CHAPTER II
LITERATURE REVIEW

2.1 Parkinson's disease (PD)

2.1.1 Neuropathology (51)

The histopathology of PD is a loss of dopaminergic neurons in the substantia nigra pars compacta. Degenerate neurons accumulate Lewy bodies (LBs). The LBs is cytoplasmic inclusion bodies composed of α-synuclein which has function for modulating of the activity of tyrosine hydroxylase. The tyrosine hydroxylase play a role in synaptic vesicle trafficking in dopaminergic neurons. It undergoes phosphorylation, and phosphorylated forms are enriched in LBs.

2.1.2 Symptoms and impairments

2.1.2.1 Tremor (52, 53)

Resting tremor is one of cardinal symptoms of PD. Tremors are unilateral and spread from one hand to the other. Rhythmic resting tremors represent in 4–6 Hz. It is often appeared as a pill-rolling tremor involves the fingers, hands, and arm and can also involve lips, chin, jaw and legs, the neck/head or voice. It will be disappeared when the patient begins a voluntary movement and during sleep (53, 54). Beside from resting tremor, most patients also have postural tremor or tremor during performing activity which represent in 5 – 8 Hz. It may be more prominent and disabling than the resting tremor.

<u>*Influential factors for occurrence of resting tremor*</u>

- Emotional state of the patients
- Alcohol consumption and beta-blockers medicine which lead to disappear tremor

2.1.2.2 Rigidity (e.g., 55)

Rigidity is characterized by increased resistance. Intensity of resistance is fluctuated while limb is passively moved in both flexor and extensor muscles throughout entire range of motion, so called ‘‘cogwheel’’ phenomenon. Rigidity may occur at neck, shoulders, hips, wrists or ankles. However, it is often detected in the distal part of limb, mainly the wrist joint. Postural deformities including flexed neck, trunk, elbows and knees are associated with rigidity.

2.1.2.3 Akinesia (e.g., 55)

The term akinesia or “lack of movement” consists of 2 types including hypokinesia and bradykinesia. Hypokinesia was characterized by reducing frequency and amplitude of spontaneous movement. For instances of hypokinesia are loss of facial expression (*hypomimia*), decreased blinking, disappeared associated movements such as rising from a chair and waving, *micrographia*, short stepping and *shuffling gait* accompany with reduced arm swinging.

Bradykinesia is the most characteristic symptom of PD patients (80% - 90%). It is characterized by reduced speed when initiating and performing movement. This symptom is correlate with dopamine deficiency level. This correlation indicate that reduced dopaminergic function induce a disruption in normal motor cortex activity and then resulting in bradykinesia.

Bradykinesia can be manifested by:

1) Delayed initiating movement, as measured by longer reaction time (RT) when compare to non-disabled adults. It results from disconnection between the basal ganglia and supplementary motor area. Furthermore, PD patient shows inability to use sensory information to initiate or select a movement. Cognitive impairment in PD also affects the RT.

2) Slowness of execution of a movement as represented by longer movement time (MT). The slow speed of movement results from abnormal processing of sensory input necessary for the generation and execution of movement.

3) Decreasing amplitude and speed of repetitive movement

4) Inability to execute simultaneous or sequential actions

5) Drooling due to impaired swallowing of saliva

6) Monotonous (*hypokinetic*) dysarthria

7) *Bradyphrenia* is slowness of thought.

8) *Kinesia paradoxical* due to difficulty in utilizing the programs without the help of an external trigger, such as a loud noise, marching music or a visual cue.

Influential factors for occurrence of bradykinesia

- Emotional state of the patients

2.1.2.4 Postural instability (e.g., 55)

Postural instability is the most common cause of falls and correlated with the severity of disease. The loss of balance associated with propulsion and retropulsion is probably the least specific, but most disabling, of all parkinsonian symptoms.

Influential factors for occurrence of postural instability in PD

- Orthostatic hypotension
- Age related sensory changes
- Ability to integrate visual, vestibular and proprioceptive sensory input (kinesthesia)
- The fear of falling

2.1.2.5 Gait disturbances (e.g., 56, 57)

Gait disturbance is often occurred in PD, especially in severe states of the disease. PD gait disturbances can be manifested by slow gait, postural changes, festination and freezing of gait (FOG).

Influential factors for occurrence of FOG in PD

- Emotional stress situations or the limitation of time or space to execute walking such as crossing a busy street before the traffic light changes (56).
- The external cues can improve FOG.
- Cognitive load or dual tasking
- Stage of disease. The FOG was usually reported in patients with Hoehn-Yahr stages 3 and 4.
- State of medication

2.1.2.6 Other motor manifestations (55)

There are various other symptoms which related to aforementioned cardinal signs.

1) Bulbar symptoms due to orofacial-laryngeal bradykinesia and rigidity. These symptoms including dysarthria, hypophonia, dysphagia, and sialorrhea.

2) Respiratory difficulties due to 2 mains reasons including rigidity in respiratory muscles and levodopa-induced respiratory dyskinesia.

3) Various oculomotor problems

a. Impaired saccadic and smooth pursuit
b. Limitation of upward gaze and convergence
c. Oculogyric crises
d. Spontaneous and reflex blepharospasm
e. Apraxia of lid opening
f. Apraxia of eyelid closure
g. Impaired upward gaze, and convergence
h. Impaired vestibuloocular reflex
i. Decreased blink rate

4) Impaired visual contrast sensitivity

5) Levodopa-induced dyskinesia (chorea, dystonia, myoclonus, tic)

2.1.3 Prehensile movement in PD patients

PD patients frequently complain regarding having difficulty in performing manipulative tasks (4, 5). Prehension consists of 2 distinct components: transporting phase which transport hand toward an object and grasping phase which open and close of the hand aperture to grasp the object. PD patients showed deficit in the kinematic patterns (temporal and spatial parameters) of both the transport and grasp components (4). Moreover, few studies also found disruption in transport-grasp coordination in these patients (4, 41, 58). These evidences support that PD patients had deteriorate capability of reaching and grasping, and coordination of these two components. Dopaminergic medication could reduce these disruptions in reach-to-grasp action (16).

2.1.3.1 Transport component (59, 60)

PD patients demonstrated delays in movement initiation as evidenced by longer reaction time approximately 100 milliseconds (ms). The most observable characteristic in this phase is slowness arm transport which revealed the bradykinesia in PD patients. The movement time is 34% longer than the non-disabled adults. Slower transport is obviously observed when patients reach to grasp small objects and when occlude the vision. Moreover, the velocity profile is distorted including smaller magnitude of maximum wrist velocity and longer deceleration periods. Velocity profiles have more fluctuation or jerk in both the acceleration and deceleration phase which reflect the decreased smoothness of movement.

2.1.3.2 Grasp component (60)

The amplitude of maximum grasp aperture in PD patients is decreased approximately 15% when compared to non-disabled adults. The possible reason of reducing grasp aperture size may be slow movement (bradykinesia) in patients. Because the speed of movement execution is correlated to amplitude of aperture, slow movement leads to grasp with smaller amplitude when compare to fast movement. The decreasing of aperture represented the hypometria in patients. Hypometria might be result from impairment in controlling of movement amplitude, which controlled by basal ganglia.

PD patients also showed impairment in modulating the finger shape, especially during occlusion visual feedback. This impairment may be due to inability to integrate transport and grasp component correctly. Additionally, patients rely on visual feedback for controlling the execution and preshaping the hand position prior to contact the object.

2.1.3.3 Transport and grasp coordination (60)

The temporal onset of finger opening with respect to the transport onset in PD patients is delayed (9% of movement time) when compare to controls (5% of movement time). In addition, occurrence of maximum grasp aperture is nearly to the time at peak deceleration in controls (at 62% of movement time) whereas it is delayed approximately 5% from the time at peak deceleration in PD patients. This finding represents the impairment in temporal coordination between transport and grasp component in which patients compensate the task demand by slow initiating finger closure. The disrupted temporal coordination was obviously observed when perform the high accuracy task (reach for grasping small objects) and when visual feedback is reduced (blocked vision).

In contrast to temporal coordination, the spatial coordination is not deficient in these patients as evidenced by relatively stable closure distance. It demonstrates maintained coordination between transport and grasp component for estimating the spatial distance between hand and object.

The mechanisms of reach-to-grasp problems

1) Motor deficit

Lesser maximum grip aperture and shorter aperture closure distance in PD might be the resulting from hypometria and longer movement time and decreased maximum velocity reflect bradykinesia.

2) Sensorimotor processing impairment

PD patients exhibited a deficit in the processing of proprioceptive information about velocity and acceleration during aiming movements (e.g., 41, 61). Apart from proprioceptive processing, PD had difficulty to transform visual input into the necessary motor commands for the producing appropriate hand preshaping (62). Moreover, PD patients are difficult to integrate proprioceptive inputs with concurrent or remembered visual information for guiding movements (62). Thus, the impairment of these sensorimotor processing disrupts controlling both reaching and grasping components.

3) Difficulties to specify and implement the precise motor parameters

The basal ganglia play a role in the specification and implementation of motor parameters. They receive input from both sensory and motor cortical areas and then send the outputs into motor cortical areas (63). PD induces the excessive inhibitory output from the basal ganglia to thalamus. This greater inhibition of thalamocortical cells may result in difficulties to specify and implement the precise motor parameters of action in daily life including reach-to-grasp action and may interfere the normal scaling of movement (64). The impaired specification in motor planting resulting in delayed movement-initiation and slow execution due to a (65, 66).

In prehensile tasks, PD patients were unable to specify the appropriate timing for grasping as evidenced by a delayed hand shaping time (40). The deficit might be resulting from disrupted connection between basal ganglia and ventral premotor cortex (67) which involved in the selection of specific grip types (68).

4) Loss of predictive control in PD (14, 69, 70)

Anticipatory motor control mechanisms are dysfunction in PD patients. Basal ganglia was involved in forward modeling process. A damage to the basal ganglia affect motor prediction and error detection related to action.

2.2 Motor control of reach-to-grasp (RTG) movement

2.2.1 Neural mechanism during reaching and grasping under non-barrier conditions

Prehension entails two motor processes: the 'transport'(reaching) phase, in which the arm moves towards the object, and the 'grasping' phase, in which shaping and orientation of the hand are adapted for appropriate grasping (71). For the neural mechanism of reaching and grasping begin with visual information from retina sends projections through retino-tectal-pulvina pathway and lateral geniculate body to primary visual cortex (V1). Then input is projected to two main streams of projections; ventral and dorsal stream (see Figure 2.1) (72).

A ventral stream starts from visual input from V1 projects to the inferotemporal cortex. The inferotemporal cortex has strong reciprocal connections to amygdala for mediating of social and emotional responses to visual signals (7) and also projects to the perirhinal and parahippocampal cortices and other regions of the medial temporal lobe for storing object’s information in memory (7). The roles of this stream are visual identification and recognition of objects by comparing current visual input with internal representations of recalled images (73).

The dorsal stream plays an important role in visually guided for direct movements and avoiding the barrier condition (74, 75). A dorsal stream can be separated into “dorsomedial stream” and “dorsolateral stream” which seperately control reaching and grasping, respectively (71). However , recent conflict findings demonstrate that the dorsomedial visual stream is involved in both components (7).

2.2.1.1 Reaching

Dorsomedial stream (medial parietofrontal circuit) which connects the parieto-occipital extrastriate area (PO) to dorsal premotor area (PMd) by direct and indirect pathways. The indirect pathway relays information in the intraparietal sulcus including the medial dorsal parietal (MDP), ventral intraparietal (VIP) and medial intraparietal (MIP) areas. The spatial information regarding object location from the VIP and MIP is transformed into an appropriate reaching at PMd (63, 71, 76).

2.2.1.2 Grasping

Dorsolateral stream (lateral parietofrontal circuit), V1connects to dorsal extrastriate (ES) cortex and the ventral premotor area (PMv) via the anterior intraparietal area (AIP). In this stream, object's properties (shape and size) are transformed at the anterior intraparietal area and then send to PMv for selecting the shaping of hand and finger (63, 71).

2.2.1.3 Transport and grasp coordination

The studies of Transport-grasp coordination have typically alter the one component and investigate concomitant changes in another component (8, 77). The changes in object's location during a prehensile movement induced rapid adjustments in both transport and hand aperture (8, 77, 78). These findings indicate that the disruption in transport component affect grasp formation, which reflect the coordinated between these 2 components.

2.2.1.4 The activity of single neurons

The coding of each parameter of RTG movement (7) is shown in following table;

Table 2.1 The activity of single neurons for coding important parameter during movement.

Parameter is coded	**Brain area**
Force	M1, PM
Direction of intended limb movement	M1, PM, parietal cortex
Limb velocity	Red nucleus
Target position	M1, SMA
Movement trajectory	M1, PM, SMA
Order of sequential movement	SMA

Note: SMA = Supplementary motor area, M1 = Primary motor cortex, PM = premotor area

2.2.1.5 Motor activity

Specialization of a brain region for a particular information processing operation (7) can be summarized in Table 2.

Table 2.2 The activation of brain area during control and learning motor skill.

Motor activity	**Brain area**
Simple finger movement	M1
Complex finger movement	M1, SMA
Mental planning of a complex finger movement	SMA
Movement selection	PM, SMA, Superior parietal association
Integration of spatial attributes during selection of movement	Parietal
Execution or preparation of reaching movement to visuomotor learning	M1, PM
Active in *early stage* of motor learning	Association area
Active in *later stage* of learning	Cerebello-&striato-motor-cortical loops

Note: SMA = Supplementary motor area, M1 = Primary motor cortex, PM = premotor area

2.2.2 Neural mechanism during reaching and grasping under barrier conditions

The barrier avoidance condition has been extensively used because it directly perturbs the transport path and the linkage between transport and grasp components or transport-grasp coordination in previous studies (e.g., 9, 11). Therefore, the result study could be compared to others. Moreover, it is a challenged task which could investigate effect the learning performance (32). The level of task difficulty also plays a role in increasing an individual's motivation (32). Similarly, the presence of an obstacle increased the control demands of the task as movement time increased and relatively more deceleration time or "homing-in" phase of the of the movement (12). The increased control demands might show the obvious movements' deficit in PD patients and then could obviously observe the beneficial effect of training protocol.

For the neural control under barrier avoidance condition is shown in the Figure 2.2. The dorsal stream of visual pathway play a role in the obstacle or barrier avoidance (74, 75). For supporting this finding, previous studies found abnormal response to a perturbed target position in patients with optic ataxia (whose dorsal stream is damaged) (79). Similarly, a study in optic ataxic patients concluded that the dorsal visual stream controls the observed automatic barrier avoidance (80). In contrast, patients who have damaged ventral stream did not impair their response to obstacle avoidance task (81). A recent work with a patient with damage to primary visual cortex suggests that information about the location of the obstacle can reach dorsal stream areas via pathways (retino-tectal-pulvinar pathway) outside of the geniculostriate pathway (81). They conclude that obstacle avoidance mechanisms can operate in "real-time" without direct input from primary visual cortex (81).

Apart from visual pathway, the barrier avoidance condition also affects other brain region's activity such as SMA (82). A study indicated that monkeys with SMA lesion demonstrated the impairment in reaching under a glass to catch food morsels pushed through a hole in the glass with the other paw (83).

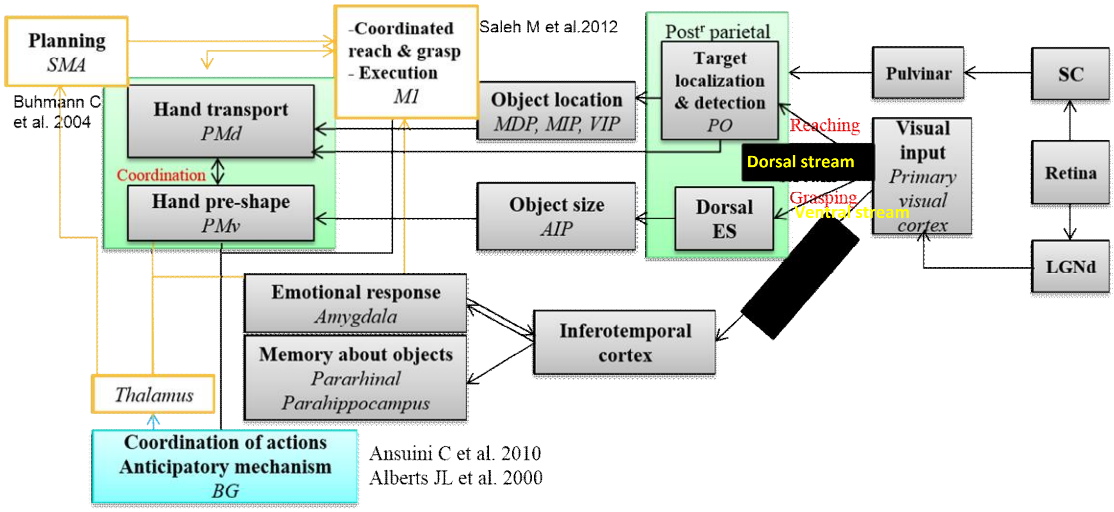

Figure 2.1 The visuomotor transformations required for reaching and grasping in normal situation

Note: SC = superior colliculus, LGNd = lateral geniculate nucleus, pars dorsalis, PO = parieto-occipital extrastriate area, Dorsal ES = dorsal extrastriate, MDP = Medial dorsal parietal, MIP, VIP, AIP = Medial, Ventral, Anterior intraparietal area, PMd = dorsal premotor area, PMv = ventral premotor area, SMA = Supplementary motor area, M1 = Primary motor cortex, BG = basal ganglia

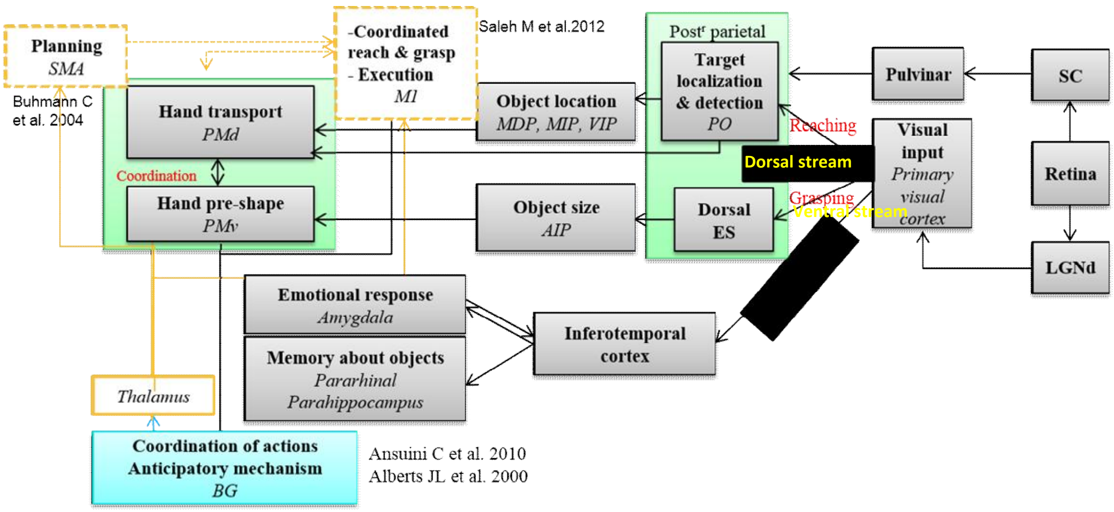

Figure 2.2 The visuomotor transformations required for reaching and grasping under barrier condition

2.3 Reach-to-grasp kinematic measurements

2.3.1 Instrumentation for kinematic analysis

Kinematic data, or data that describe a motion, are collected with a variety of instruments ranging from video to sophisticated motion-tracking systems.

2.3.1.1 Video or photoinstrumentation system

Video analysis can be as simple and rough as tracing from a video monitor onto acetate film or as complex and sophisticated as automatic computerized digitizing (84). After recording, the image may then be digitized from the monitor by a human operator or digitized directly by the computer if the subject has been marked with reflective or light-emitting markers (84).

2.3.1.2 Optoelectronic tracking systems

Optical tracking consists of two sub-systems: 1) 2D feature tracking for determining feature locations in image, 2) 3D feature tracking for computing 3D position and orientation of camera (85). Optical tracking systems are unable to operate in real-time due to the computations from raw data are too complex (85). This system uses light-emitting diodes (LED) markers attached to subject (84) then collect the data in a dark room, or used different color markers for simply detection (85). The light from these markers is detected by a sensor system. Each marker has a characteristic rapid pulse pattern that allows the sensing system to continuously identify each individual marker. The markers used can be passive or active (86). Passive markers are made of retro-reflective paper, often wrapped around small spheres (86). The active markers are infrared light-emitting diodes (LEDs) which need a power source and can encumber the subject in some movements (86).

2.3.1.3 Electromagnetic (EM) tracking devices

Electomagnetic tracking systems have found increasing use in medical applications especially in ergonomic and kinematic studies during the last few years (40, 87-95). The magnetic tracking has been used in virtual reality to produce a real-time (though not instantaneous) three-dimensional model of motion (84). Researchers use a commercial Ascension Flock of Birds magnetic tracker (85). This system can be calibrated for stationary distortions, temporary distortions (like computer monitors). Therefore, it is able to minimize a negative influence on its performance (85).

The devices use principle of electromagnetic transduction. A transmitter generates electromagnetic signals which are received by a sensor (96). They determine the position and orientation from sensors relative to a transmitter (97). They usually consist of a set of electromagnetic transmitter/sensor pairs with on pair component attached to the body, the other to a computer (84). Signals from the moving body are transmitted to the computer for processing (84). Then computer construct stick figures or contoured body forms (86).

There are two options of Electromagnetic Tracking technology; 1) Alternating-current (AC) device (or Polhemus technology) have more distorted measurement introduce from metal environment which induce eddy currents in nearby metals when compare to DC (90), 2)Direct-current (DC) device (or Ascension technology) which uses DC magnetic field generation in transmitter and sensing devices that register positions and orientations of receivers on the body (93). DC devices have less or no distortion of measurements. Because DC magnetic field has reached a steady state resulting in minimizing or dying out initial eddy currents and no producing new eddy currents (90).

<u>Accuracy of the Devices</u>

Milne and colleagues (1996) investigated positional accuracy and found mean error was -0.50 mm for all six axes (93). In addition, the mean error was 1.8% of the step size (93, 98). For rotational accuracy, Milne and colleagues (1996) also investigated rotational accuracy via measuring the error which is the difference between the Instron sweep ancle and the tracking device angle readings (93). They found mean error was 1.6% of rotational increment (93, 98).

<u>Distorted measurement</u>

Magnetic field distortions resulting from metal and electronic equipment are able to degrade the system's accuracy (87, 90, 93).

The effects of metal interference also depend on metal type and its placement positions (93). Milne and colleague demonstrated the largest interference on the positional (positional difference = 5.26 cm) and rotational (angular difference = 9.75°) data in mild steel and position adjacent to the receiver (93). In addition, different sampling rate produced different errors in metallic environment (90). During aluminum interference, increasing errors were occurred as the sampling rate increased. In contrast, during steel interference, decreased measurement errors were occured as the sampling rate increase (90). Moreover, Meskers concluded that steel reinforced concrete floor caused substantial distortions in the magnetic field even if the measurements were performed at least 1 m above the floor (99).

Sensitivity of the Devices

Milne and colleagues reported that the device is sensitive enough to read positional and rotational changes of 0.25 mm and 0.1°, respectively (93). Whereas, the manufacturer's technical literature reported resolutions of 0.75 mm and 0.1° which are equal to or slightly worse than the study of Milne and colleagues.

Optimal operating range of the Devices

Milne and colleagues (1996) demonstrated positional and rotational errors of less than 2% when utilize within the devices' optimal operating range of 22.5 – 64.0 cm (93). Whereas, Bull and Amis (1997) was confirmed previous finding with slightly difference (21.7 – 72.3 cm) (98).

2.4 Training for upper extremity dysfunction in PD

2.4.1 Virtual reality training

Virtual reality is the advance of technology to create a synthetic environment with precise control. A recent study found decreased movement time and increased peak velocity after practice the reaching in virtual reality environment with their right hand for 1 hour in parkinsonian individuals when compare to control group that turned 60 wooden cylinders at a self-placed speed with their left hand (100).

2.4.2 Constraint-induced movement therapy

Constraint induced movement therapy (CIMT) is defined by Taub and co-workers in which a task-specific intensive training method to improve meaningful use of the more affected limb through the systematic application of shaping and repetitive-use strategies over a defined period while avoiding use of the less affected limb (101). This technique restraint of less- affected upper extremity while exercising or using more affected one.

CIMT can enhance the using and improve functional ability of hemiparesis arm and hand in stroke individuals (e.g., 102). Few studies used CIMT to train more affected hand of PD person. A study in 2005 did not demonstrate the beneficial effect of CIMT on the Unified Parkinson's Disease Rating Scale or Clinical Global Impression in Parkinson's disease patients (103). In contrast, another study in 2011 found improvement of fine and gross motor performances of the upper limb after patients completed modified version of CIMT for 4 weeks (104).

2.4.3 Action observation combined with physical training

Action observation (AO) training is the training by observing another person's action. During observe other perform the action, the motor areas in the brain are recruited as during executing that movement but weaker (see review (36)). These brain areas are so called "Mirror neurons". AO had positive impact on upper extremity performance in both healthy subjects (eg., 30, 105) and disabled people such as stroke patients (38). Moreover, AO combined with physical training could enhance reaching performance by improving bradykinesia and akinesia in PD patients (39).

Beside from reaching and grasping, the repetitive finger movement training with AO could improve spontaneous rate and decrease intertapping interval (34). This effect could be retained over time (45 minutes and 2 days after training) (34).

2.5 Mirror neurons

Mirror neurons (MNs) are visuomotor neurons that are activated both when performing actions , and when observing the similar action (106). They could coupling action execution and action observation both in terms of the muscles involved and the temporal sequence of the action (107). These neurons are activated during observation of object manipulation or **goal-directed** action by hand, mouth and foot (108).

The MNs system has positive impact to rehabilitation program including stroke and autism recovery via enhancing motor learning and training effectiveness ((109) and see review (107)). The concepts of MNs were applied to neurological patients for improving their deficits such as aphasia, limb apraxia, and upper limb and lower limb dysfunction and applied to solve emotional disorder in autism ((109) and see review (107)). The roles or mechanism of MNs in motor and training facilitation are showed below:

2.5.1 Functional roles of mirror neurons

1) Aware of the outcome of observers' own motor acts during observing (110).

2) Action understandings including understanding the **goals**, intentions and emotions of other people (e.g., 111). When observing the actions of others person, the visual information is initially processed and then be sent to higher order association areas for sophisticated cognitive mechanisms and compared with previously stored data. Thus, the end of this process, observer would know what others are doing (see review (110)). The mirror hand areas were heavily active during the observation of movement that coupling between movement curvature and velocity than other motions (112).

3) Imitation learning of novel complex actions (110, 111).

4) Internal rehearsal (111) and motor memory formation (42, 110). When observed movement and executed movement are congruent, motor memories were strongly formed and then facilitate long-term plasticity in the motor cortex (see review (110)).

5) Enhancing error detection and correction process. Mirror neurons system play a role in monitoring action and linking an ongoing action to a goal for error correction (113). A recent study found that during stroke patients observing

partner's movement, they also searched for errors and the way to solve those errors (38).

2.5.2 Training protocols using Mirror neurons concept

2.5.2.1 Mirror therapy

In mirror therapy, a mirror is placed in the patient's midsagittal plane. Practitioners with stoke would see their unaffected arm in the mirror as if it were the affected arm (114). This protocol increasing awareness of the affected limb. The mirror illusion might reduce learnt non-use (115). Michielsen and co-workers found improvement in Fugl-Meyer score (upper limb part) after 6-week mirror therapy program when compare to control group (116). An another study found similar result that 4 week of the mirror therapy can improve upper-extremity motor recovery, spasticity, and hand-related functioning of patients with subacute stroke (117). The mirror illustrates a normal movement. During looking at mirror, premotor cortex is recruited (118). Therefore, this technique is able to facilitate connection between visual input and premotor areas (118). Visual feedback from mirror enhances successful performance, then help stroke patients to imagine that they perform successful action with the impaired limb (119).

2.5.2.2 Motor imagery of mental practice

Motor imagery is a dynamic state of internal action representation without overt motor output (120). For the activation of mirror system, the prefrontal cortex, frontal motor areas (PMv, PMd, precentral gyrus, inferior frontal gyrus; IFG, SMA), parietal cortex (superior and inferior parietal lobe; SPL, IPL, supramarginal gyrus) , dorsolateral prefrontal cortex, inferior frontal gyrus, superior temporal gyrus, anterior cingulate cortex, M1, basal ganglia, and cerebellum were activated during motor imagery (121, 122). This finding indicate rebuild planning and preparation during motor imagery (see review 122).

Numerous evidences show the positive effects of motor imagery practice on motor performance and learning in many populations such as athletes, healthy individuals, and individuals with neurological impairment (eg, stroke, spinal cord injury, Parkinson disease) (e.g., 123). When applied the motor imagery to stroke patients for 6 weeks showed reduced motor impairment and increased use of the affected limb compared with motor training (see review 122). In addition, structural and functional changes, including synaptic and cortical map plasticity, after motor imagery training is also found similar to motor training after stroke (see review 122).

2.5.2.3 Imitation

Motor imitation has been revealed significant functional improvement of hand after 18 day of training with imitation the observed movement in stroke population (124). The imitation mechanism is converting a visual representation of observed actions from the superior temporal sulcus to an object-oriented kinesthetic representation at the parietal MNs system. Then motor programming related to action goal is selected at the frontal mirror system (see review 122). Parietal cortex also compare predicted sensory feedback that to actual sensory feedback for online (see review 122). Moreover, the imitation is involved in the building of motor memories (110). The activation of brain area during imitation including dorsolateral prefrontal cortex, PMd, pre-SMA, IFG and SPL, involve working memory and motor preparation (111, 122).

2.5.2.4 Action observation

Action observation activates motor-related brain regions, including the pars opercularis of the IFG, PMv, SMA, rostral IPL and cerebellum (see review (122, 125). These regions have an active role in action understanding (126). At the same time, PMv neurons in observation induced plasticity (42). Moreover, it can form a motor memory of the observed action to M1 (42). Beside from action understanding and forming memory, the attentional system were also engaged during observation (127). Thus, action observation is involved to enhancing motor learning via aforementioned mechanisms. The evidences demonstrated the advantage of action observation combined with physical training in stroke (e.g., 124, 128), and PD patients (129). For instance, PD can improve freezing gait via watching video clips showing specific movements (129).

Recent protocol, dyad training, is related to action observation. The dyad protocol was applied to stroke patients and found increased effectiveness in upper limb training compare to conventional (individual) training (38). This protocol can enhance memory, error recognition, attentional resource and increase motivational level, and may activate MNs (38).

2.5.3 Neural activity (129)

For summarization, the MNs activation could promote motor performance and learning because they activate the brain area that important for movement execution, planning and learning prior to execute the movement. For instances of these areas are showed below:

1) Inferior frontal gyrus (IFG) encode the kinematical description
2) Inferior parietal lobe (IPL) encode goal/object description
3) Primary motor cortex (M1) important area for
    a. Formation of motor memory
    b. Encode force
    c. Encode direction of limb
    d. Encode target position
    e. Encode movement trajectory
4) Supplementary motor area (SMA) important area for
    a. Mental planning
    b. Movement selection
    c. Encode target position
    d. Encode movement trajectory
    e. Encode order of sequential movement
5) Basal ganglia including subthalamic nucleus (STN) encode information related to the mechanisms of action understanding

Fagg and Arbib developed Fagg-Arbib-Rizzolatti-Sakata or FARS model in 1998 (130) by interpreting the findings from studies Sakata and Rizzolatti (e.g., 131, 132) The FARS model aimed to describe the linkage between circuitry of visually guided grasping and MNs. There were linking the pathways in FARS model with area F5 in monkey's MNs. The MNs require an interaction between the state of hand and the object to be grasped. They have importantly functional role in action understanding. Therefore, the FARS model provide the explanation how the action could be transformed and understanded by the linkage of action perception and MNs. The recent version of FARS model in 2002 (133) is shown in Figure 2.3. The receiving visual information was provided to 3 main areas; 1) caudal intraparietal sulcus (cIPS) perceives object features such as size and shape, and then knows what the object is, 2) ventral intraparietal area (VIP) codes the object's location and orientation (130), 3) the cortex of caudal superior temporal sulcus (STS) codes spatial information for recognizing hand shape and detecting hand motion. Subsequently, the object's location and orientation is passed to F4 (a part of inferior premotor cortex) for setting up the reaching program. The object features from cIPS are passed to anterior intraparietal area (AIP) for extraction the object affordance from AIP for extracting the object affordance. After STS recognizes how the hand is moving and knowing the object features (at cIPS), then 7a (a part of inferior parietal lobe) analyses the relation between spatial information of hand and object. The information about object affordance (from AIP), hand shape (from STS), and spatial relation between hand and object are passed to 7b (another part of inferior parietal lobe) for integrating to object affordance-hand state association. The gray rectangle in Figure 2.3 represents 2 regions of core mirror circuit. Beside from connection between AIP and 7b, AIP also connects to F5 canonical neurons for motor programing of grasp component. Subsequently, motor program from F5 canonical neurons and information from 7b are integrated at F5 mirror to determine whether the current hand motion is appropriate to its affordance. This is the process for action recognition. Finally, the motor program for reaching (or transport) and grasping component are executed at primary motor cortex (M1).

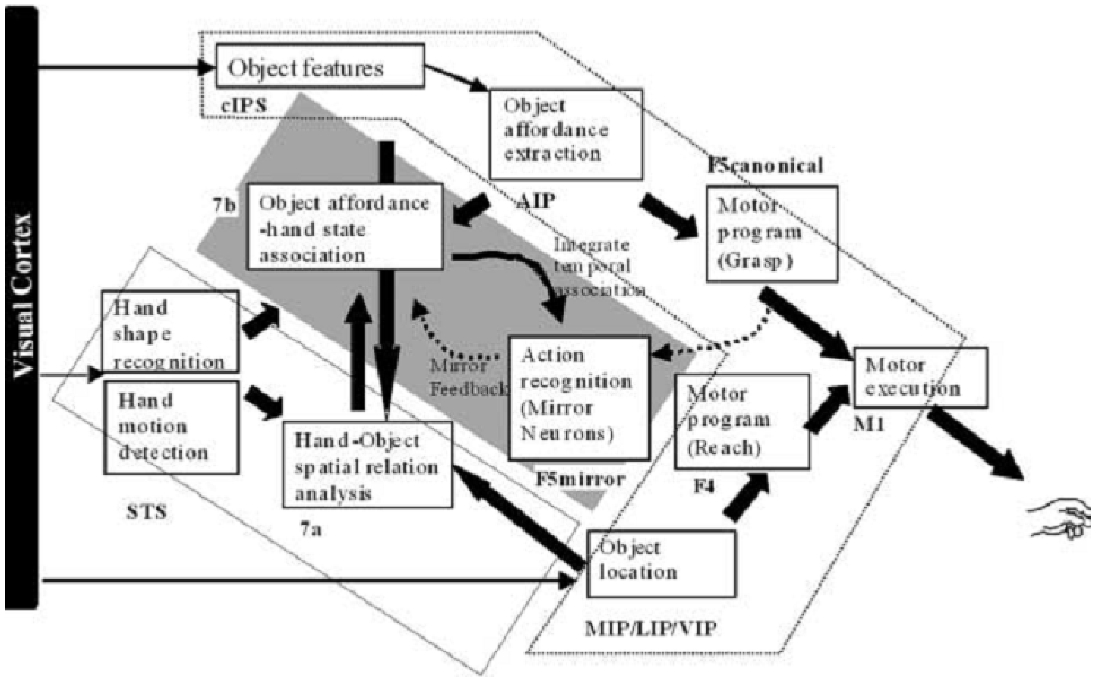

Figure 2.3 Fagg-Arbib-Rizzolatti-Sakata or FARS model in monkey's brain

Note: cIPS = caudal intraparietal sulcus, STS = superior temporal sulcus, MIP = parieto-occipital extrastriate area, LIP = Lateral intraparietal area, VIP = Ventral intraparietal area, AIP = Anterior intraparietal area, M1 = Primary motor cortex

2.5.4 Influential factors for action observation protocol

Many factors might be influenced to the effective of training with action observation protocol. Thus, therapists should consider these possible influential factors prior to apply this protocol to training session.

2.5.4.1 Type of model and model's skill

An evidence found that observing unskilled models resulted in better observational learning than skilled models (134). This finding indicate that model should not have quite different level of performance as observer. For instance, response time of child observer was faster when practice with observing child model compare to adult model (135). A recent study in PD observers found facilitation effect when observing reach-to-grasp movement from PD model (39).

2.5.4.2 Perspective of model

When compare the mirror-image (model and observer perform the task with opposite hand but when face to each other performing hands look like the same side as we look to the mirror) and anatomical perspective (model and observer perform action with the same side of hand) during observing, the evidences are still inconsistent. A study in 2007 found similar effect of both perspective in healthy subjects, but found that frontal lobe patient have superior performance when observe mirror-image (136). Another study in 2008 found that observing with anatomical image is more effective than mirror image (47). Both mirror-image and anatomical view are the third person perspectives which look like to see other person perform action. However, another evidence revealed more advantage of 'own perspective' than 'other perspective' (137).

2.5.4.3 Compatible action of observation and execution

Observer can automatically imitate model when actions during observing and executing are compatible in type and direction (e.g., 138, 139). For instances, reaction time could be facilitated when observed and performed index lifting, while incompatible direction between observed and executed finger movements interfered observer's performance (138, 140).

2.5.4.4 Observation stimuli

The stimuli during observing has critical role to executed performance. Firstly, the stimuli should be human movement. For example, some studies compared executed arm performance after observing between human making an arm movement and a ball moving, researchers found that only observation of human action can facilitate executed movement (141, 142).

2.5.4.5 Complexity and type of task

For task complexity, when practice the difficult task participant need more useful information to improve their skill, so the observation could give that information (143). The goal and type of task is another important factor for training with mirror neurons concept. The MNs system will be activated when observing the goal-directed movements (106, 110).

2.5.4.6 Attention of observer

The last factor is attention, if participants pay attention to the task which they observe, they will automatic imitate the action (144, 145).

2.6 Motor learning

Motor learning is defined as a change in the capability of a person to perform a skill that must be inferred from a relatively permanent improvement in performance as a result of practice or experience (146, 147). Motor learning is distinct to performance. Performance is execution of skill at a specific time and in specific location or situation, while learning is a change in performance resulting from practice or experience (147).

2.6.1 Characteristics of motor learning

When practitioners learn the skill, four performance characteristics could be observed (146); 1) improvement (so called "skill acquisition"), 2) consistency or become more stable when compare to early learning phase that has greater variability of performance, 3) persistency or relatively permanent over a period of time, 4) adaptability in novel environment, task, or personal characteristics.

2.6.2 Stage of motor learning

The motor learning has been classified into 3 stages (146).

2.6.2.1 Cognitive stage

This is the first learning stage that beginners use cognitive processes to get general idea of the movement (146, 147). Beginners focus to goal of the task and try to understand how to accomplish that goal (146). In this stage, performance shows marked error and high variability which represents the inconsistent performance (146), thus practitioners need to know the correct movement (147). Learners always talk to themselves about what they are doing, then they try to explore the strategies which might could improve their performances. They require a lot of attention to the task for minimizing the errors and achieving the goal.

2.6.2.2 Associative or motor stage

In this stage, learners have learned general idea of the skill via associating certain environmental cues with the movement (146). Thus, they shift their focus to explore more effective strategies for better performance. Leaners begin to detect their own errors via their own feedback. Thus, the movement demonstrates lesser errors, while the performance is improved (e.g., quicker and more smooth) (147) and more consistent (146) which reflect more sophisticated performance.

2.6.2.3 Autonomous stage

When learners has experience after extensive practice, skill performance become almost automatic (146). Learners become more skillful as evidenced by the best performance do not require conscious though regarding what they are doing and they can detect their errors during performing the skill (146). Moreover, they can engage in higher-order cognitive activities such as shifting their attention to secondary task during performing primary task. In this stage, person perform the task with more self-confidence, and lesser physical and mental effort.

2.6.3 Assessment of motor learning

1) Learning or performance curve in acquisition

Acquisition refers to the measurement of acquiring a skill or performance experience (147). One way for assessing acquisition of motor skill is measuring the changes of performance at each period of time during skill practicing (146). The plotting of these changes over time is "performance curve", which vertical axis might always be performance's level and horizontal axis is time (e.g., seconds, minutes, hours, days or trials) which performance is assessed (146).

2) Retention tests

The method to measure the persistence of performance is retention tests which performs following an interval of non-practice time after the end of practice sessions or acquisition trials (146). Retention tests reflect relatively permanent change in performance (147). After some period of no practice time (retention interval), a new performance is measured in small number of trials (147). The delayed tests after retention interval can be divided into a few sub-tests such as saving and forgetting capability tests. For instance, Winstein and colleagues in 1999 (148) used forgetting and saving to test retained capability in their studies. For forgetting, they compared between the performance at the end of acquisition and the early retention phase while saving is analyzed between the first acquisition and the first retention period (148). *Forgetting* refers to the loss of or inability to retrieve information form memory (147). It can measure the memory which stored in one of memory systems before being permanently encoded in long-term memory (147). Thus, it can analyze the loss of memory or indirectly measure persistency during no-practicing period by comparing the ability between before and after retention interval. *Saving* is another way to measure retained capability by comparing to baseline performance, it is the indirect method to measure consistency when compare to early acquisition period (148).

3) Transfer tests

The examining the adaptability of skillful performance is transfer tests which tests in novel situations such as new physical environment, personal characteristics, or skill variations (146). Transfer test is a type of retention test (147).

4) Coordination dynamics

Another method for measuring learning capability is observation the stabilities and consistency of movement coordination relate to performing the skill (146).

2.6.4 Neural plasticity (see review 149)

Motor learning induces the cellular and molecular change to form either short- and/or long-term memory, so called "plasticity". For short-term memory of motor learning, the neural circuits are changed in pre-existing neuronal networks. The formation processes of short-term memory include: 1) changes in the excitation-secretion coupling at the presynaptic level via phosphorylation and Ca2+ influx; 2) Ca2+ influx at the postsynaptic level and increase neurotransmitter release. If short-term memory is reinforced, it will be transformed to be long-term memory. The sustained stimulation leads to persistent activation of the protein kinase A (PKA) and MAP kinase Erk (MAPK) pathways. In turn, PKA and MAPK phosphorylates and activate or inactivates CREB target genes. These changes, both increase and decreases, in the expression of proteins involved in protein synthesis, axon growth, synaptic structure and function.

2.6.5 Principle of experience-dependent neural plasticity in rehabilitation (see review 150)

The plasticity in neural circuit depend on 10 principles of experience-dependent including;

2.6.5.1 Use it or lose it

If neural circuits do not activate for a long period of time, they will be degrade. For instance, the somatosensory cortex of a removed digit for 2 – 9 months in owl monkey was disappeared and replaced by adjacent digits. The rehabilitation session should concern this principle, the functional training can prevent the loss of neural circuits and promote functional reorganization. One technique that use this principle is constraint induced movement therapy which constraint non-affected arm of stroke patients for enhancing the use of affected arm. The result showed that patients improved their impaired limb function and this technique could promotes the activation in the remaining cortex.

2.6.5.2 Use it and improve it

Contrast to first principle, the extended training can induce the plasticity or reorganization in specific brain region via increasing synaptogenesis. Nowadays, the more directed training experience in unilateral cortical damage can both improve motor function and restored the remaining cortex.

2.6.5.3 Specificity

Specific training induced changes in specific region of brain. For instance, a research in human showed that the ankle movement training enhanced corticospinal excitability, while people who trained unskilled movement did not.

2.6.5.4 Repetition matters

Non-repetition engaging of a neural circuit cannot induces plasticity. The lasting neural plasticity requires the repetition of newly learned or relearned movement, then performer obtain improvement in behavior and brain reorganization.

2.6.5.5 Intensity matters

Similar to repetition, the intensity of training is also another factor that induce neural plasticity. The amount of intensity should be sufficient for increasing the synapse number within cortical area. The low-intensity training can induce a weakening of synaptic response, while high-intensity training induce long-term synaptic changes. For example, the reaching training for 400 times per day can increase in synapse number of motor cortex in animals, while training for 60 times per day cannot.

2.6.5.6 Time matters

Time after training is a factor which has the effect on the stability of neural plasticity and behavioral changes because the consolidation of memories requires time. For instance, the stepping training in rats with 3 months post spinal cord injury for 3 weeks improved stepping function. In human research found that training in patients with 1 month after cortical infarction was the effective method to improve the function.

2.6.5.7 Salience matters

The sufficient saliency of stimuli induce the sufficient motivation and attention and then can promote the memory consolidation and performance.

2.6.5.8 Age matters

The neuroplastic responses depend on the age of brain. The aging brain reduce the ability of the synaptogenesis and cortical map reorganization. Cognitive decline in elders may be another possible factors for poor plasticity.

2.6.5.9 Transference

Kleim and Jones defined the transference that "the ability of plasticity within one set of neural circuits to promote concurrent or subsequent plasticity". For example, the digit movement training increased corticospinal excitability and hand representation in motor cortex, then applied repetitive transcranial magnetic stimulation to that motor cortex, it enhanced skill acquisition. Thus, the combined training had beneficial effect to each other.

2.6.5.10 Interference

Inference is "the ability of plasticity within a given neural circuitry to impede the induction of new or expression of existing, plasticity within that same circuitry. It meant that some training might can both induce and, in turn, interrupt the learning. Instantly, the training in unaffected limb in rats with unilateral infarcts affected the performance and the use of affected limb.