Time is the substance of which I am made.

Time is the river that carries me away ... but I'm the river.

Jorge Luis Borges (1899-1986)

Time does not exist, is just one dimension of the soul. The past does not exist because there is no more, the future does not exist as yet to be, and this is just a non-existent instant separating past and future!

Saint Augustine (354-430)

INTRODUCTION

The human mind can be considered the result of the operation of three different functional systems (Lezak, 1994):

1. **Cognition**, i.e. the ability to manipulate information.
2. **Emotions**, i.e. the ability to feel emotions and feelings and to generate motivational drives;
3. **Executive functions**, which relate to the mode of expression of behavior.

These three functional systems express our mental activity as well as length, width and height express the form of an object.

In neuropsychology, cognitive functions have received much more attention than emotions and executive functions. This is partly due to the fact that cognitive deficits of patients with organic lesions are an important part of their symptoms, either because they can be easily measured and correlated with anatomically identifiable neural systems, and also because most of the psychometric tests are unable to capture subtle changes in the sphere of emotions.

It is clear, however, that brain damage is very unlikely to affect only one of these three functional systems, and clinical experience shows us that a central lesion, regardless of size and location, involves the three systems in a holistic manner (Lezak, 1994).

COGNITIVE FUNCTIONS

The four main abilities considered to be cognitive functions are the same skills that characterizes any computer, i.e., to receive information, to store it, to build connections with other data and to generate an output.

In humans, therefore, the four classes of cognitive functions are:

1) *the receptive capability*, i.e. the gnosic and attentional functions;
2) *learning and memory*, both explicit and implicit;
3) *the thinking*, i.e. the ability to find correlations between phenomena and to grasp the causal link; this feature also enables us to attribute mental states to ourselves (such as thoughts, desires, intentions, etc.) and to recognize mental states in other people (theory of mind);
4) *the expressive function*, i.e. the ability to produce output in a form able to connect us to the extra-personal environment, such as praxis and language skills

Each class is comprised of various functional discrete activities and usually, although they are independent classes, they work in an interdependent way (Coren et al. 1999).

EMOTIONS

The term emotion will indicate the sum of psycho physiological experiences of an individual induced by both internal and environmental influences. In humans, emotion involves the physiological attention, the behavioral expression and the conscious experience (Myers 2004). It is associated with mood, temperament, personality and motivation. Emotion derived from the Latin verb *emovere*, that means to pull out.

The emotions are characterized by an inseparable duality: on the one hand, the psychological feeling (fear, joy, etc..) and on the other hand a set of physiological effects associated with it (tachycardia, pallor, mydriasis, etc.).

From an evolutionary point of view, emotions represent a way to force the individual to react automatically to a significant event, not just a psychological response (pleasant or unpleasant), but also with a physiological adjustment capable to prepare the body, e.g., for a fight or a flight, as to increase cardiac output, pulmonary ventilation, blood sugar, etc..

At the end of the ‘800’s, William James (1884) and Carl Lange (1887) suggested that an event which causes, for example, “fear” leads initially, as an automatic response, all the physiological changes. Our brain would notice these changes and, in response, generate the psychological sense of fear; in other words, “I tremble for fear”.

This theory was criticized mainly on the basis of the observation that the same physiological sign, such as tachycardia, may be associated with opposite emotions (fear and joy) or situations that do not generate emotions (exercise or fever). The result was that two American physiologist Walter Bradford Cannon (1927) and Philip Bard (1929), formulated a theory diametrically opposed: the event that generates emotion initially induces the psychological reaction and only then our brain will induce physiological changes associated with it; in other words, “I tremble because I am afraid”.

An interesting aspect is that the neural structures involved in emotional processes are different from those underlying cognitive processes. The emotions are in fact generated by a zone of the

cerebral cortex, the so-called limbic lobe, located in the medial cerebral hemisphere, while the cognitive functions mainly derived from the bark of the lateral surface of the cerebral hemisphere, such as that of the frontal, parietal and temporal lobes.

The American anatomist James Papez (1937) showed how emotions do not arise only from the activity of the limbic lobe's cortex, but also involves sub cortical structures such as the hypothalamus and the anterior part of the thalamus (Papez circuit).

An important aspect of emotions in humans is the fact that we are able to analyze our emotions cognitively.

This led to the emergence of cognitive theories of emotions, such as that postulated by Richard Lazarus (1991), which assumes the following sequence of events:

1) *individual cognitive assessment*: the event is initially assessed cognitively and then activates an emotion.
2) *physiological changes*: the cognitive reaction starts physiological changes, such as tachycardia or activation of the pituitary-adrenal axis.

3) *action*: the individual feels the emotion and chooses how to react.

For example, I see a snake and 1) I cognitively value his presence and, as a result, I fear, 2) my heart starts to run faster and adrenaline is injected into the circulation, 3) I scream and run.

It was also suggested that emotions are often used as shortcuts to process information and change attitudes. The Affect Infusion Model (AIM) is a theoretical model developed by Joseph Forgas (1995) that attempts to explain how emotions and moods interact with our ability to process information.

EXECUTIVE FUNCTIONS

The term "executive function" was used by Muriel Lezak (1983) to describe the skills that make an individual able to take on successfully an independent, objective and self-preservative conduct.

Alan Baddeley (1986) subsequently described the executive functions as behaviors which include interference's control, flexibility, decision-making, planning skills and ability to anticipate and initiate intended activities. The same Baddeley coined the term "disexecutive syndrome" to describe the change in the executive functions, whose symptoms include impaired memory ("working memory" a short-term memory that allows the conduct of the action); deficit of learning strategies, difficulties in planning and problem solving, difficulties in set-shifting, with failure to modify behavioral strategies in a flexible manner and in relation to changes in the environment, inability to inhibit automatic responses and reduced verbal fluency.

PREFRONTAL CORTEX

From a neuroanatomical point of view the frontal lobe and, in particular, the prefrontal areas play a key role in the performance of executive functions (Passingham, 1993).

By using a cytoarchitectonic criterion, in the frontal lobe are traditionally distinguished three regions: *a posterior region*, poor of granules and rich of pyramidal cells, including according to the classification of Brodmann the areas 4 (motor) and 6 (premotor), *an intermediate region*, with more granules and less pyramidal cells, corresponding to the Brodmann's areas 8 (oculomotor) and 44 (Broca's), and an *anterior prefrontal region*, where the granules are predominant and the pyramidal cells are poorly represented, corresponding to 9, 10, 11, 12, 13, 14, 32, 33, 45, 46 and 47 Brodmann's areas.

During phylogeny, the frontal cortex, especially the prefrontal areas, shows a greater development in proportion to the remaining cortex. The differentiation of the frontal cortex in its various cytoarchitectonic components is already present at birth, but takes the final appearance only at puberty (Kostovic, 1990).

From the functional point of view the prefrontal region can be divided into three portions (Damasio, 1985): the *dorsolateral area*, which is the critical region for the “executive functions”, the *orbital sector*, which is important for the personality, emotions and some aspects of a goal-oriented behavior, and the *mesial sector*, which is responsible for mood, feelings and communication processes. These three portions of the prefrontal cortex have special connections with the basal ganglia, forming three cortico-strio-thalam-cortical circuits, parallel and relatively independent (Alexander et al., 1990):

1) The *dorsolateral prefrontal cortex* sends fibers to the head of the caudate nucleus which, via the globus pallidus and the substantia nigra pars reticulata, projects to the dorsal lateral and ventral anterior nuclei of the thalamus. From here, gives rise a projection that returns to the dorsolateral prefrontal cortex, by closing a circuit that seems to be involved in executive functions.
2) The *orbitofrontal cortex*, namely the lateral prefrontal cortex, that projects to the ventral part of the caudate nucleus which,

via the globus pallidus and the substantia nigra pars reticulata, sends its efferents to the thalamus. Hence, a projection comes back to the orbitofrontal cortex, creating a circuit that seems to be involved in the ability to socialize and to assume rules of conduct.

3) The *mesial prefrontal cortex*, along with that of the anterior cingulate gyrus, projects to the ventral part of the striatum that, through the globus pallidus and substantia nigra pars reticulata, is connected to the medial dorsal nucleus of the thalamus. Hence, a projection returns to the anterior cingulate gyrus, creating a circuit that seems to be involved in motivation and learning.

Damages to the medial cortex lead to a “pseudodepressive syndrome” characterized by apathy, inertia and depressed mood, while lesions of the orbital cortex constitutes a “pseudopsychotic syndrome” dominated by impulsivity, selfishness, fickleness and bipolar mood. In addition, damages of medial areas of orbital frontal lobe is able to induce the so-called “environmental dependency syndrome”, characterized by imitative behavior

(Lhermitte, 1983). In normal conditions, the parietal lobe creates a dependency between the subject and environmental stimuli, while the frontal lobe allows the subject to remain independent from the outside world, modulating and inhibiting the activity of the parietal cortex; a lesion of the mesial frontal cortex would result in the loss of this independence, causing the environmental dependency syndrome.

Lesions of the portion of the dorsolateral prefrontal cortex (areas 9 and 10) determine executive dysfunction.

DOPAMINE

Dopamine is a catecholamine present in a wide variety of animals, including vertebrates and invertebrates. In the brain, dopamine functions as a neurotransmitter, activating five types of dopamine receptors (D1, D2, D3, D4 and D5) and their variants.

Dopamine is produced in different areas of the brain, including substantia nigra and the ventral tegmental area. Dopamine is also a neuro-hormone released by the hypothalamus, its main function being to inhibit the release of hormone prolactin from anterior pituitary.

Dopamine has been synthesized in 1910 by George Barger and James Ewens at the Wellcome Laboratories in London. It was called “dopamine” because it is a monoamine and its synthetic precursor is L-3,4-dihydroxyphenylalanine (L-DOPA). The role of dopamine as a neurotransmitter has been identified in 1958 by Arvid Carlsson and Nils-Åke Hillarp at the Laboratory of Chemical Pharmacology National Heart Institute in Sweden (Benes, 2001). Arvid Carlsson was awarded the 2000 Nobel Prize in Physiology or

Medicine for showing that dopamine is not just a precursor of noradrenaline and adrenaline, but also a neurotransmitter.

There are two basic pathways of dopamine. In most areas of the brain, including the striatum and basal ganglia, dopamine is inactivated by its re-uptake through the dopamine transporter (DAT1), and then enzymatically degraded by monoamine oxidase (MAO-A and MAO-B) in 3,4-dihydroxyphenylacetic acid. In the prefrontal cortex, however, there are very few dopamine transporters and, thus, dopamine is inactivated by its re-uptake by the norepinephrine transporter (NET), presumably on neighboring norepinephrine neurons, then enzymatic breakdown by catechol-O-methyl transferase (COMT) into 3-methoxytyramine (Carboni et al., 1990).

CENTRAL ACTIONS OF DOPAMINE

Dopamine has many functions in the brain, including behavior, cognition, voluntary movement, motivation, reward-punishment combination, inhibition of prolactin production (involved in lactation and sexual gratification), in sleep, in mood, attention, working memory and learning.

It has been suggested that dopamine transmits a signal in the presence of a reward, although this has been questioned (Redgrave and Gurney, 2006). According to this hypothesis, the phasic response of dopamine neurons is observed when an unexpected reward is presented. These responses lead to the emergence of a conditioned stimulus after repeated pairings with the reward. In addition, dopamine neurons are depressed when the expected reward is omitted. The dopamine neurons appear to encode the prediction error of gratifying results. In nature we learn to repeat behaviors that lead to maximizing the reward. Dopaminergic neurons, therefore, are considered capable of generating a learning signal direct to those parts of the brain responsible for the acquisition of new behavior (Schultz 2007).

Dopaminergic neurons (i.e. neurons in which the main neurotransmitter is dopamine) are present mainly in the ventral tegmental area (VTA) of midbrain, in the substantia nigra pars compacta and in the arcuate nucleus of the hypothalamus. From these three subcortical structures arise four major dopaminergic projections (Kruk and Pycock1993):

1) The mesocortical pathway, which connects the ventral tegmental area to the prefrontal cortex; is considered to be involved in modulation of cognitive functions.

2) The mesolimbic pathway, which connects the ventral tegmental area to the nucleus accumbens, through the amygdala and the hippocampus; it is thought that it is involved in the modulation of emotional responses.

3) The nigrostriatal pathway, running from the substantia nigra to the neostriatum, i.e. the caudate nucleus and putamen; is considered to be involved in control of movement.

4) Tuberoinfundibular pathway that runs from the hypothalamus to the pituitary gland; hypothalamic dopamine controls the release of

hormones such as Growth Hormone (GH) and Prolactin inhibiting factor (PIF).

DOPAMINERGIC THEORY OF MIND

The dopaminergic theory of mind tries to explain the differences between modern humans and their hominid relatives, focusing on changes in dopamine (Previc, 2009). It is theorized that increased levels of dopamine is part of a general physiological adaptation began with an increase in meat consumption, happened about two million years ago in Homo Habilis, and enriched with dietary changes and other environmental social factors approximately 80,000 years ago.

According to this theory, the “personality with high levels of dopamine” is characterized by high intelligence, a sense of personal destiny, a concern for cosmic/religious aspects, an obsession for the attainment of objectives and achievements, an emotional detachment, that in many cases leads to the ruthlessness, and a risk-taking mentality. High levels of dopamine are proposed to underlie the increase in psychological disorders in industrialized societies. According to this hypothesis, a “dopaminergic society” is extremely focused on the target, rapidly changing, and is also a manic society because “dopamine is

known to increase activity levels and creates a preference for novelty rather than for environmental stability” (Previc, 2009).

Although behavioral evidences and some indirect proof support anatomical dopaminergic expansion in humans (Rapoport, 1990), there is still no direct evidence that dopamine levels are higher in humans than in other anthropoid primates (Raghanti et al., 2008).

PARKINSONISMS AND EXECUTIVE FUNCTIONS

The executive functions are impaired in patients with Parkinson's disease (PD). The alterations are evocative of the cognitive deficits observed in patients with damage in the frontal cortex (Rowe et al., 2002). It is known that the PD is characterized by loss of dopaminergic cells in the substantia nigra and ventral tegmental area (VTA). The ascending system that originates in the substantia nigra is brought to the striatum and appears correlated with motor function, which originates from the VTA reaches the ventral striatum, the amygdala and the frontal lobe and is involved in emotional and cognitive functions. The dysfunction of the latter circuit determines the disexecutive disorder observed in the PD.

Deficit of executive functions have also been observed in patients with parkinsonian syndromes (Lange et al., 2003, Graham et al., 2003), such as multi-systemic atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).
The comparison of these patients with healthy subjects revealed significant changes in verbal fluency, visual and verbal working memory and problem-solving skills, also understood as the ability

to infer rules, to have a cognitive flexibility and planning strategies (Godefroy 2003; Reverberi et al., 2005). Patients with PSP and CBD have both phonemic and semantic changes in verbal fluency, more severe than in patients with PD or MSA. In particular, it was found that in patients with PSP deficits involve semantic and phonemic verbal fluency (Lange et al., 2003), while in patients with CBD deficits are configured mainly as non-fluent aphasia (Graham et al ., 2003).

With regard to the ability to solve problems, it was found that patients with CBD and MSA exhibit deficits that seem to be much more severe than in patients with PD or other forms of parkinsonism (Halpern et al., 2004, Dujardin et al. 2003).

Finally, as regards to the working memory, both verbal and visual, it was found that patients with PD have more severe deficits of short-term memory (Mohr et al., 1990) than those presented by subjects with MSA (Robbins et al., 1992), but less severe than those with PSP (Robbins et al., 1994) or CBD (Halpern et al., 2004).

PATHOPHYSIOLOGICAL CONSIDERATIONS

The pathophysiology of executive functions disorders is due to an impairment of the fronto-strio-thalamo-cortical circuit, which seems critical in the implementation of these functions (Alexander et al., 1990). However, as it was pointed out earlier, the executive functions are not affected evenly in the various forms of parkinsonism. That finding suggests that quantitative and qualitative differences can determine the degree of involvement of structures located between the basal ganglia and prefrontal cortex. Although these differences cannot yet be able to identify disexecutive patterns specific for a particular condition, the tests assessing frontal functions may be able to differentiate populations of patients with PD, MSA, PSP and CBD.

THE PERCEPTION OF THE FLOW OF TIME

The subjective perception of the flow of time remains one of the most important cognitive skills in everyday life and, because of its subjectivity, it felt the need for objective measurement of the flow of time such as sundials, clocks, calendars, etc..

Humans have an excellent ability to analyze the flow of time, such capacity is vital in making forecasts and motor control (Diedrichsen et al., 2003; Ivry, 1996; Ivry and Richardson, 2002, Spencer et al., 2005). From an evolutionary point of view, the ability to measure intervals of seconds and minutes it is important to make decisions about environmental situations, such as the appearance of a predator or a prey (Bateson, 2003, Gallistel and Gibbon, 2000).

The ability, however, to evaluate intervals in the millisecond is important for motor control and for rapid sequences of cognitive operations, such as the updating of working memory or language processing (Ivry and Justus, 2001; Lustig et al., 2004, Meck and Benson, 2002; Schirmer, 2004). The ability to measure time and, then, to notice differences between temporal events obeys to the

Weber's law: “a sensory change may be perceived only if the amendment is in a certain proportion larger than the original one (cf. Matell and Meck, 2004).

The human ability to consciously perceive the flow of time has been analyzed by many authors, but in 1984 Paul Fraisse proposed an hypothesis representing a sufficiently rational frame for our ability to perceive and measure time. Fraisse (1984) has divided our perception of time, on the basis of the perceived length of time, in 3 different components: a) the time perceived as “instant” for a duration of less than 0.1 sec, b) the time perceived as “present”, lasting between 0.1 and 5 s, c) time intervals greater than 5 s, perceived in a way that Kinsbourne and Hicks (1990) called “extended present”. These authors, however, believe that this period is perceived as “extended present” only for intervals greater than 20-30 s.

A series of experimental evidence has shown that the perception of the “extended present” depends on the integrity of the long-term memory (LTM) systems. E.g., Richard (1973), analyzing the patient HM who owned the short-term memory but

not the LT (Scoville and Milner, 1957), observed that he correctly assessed the time intervals of less than 20 s, while he perceived as 1 hour an interval of 3 min and as one day that of 15 min.

The perception of time is now believed to be due to a pacemaker, a real time clock, which generates regular pulses that accumulate in a reference memory where they would be counted. The elapsed time is proportional to the number of pulses stored in the accumulator (Pashler 2001; Matell and Meck, 2004).

It has been suggested by Santamaria (2002), and then perfected by Meck (2005), that the internal clocks may be two (Figure 1): a first internal clock, involving the cerebellar circuitry, which could operates in the range of milliseconds and would be important for motor coordination, and a second internal clock, involving the fronto-striatal circuits, which manages intervals between seconds and minutes and would be important for cognitive processes pertaining the frontal cotex.

In this regard, a series of data shows that time production requires the integrity of the striatum and of dopaminergic nigro-striatal afferents (Clarke and Ivry, 1997, Dallal and Meck, 1993,

Matell et al., 2000, Meck, 2006). In fact, if dopamine is directly administered in the striatum of a rat, there is an acceleration of timing, but if a dopamine antagonist is administered, the timing is slowed down.

One of the most reliable models to define the neural organization of the internal clock is the one proposed by Gibbon (1977), which is called the Scalar Expectancy Theory (SET). Since the cells of the substantia nigra pars compacta (SNPC) have a very regular discharge of impulses (5 Hz), it has been hypothesized that they represent the Pacemakers. Since, in turn, SNPC cells project to the striatum, the latter should be the location of the counter where the pulses are accumulated and measured. The striatum, finally, sends the processed data from the counter to the frontal cortex, via the paleostriato-thalamo-cortical loop, which would be managed as working memory.

Church and Broadbent (1990) have proposed a different model from the set with the presence of multiple pacemakers that work in parallel. Matell and Meck (2004) have localized oscillators

in the frontal cortex where impulses to the striatum are send (via cortico-striatal projections).

In the model of Matell and Meck (2004) the role of the SNPC is that of the modulator of striatal neurons and not that of a pacemaker, with opposing influences on striatal neurons originating the striato-pallidal via direct than the indirect pathway. As described by Robertson et al. (1992), dopamine on neurons of the first pathway, via D1 receptors, is excitatory, while on the neurons of the indirect pathway, where are the D2 receptors, is inhibitory. This duality could be useful on the behavioral level when the appearance of a interesting stimulus would activate the SNPC leading to an acceleration of the direct pathway, which in turn would facilitate the action.

It is well known that patients with Parkinson's disease (PD) have a significant difficulty in the perception of time (Nakamura et al., 1978), which appears to be independent of motor execution (Gibbon et al., 1997). E.g., Patients with PD wrongly perceive the interval between two stimuli and that error is reduced by drug therapy (Artieda et al., 1992). The same research group (Pastor,

1992) showed that the error was present for periods of less than 27 s. However, since patients measured the flow of time by mentally counting, an action that provides a sub-vocalization, the error could indicate a slowdown in motor rather than a real change in the perception of time (Riesen and Schnider, 2001). This observation led these authors to implement an experimental protocol in which, prevented PD patients of evaluating the flow of time by mentally counting. The results showed that while PD patients wandered significantly in measure intervals shorter than 12 s, they showed no significant deficits in the assessment of intervals between 12 and 48 s. However, in their research, Riesen and Schnider (2001) did not compare in the same subject the ability to measure the time by using their protocol and by utilizing the mental count. In addition, although all their patients were treated with levodopa (280 to 1,000 mg / day), they have not evaluated the possible influence represented by the pharmacological condition (ON / OFF) on the ability to discriminate the time.

AIM OF THE RESEARCH

The purpose of this study was to analyze the ability to estimate the time in patients with PD, by overcoming these limitations. In fact, their ability to assess time intervals in the “present” range (less than 5 s) and in the “extended present” range (lasting from 40 to 90 s) was compared. The evaluation was performed using both a protocol that allowed the subjects to count mentally (quantitative method) and with a protocol, obtained by adapting that proposed by Riesen and Schnider (2001), which prevented the subject from mentally counting (qualitative methods).

It was, finally, evaluated in PD patients the effect of levodopa therapy on their ability to estimate the flow of time, by comparing the tests carried out in ON-drug condition with those made in the OFF- drug state.

MATERIAL AND METHODS

Patients

Ten subjects (6 males and 4 females) with PD in accordance with the criteria of the United Kingdom Parkinson's Disease Society Brain Bank of London (UKPDSBB; Hughes, 1992), with a mean age of 57.1 years (± 11 0, DS) and a mean education of 11.0 years (± 5.0 SD). The patients had a mean disease duration of 34.1 months (± 6.3 SD) and a severity of disease, according to the scale of Hoehn and Yahr (1967) as amended by (Fahn et al., 1987), with a mean value of 2.0 (± 0.6 SD) in ON phase and 2.1 (± 0.7 SD) in OFF phase.

Clinical conditions were evaluated with the Unified Parkinson's Disease Rating Scale - section III motor examination (UPDRS-ME, Fahn et al., 1987), with an average score of 18.5 (± 7.3 SD) in ON phase and 25.7 (± 11.0 SD) in OFF phase

Participants were first assessed with the Mini Mental State Examination (MMSE, Folstein et al., 1975), to exclude from research patients with a score under 24. The 10 patients recruited for this study had an average value of the MMSE 28.0 (± 1.9 SD).

We selected patients who followed the following regimen: 250 mg of levodopa plus 25 mg of carbidopa at interdoseintervals of 24 or 12 hours, starting at 8 am.

The clinical condition and the ability to estimate the flow of time have been studied both in OFF-drug condition (12 or 24 hours after the last dose) and in ON-drug condition (two hours after taking the drug).

Table 1

PATIENTS 6 male 4 female	**Age**	**Education**	**MMSE**	**HY**	**UPDRS-ME**	**Mesi**
On	57.1±11.0	11.0±5.0	28.0±1.9	2.0±0.6	18.5±7.3	34.1±6.3
Off				2.1±0.7	25.7±11.0	
CONTROLS 6 male 4 female	**Age**	**Education**	**MMSE**			
	54.2±8.4	10.7±4.1	28.5±1.3			

Each recruited patient was informed about the nature of the study and gave his consent.

Table 1 summarizes the data for both patients and controls.

Controls.

We used as a control group represented by ten subjects (6 males and 4 females), matched for age and education to patients with PD (mean age: 54.2 years ± 8.4 SD; education: 10.7 years ± 4.1 SD). The subjects were free from neurological and / or psychiatric diseases, not taking medication that interfere with their cognitive performance and did not match with DSM IV (APA, 1994) and ICD-10 (WHO, 1993) criteria for deterioration cognitive. The 10 control subjects had an average value of the MMSE of 28.5 (± 1.3 SD).

Methods for the qualitative assessment of the time

The subjects were asked to assess both short time intervals (less than 6 seconds) or long duration (40 to 90 sec), using two

separate protocols that prevented them from assessing the flow of time by mentally counting.

Evaluation of the "present" (intervals shorter than 6 s). The first protocol was an adaptation of the method of Riesen and Schnider (2001). The subject was placed in front of the computer screen on which appeared two blue boxes, of equal size, one above the other. At one point, without warning, the higher box will turn yellow and, after a brief interval, the lower box also became yellow. After a programmed time interval, the two boxes separately returned to the starting color. The subject had to say which of the two boxes had been for longer time yellow (Figure 2).

The duration in seconds of the yellow of the two boxes was scheduled in the following five combinations: a) 5 and 6, b) 4 and 5, c) 3 and 4, d) 2 and 3,) 2 and 4; in this way, although in absolute terms the difference was 1 or 2 s, the difference in percentage increases from a minimum of 16% to a maximum of 50%. The five combinations were also repeated two times with the values inverted in random order, so it was impossible for the subject to

predict whether the box yellow for more time was left was the top or bottom one.

Evaluation of the "extended present" (time intervals from 40 to 90 s). On a computer screen appeared a sequence of slides that carried a brief history (duration of the sequence: 40, 60 and 90 s), taken from the tables of Phaedrus, that the subject had first to read and then to summarize. After reading, he was asked to estimate the duration of the sequence. In this way the subject, having to be concentrated on the content to be able to sum up it, he could not assess the low of time by mentally counting (Figure 3).

Methods for the quantitative assessment of the time

The subjects were asked to assess time intervals of short (1 to 5 s) and long (40 to 90 sec) duration, by using two separate protocols that allowed an estimation of time with mental count.

Evaluation of the "present" (intervals shorter than 6 s). The subject was placed in front of a computer screen at the center

of which there was a yellow circle. When the examiner gave the “go”, after an interval between 1 and 5 s, below the yellow circle, duration a blue square. The subject had to assess, by mentally counting, how much time had elapsed between the “go” and the appearance of the blue square (Figure 4).

Evaluation of the “extended present” (time intervals from 40 to 90 s). The subject was placed in front of a computer screen at the center of which there was a blue circle. When the examiner gave the “go”, after an interval of 40, 60 or 90 s, appeared below the blue circle a blue star. The subject had to assess, by mentally counting, how much time had elapsed between the “go” and the appearance of the blue star (Figure 5).

STATISTICAL ANALYSIS

The data obtained from both patients and controls were analyzed by using the statistical program GraphPad Prism, version 4.00 for Windows, the GraphPad Software (San Diego, California, USA).

The data of the qualitative assessment of the “present” were distributed in a table where the rows refer to the number of correct and incorrect answers, while the columns were represented by the controls, by patients in ON-state and by patients in OFF-state. In order to verify whether there was a relationship between the variables on the rows and the variables on the columns, the data was analyzed with the chi-square test.

The data on the qualitative assessment of the “extended present”, as well as those relating to the quantitative assessment of the “present” and the “extended present”, data were analyzed by nonparametric Kruskal-Wallis test of analysis of variance (ANOVA), followed by Dunn's post-hoc test.

RESULTS

Qualitative assessment of the "present".

Table 2 and Figure 6 show the results obtained from 10 patients and from 10 controls, each of whom performed 10 trials, by using the protocol for the evaluation of short time intervals without being able to count mentally.

Table 2			
	controls	**ON**	**OFF**
Errors	7	29	15
No errors	93	71	85

Number of correct and wrong answers committed by healthy subjects, as well as by the patients during both ON and OFF phase.

It can be seen that the patients committed a greater number of errors compared to controls. The number of errors was higher

when patients were in ON than when they were in OFF phase. The Chi-square test reveals that the number of errors committed by patients in ON phase was significantly higher either compared to the controls ($P < 0.001$) and compared to the same patients when they were in OFF phase ($p < 0.05$). However, the difference was not significant between controls and patients in OFF phase.

Quantitative assessment of "present".

Table 3 and Figure 7 illustrate the results obtained both from 10 patients and from 10 controls, each of whom performed 10 trials, by using the protocol for the assessment of short time intervals that allowed the subject to be able to count mentally.

TABLE 3						
True (s)	**Controls (s)**	**%**	**ON (s)**	**%**	**OFF (s)**	**%**
3	4.1	+36.67	4.90	+63.33	5.80	+93.33
5	6.6	+32.00	6.80	+36.00	9.40	+88.00
1	2.1	+110.00	1.90	+90.00	2.00	+100.00
4	5.2	+30.00	5.80	+45.00	8.10	+102.50
2	2.8	+40.00	2.70	+35.00	4.50	+125.00
1	1.6	+60.00	2.20	+120.00	2.70	+170.00
3	4.4	+46.67	4.80	+60.00	5.70	+90.00
4	5.8	+45.00	6.30	+57.50	8.20	+105.00
2	2.6	+30.00	3.40	+70.00	4.70	+135.00
5	6.3	+26.00	6.90	+38.00	9.80	+96.00

Difference, expressed as a percentage, between the real time intervals and those reported by the subjects.

It was seen that both controls and patients tended to over-estimate the time interval that had to be measured. On average, the over-estimation was +45.6% (± 24.8 SD) in control subjects, + 61.4% (± 26.9 SD) in patients in ON phase and +110.5 % (± 25.8 SD) in OFF phase.

The ANOVA nonparametric Kruskal-Wallis test, followed by Dunn's post-hoc test, reveals that the over-estimation committed by patients in OFF phase by mentally counting, was significantly higher compared to both controls ($P < 0.001$) and to the same patients when they were in ON phase ($p < 0.05$). The difference, however, was not statistically significant between controls and patients during ON phase ($p > 0.05$).

Qualitative assessment of the "extended present".

Figure 8 shows the results obtained from 10 patients and 10 controls by using the protocol for the evaluation of time intervals, ranging between 40 and 90 s, which did not allow them to count mentally.

It can be seen that both control subjects and patients in ON phase tended to estimate with an acceptable accuracy the duration of the interval to measure. Instead, when patients were in OFF phase, tended to over-estimate the range to be measured. The ANOVA nonparametric Kruskal-Wallis test, followed by Dunn's post hoc test, reveals that the over-estimation of the time committed by patients in OFF phase in these experimental conditions, although modest, was significantly higher compared to the same patients when they were in ON phase ($p < 0.05$) only when the duration was 60 or 90 s. The difference was not statistically significant in all the other experimental conditions ($p > 0.05$).

Quantitative assessment of the "extended present"

Figure 9 shows the results obtained from 10 patients and 10 controls by using the protocol for the evaluation of time intervals between 40 and 90 s, which allowed the subject to count mentally.

It can be seen that patients in phase ON tended to under-estimate the time interval that had to be measured, with respect to controls; the same patients, however, in OFF phase tended to

over-estimate the range to be measured. The ANOVA nonparametric Kruskal-Wallis test, followed by Dunn's post hoc test, reveals that the magnitude of under-estimation and over-estimation of the time interval in these experimental conditions was generally not statistically significant. In fact, the difference in the estimation of time was significant between patients in ON phase and OFF phase only for 40 s ($p < 0.05$) and 60s ($p < 0.05$) intervals. The difference was not statistically significant in all other experimental conditions ($p > 0.05$).

DISCUSSION

The results obtained can be summarized as follows.

a) In the assessment of short intervals (less than 5 s), PD patients had significant changes in their perception of time. These changes are of opposite sign if the assessment was carried out by mentally counting than when it was not possible: it was observed, in fact, that the error is greater if the assessment is performed in OFF phase, if the estimation comes from the mental count of time, while is in ON phase in the tests where this is not possible.

b) In the assessment of longer time intervals (40 to 90 sec), patients with PD have limited alteration of their perception of time. These changes, which consist of a modest overestimation of the time, are present when patients are in OFF phase, with no significant differences between the conditions where the evaluation comes from the mental count compared to those where this is not possible.

As already reported by Riesen and Schnider (2001), in this study it was observed that the PD affects significantly the ability to estimate time intervals in the range of a few seconds compared to those in the range of minutes.

The original data that the survey has highlighted is that, in short intervals, there was an error that appears linearly related to the availability of dopamine, but that results in opposite effects compared to the methods used by the subject to estimate the time. In fact, if the person uses the mental count, the error increases with decreasing availability of dopamine, whereas if the evaluation of time is carried out without mental count, the error increases with the availability of dopamine.

This implies that the two methods of assessing the flow of time are dependent on corticostriatal circuits on which the influence of dopamine is of opposite sign. In the mental count, as already suggested by Riesen and Schnider (2001) and reiterated by Perbal et al. (2005), dopamine speeds internal clock, with the result that its deficiency results in a slowdown of the estimated time that is parallel to motor slowing.

The observation that treatment with dopamine increases the error in the estimate of the time when the mental count is not possible, leads to the conclusion that the internal clock is negatively affected by dopaminergic input.

This conclusion is in line with the observation of Gotham et al. (1986), later confirmed by many authors (see Frank, 2005), in patients with PD language performance deteriorates when they are in ON phase and not in OFF phase, while cognitive tests involving the prefrontal cortex worsen during ON and not OFF phase.

From a circuitry point of view, it can be supposed that the internal clock used in the mental count is part of cortico-striatal circuits involved in motor control, while the latter might be part of the cortico-striatal circuits underlying cognitive functions, controlled by the prefrontal cortex.

This hypothesis is consistent with the observations of Matell et al. (2003), Poldrack and Packard (2003) and Xiao and Barbas (2004) that have suggested a role of hippocampal projections to the striatum in modulating the perception of time (Figure 10) .

According to these authors, hippocampus and striatum were antagonists in modulation of inner timer, since a lesion of the hippocampus increases the concentration of dopamine in hippocampus projection area of striatum, an increase which is associated with an exaltation of the striatal time generator.

Another possibility is that the internal clock used for the quantitative evaluation is part of the transcortical circuits involved in motor control, while that used for the qualitative evaluation is part of circuits involved in cognitive functions. In fact, it is well known that depletion of dopamine in PD initially affects the dorsal striatum and only in a second moment the ventral striatum (Bernheimer et al. 1973; Kish et al. 1988).

This difference in the progression of dopamine depletion in space and time implies that in the dorsal striatum, in which there is a lack of dopamine, levodopa improves motor performance, while the ventral striatum, with normal dopamine content, the administration of levodopa causes an “overdose” effect (Cools 2006). This leads to the hypothesis that the internal clock used for the quantitative estimation of short time intervals (from 1 to 5 s)

involves the dorsal striatum, while that used for qualitative estimation of these intervals, the ventral striatum.

When considering the “extended present”, i.e. time intervals between 40 and 90 s, the observed results are consistent with the hypothesis that in this assessment, unlike the evaluation of the “present”, the estimation of the time does not involve the ventral striatum, but only the dorsal one, because the dopamine improves the performance of time estimation made both quantitatively and qualitatively.

In conclusion, this study allows us to consider the short intervals (1 to 5 s) as a “special” temporal category, with the involvement of the dorsal striatum, the most closely related to cognitive functions (Tang et al., 2007), in the mental count, and the ventral striatum, a structure involved in behavioral processes related to emotional valence, how to obtain a reward (Pippas-Gregorios et al, 2009), when mental count is not used.

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FIGURES

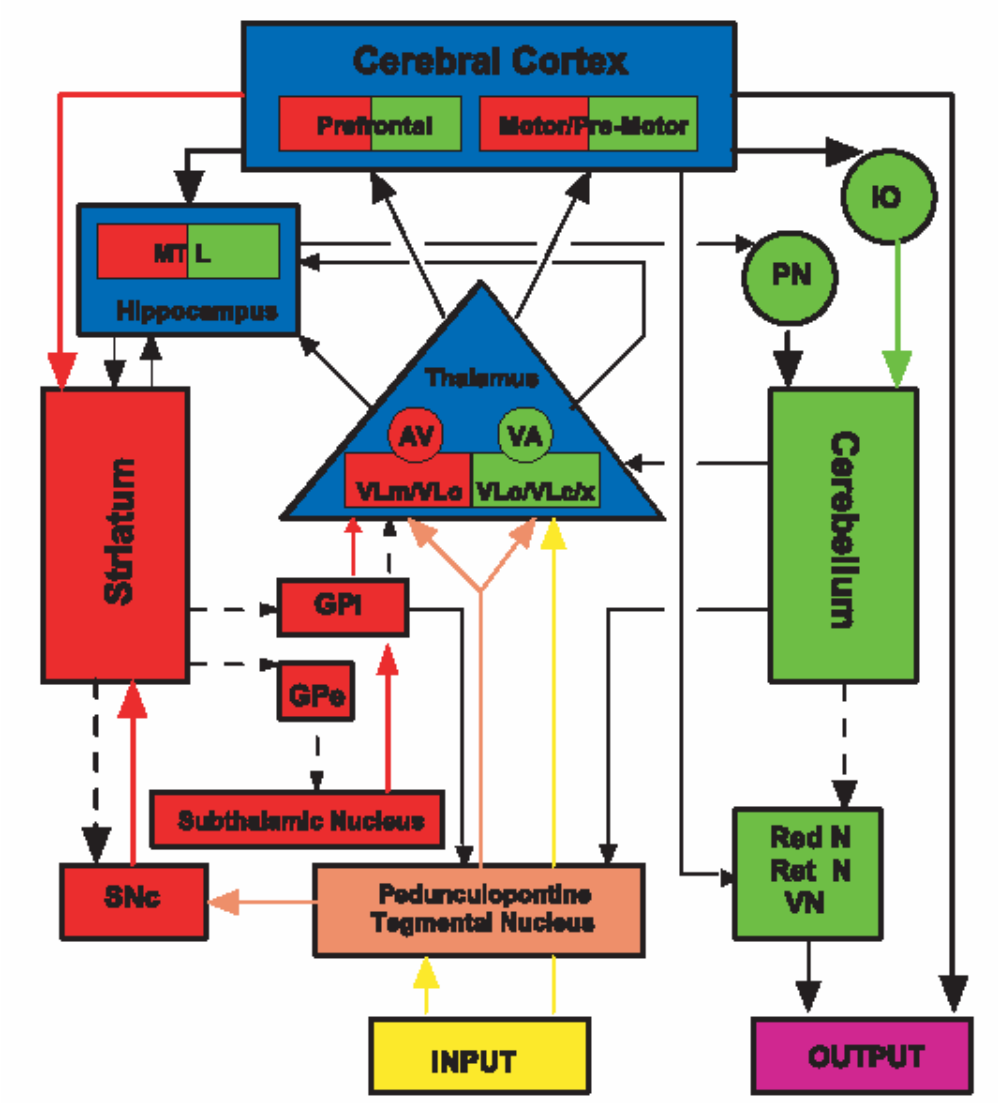


Figure 1. Schematic representation of the cortico-striatal and cortico-cerebellar circuits involved in the measurement of time. Clear lines represent excitatory input while the dark ones inhibitory afferents (Meck, 2005).

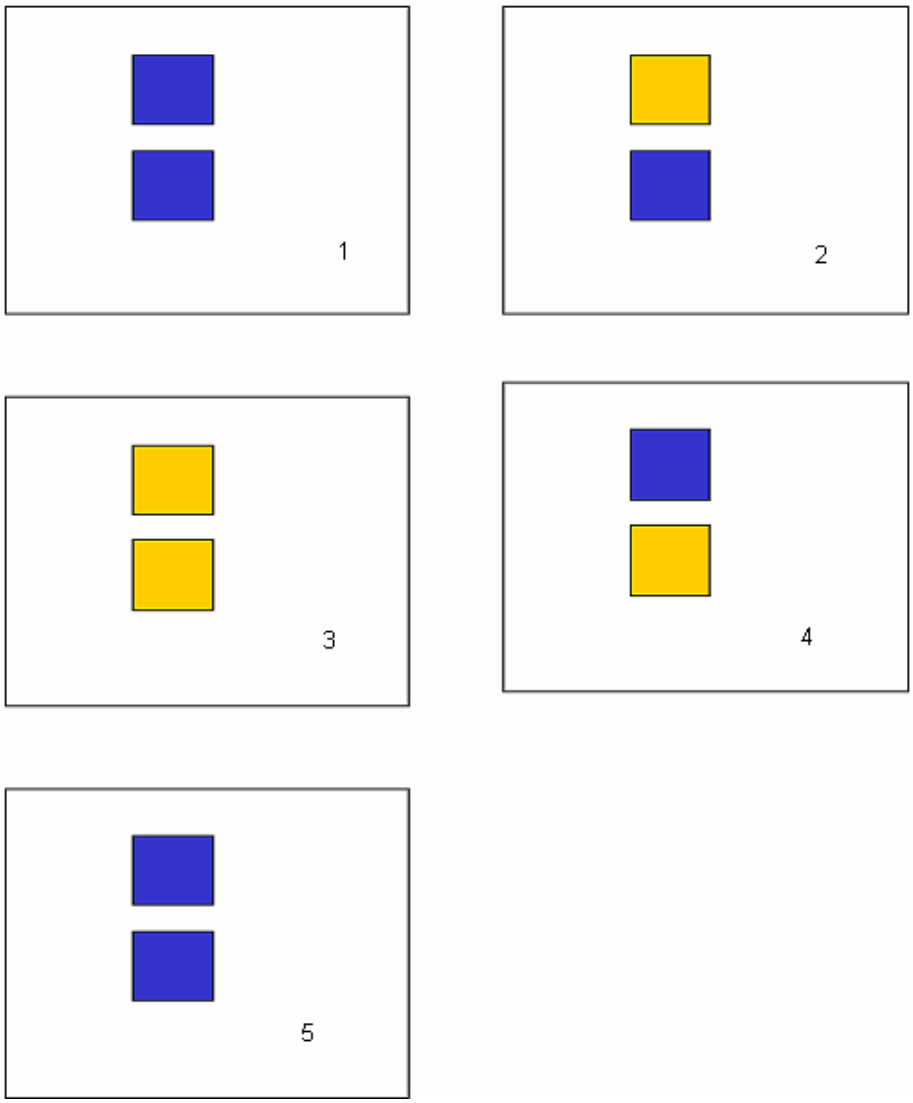


Figure 2. Qualitative assessment of the "present".
On a computer screen there were two blue squares, of equal size. At one point, without warning, the higher square will turn yellow and, after a brief interval, the inferior square also became yellow. After a programmed time interval, the two square separately returned to the starting color. The subject had to say which of the two squares had been yellow for more time.

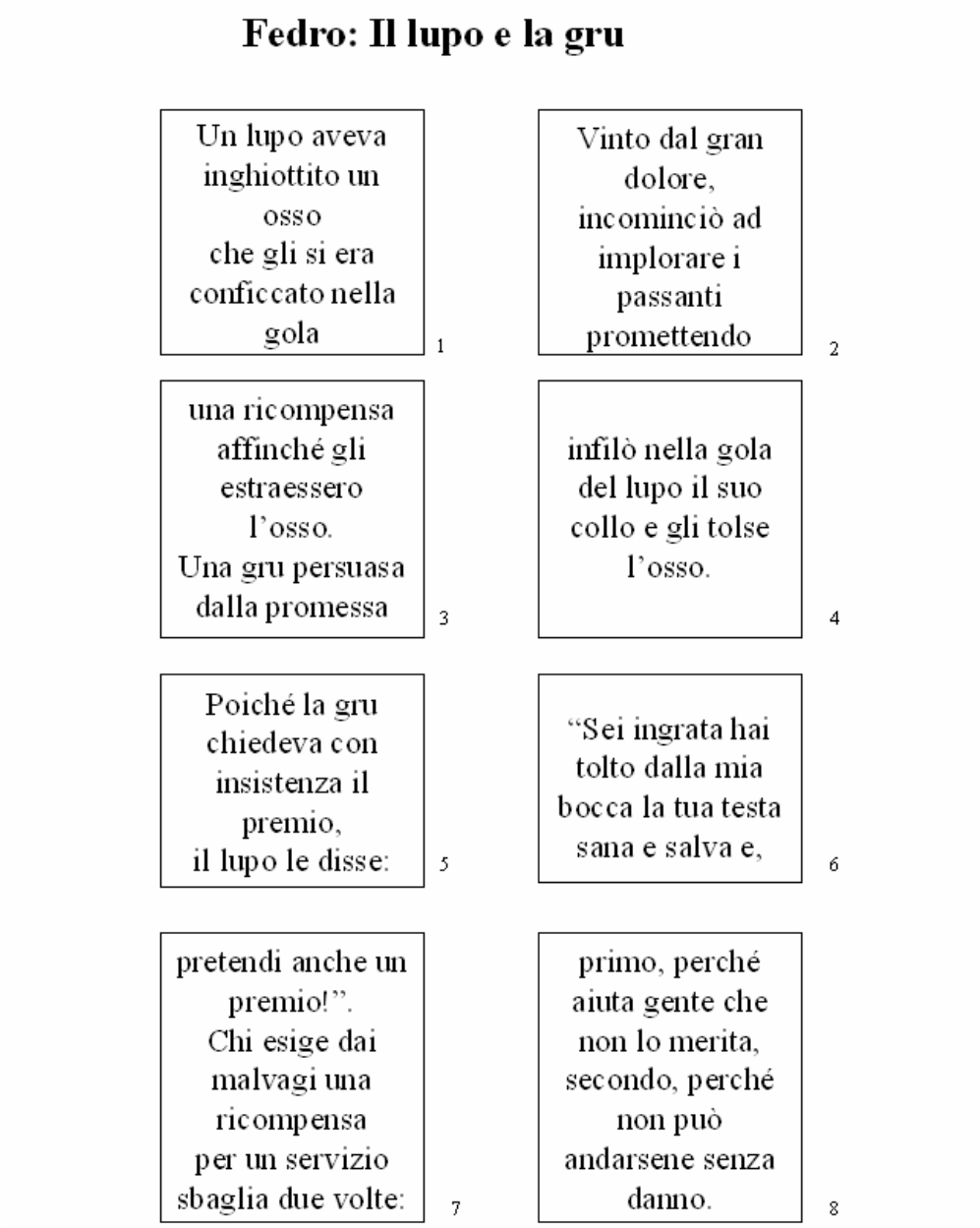


Figure 3. Qualitative assessment of the "extended present".
On a computer screen appears a sequence of slides that carried a brief history (duration of the sequence: 40, 60 or 90 s), taken from the fables of Phaedrus, that the subject had to read and summarize. At the end, the subject was asked to estimate the duration of the sequence. In this way the subject, having to concentrate on the content to be able to sum up it, could not assess the flow of time by mentally counting.

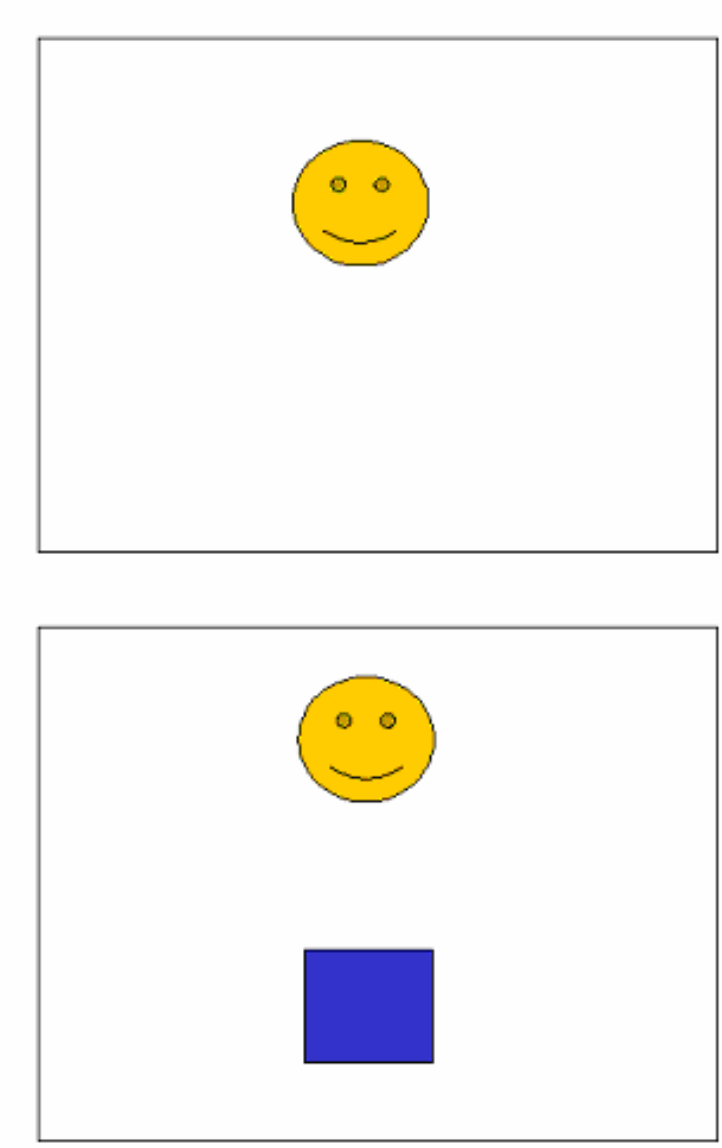


Figure 4. Quantitative assessment of "present".
On a computer screen there was a yellow circle. After a certain interval of time between 1 and 5 s appeared, below the yellow circle, a blue square. The subject had to assess, by mentally counting, how long does the blue square appeared.

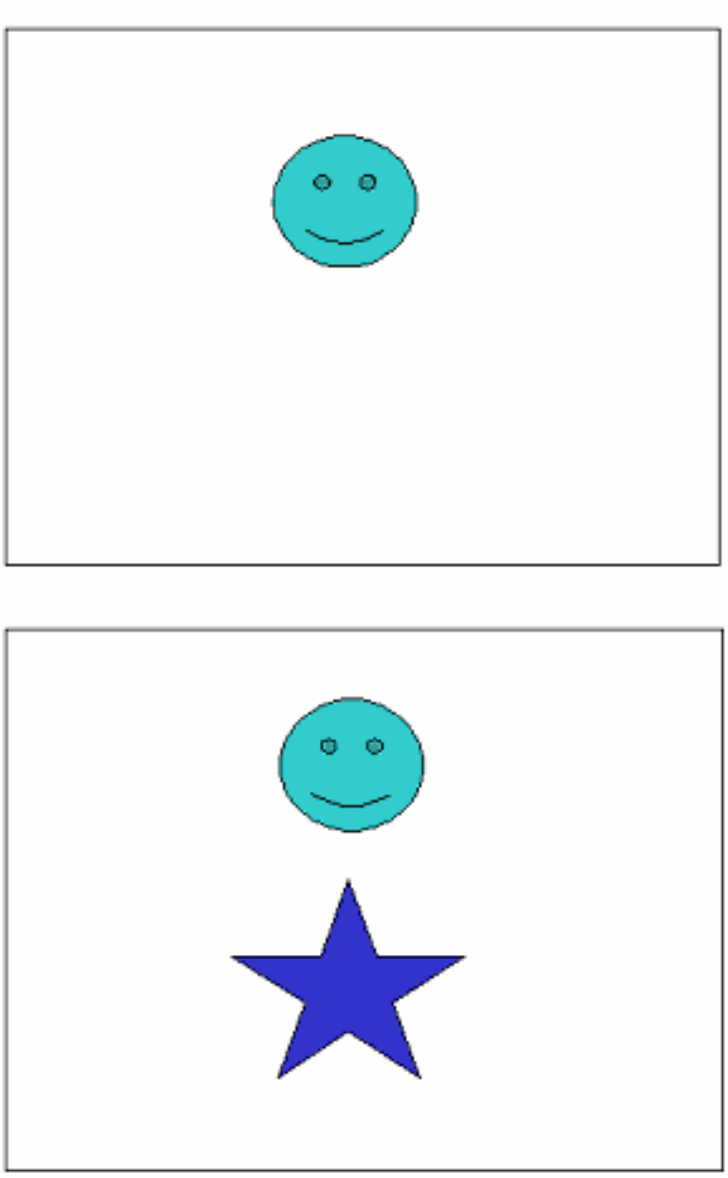
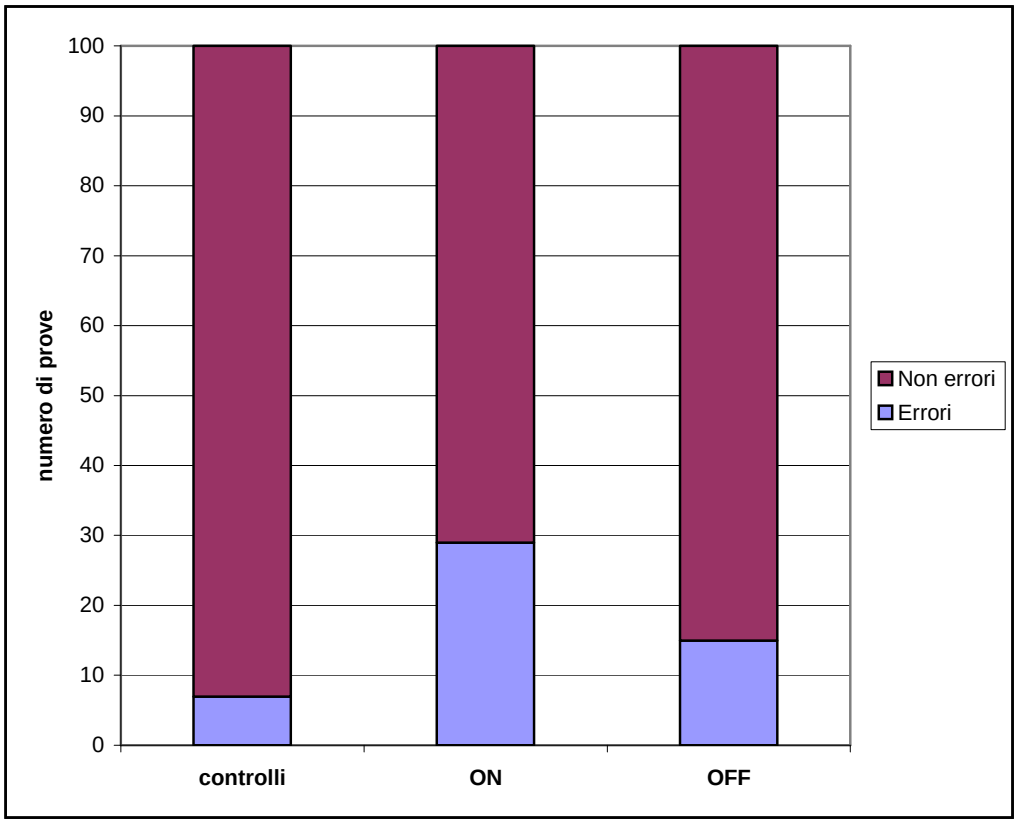


Figure 5. Quantitative assessment of the "extended present".
On a computer screen there was a blue circle. After an interval of time between 40 and 90 s appeared, below the blue circle, a blue star. The subject had to assess, by mentally counting, after what time appeared the star blue.

Qualitative assessment of the “present”



controlli vs ON: *p*>0.001
controlli vs OFF: *p*>0.05
ON vs OFF: *p*<0.05

Figure 6. Results obtained from 10 patients and 10 controls, each in 10 trials, by using the protocol for the qualitative assessment of short time intervals. It can be seen that the patients committed a greater number of errors compared to controls. The number of errors was higher when patients were in ON phase than when they were in OFF phase.

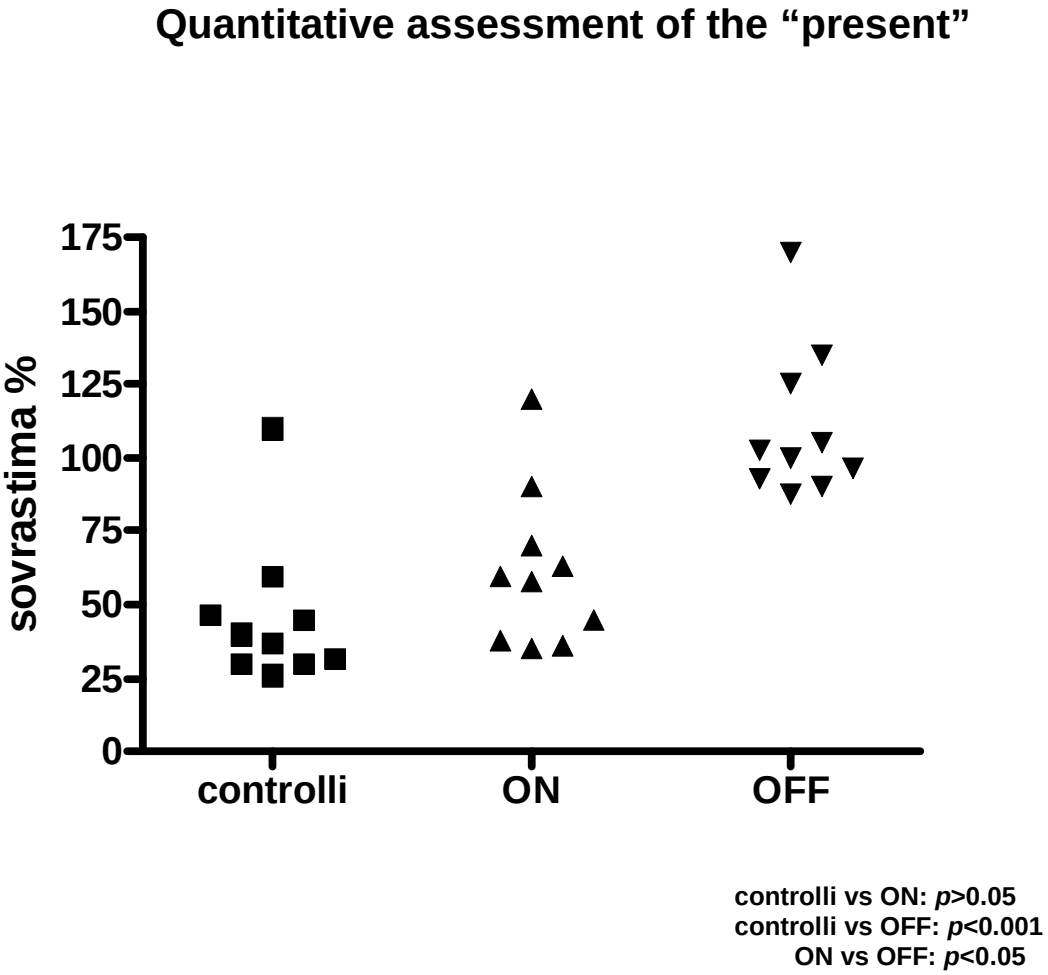
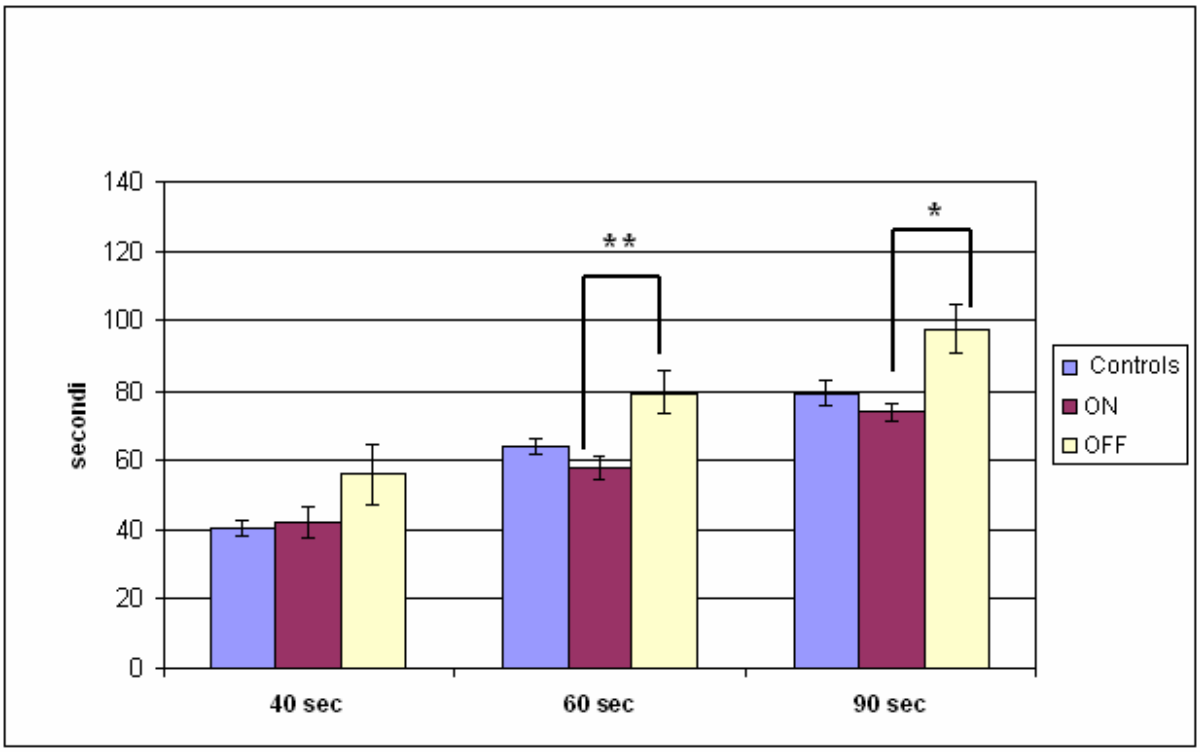


Figure 7. Results obtained from 10 patients and 10 controls, each of whom performed 10 trials, by using the protocol for the assessment of short time intervals that allowed the subject to count mentally. It can be seen that both the controls and patients tended to overestimate the length of time that had to be measured.

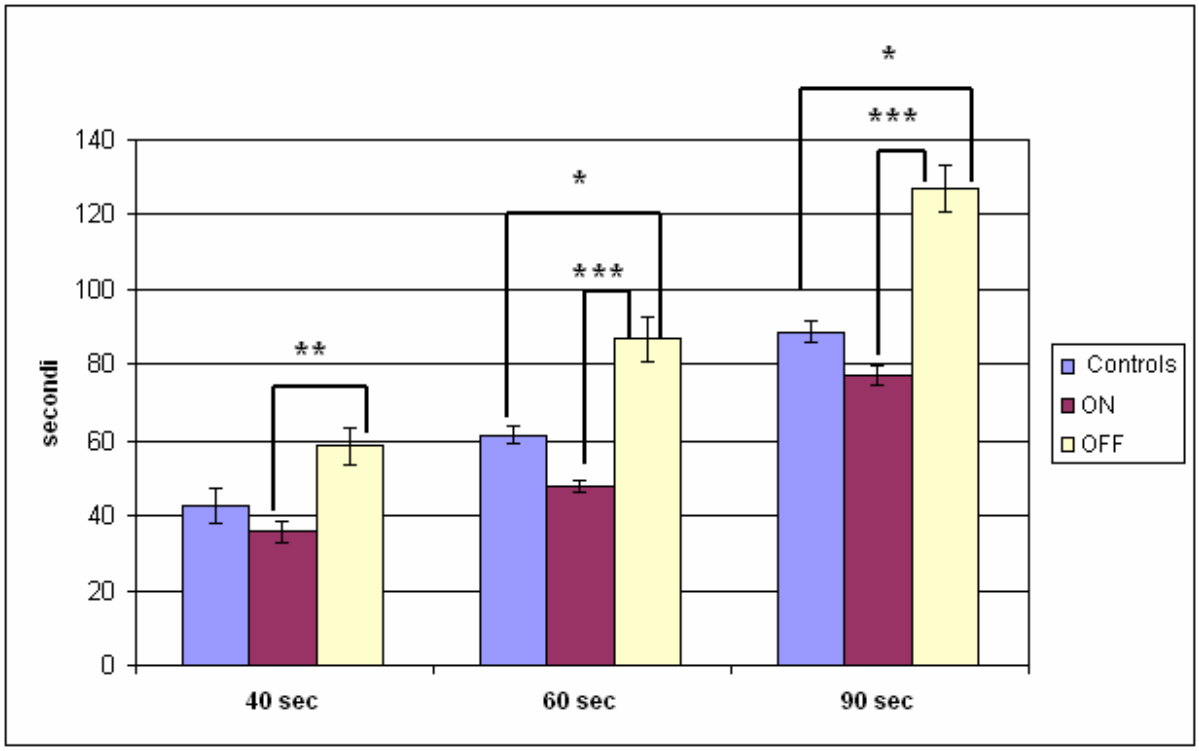
Qualitative assessment of the “extended present”



* p<0,05; ** p<0,001

Figure 8. Results obtained from 10 patients and 10 controls by using the protocol for the evaluation of time intervals, ranging between 40 and 90 s, which did not allow to count mentally. It can be seen that both control subjects and patients in ON phase estimate with an acceptable accuracy the duration of the measured interval. Instead, when patients were in OFF phase tended to overestimate the interval to be measured.

Quantitative assessment of the “extended present”



*** *p*<0,05; ** *p*<0,001; *** *p*<0,0001**

Figure 9. Results obtained from 10 patients and 10 controls by using the protocol for the evaluation of time intervals between 40 and 90 s, which allowed the subject to count mentally. It can be seen that patients in ON phase tended to underestimate the time interval that had to measured with respect to controls; the same patients, however, when they were in OFF phase tended to overestimate the range to be measured.

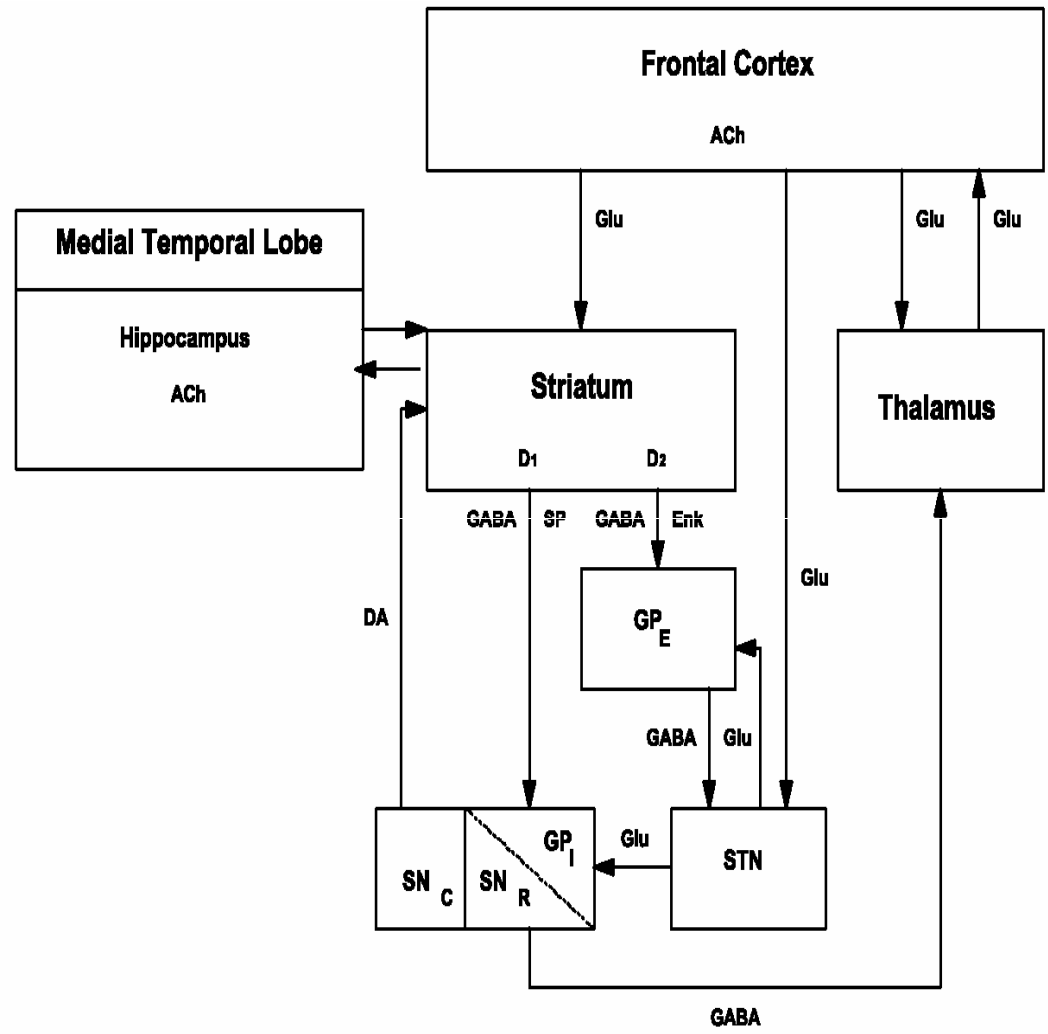


Figure 10. Schematic representation of the striato-hippocampal interconnections with the indication of the main involved neurotransmitters (Meck, 2005).

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