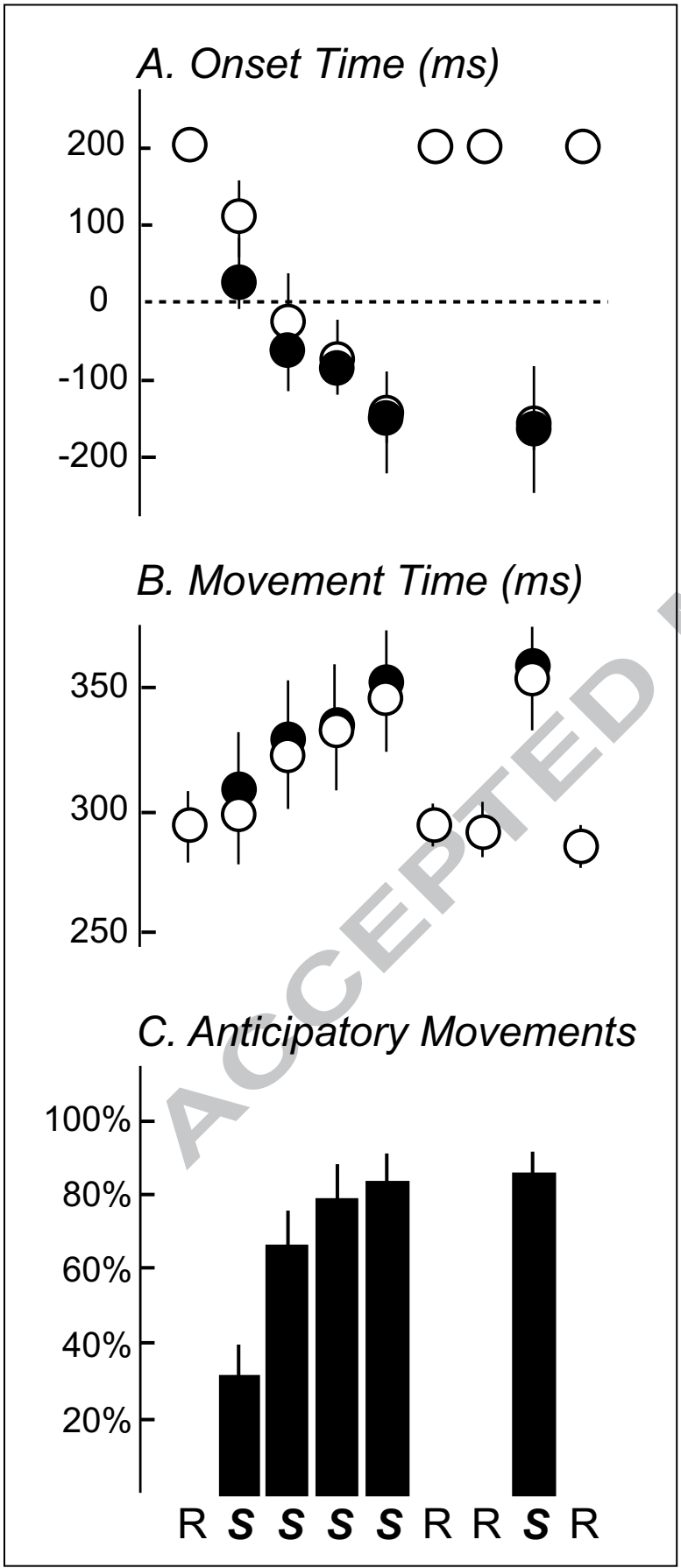


Figure 4



1. *Intentional Sequence Learning*



2. *Incidental Sequence Learning*